JARI LEPPÄLÄ

Effect of Musculoskeletal Injuries and Disorders on Bone Mineral

University of Tampere
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ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the small auditorium of
Building K, Medical School of the University of Tampere,
Teiskontie 35, on April 28th 2000 at 12 o'clock.

University of Tampere
Tampere 2000

*To my son **Leevi***

CONTENTS

1. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to as I - VI in the text:

I. Leppälä J, Kannus P, Natri A, Pasanen M, Sievänen H, Järvinen M, Vuori I (1999):
Effect of anterior cruciate ligament injury of the knee on bone mineral density of spine and affected lower extremity: A prospective one-year follow-up study. Calcified Tissue Int 64: 357-363.

II. Kannus P, Leppälä J, Lehto M, Sievänen H, Heinonen A, Järvinen M (1995):
A rotator cuff rupture produces permanent osteoporosis in the affected extremity, but not in those with whom shoulder function has returned to normal. J Bone Miner Res 10:1263-1271.

III. Leppälä J, Kannus P, Sievänen H, Vuori I, Järvinen M (1999):
A tibial shaft fracture sustained in childhood or adolescence does not seem to interfere with attainment of peak bone density. J Bone Miner Res, 14:988-993.

IV. Leppälä J, Kannus P, Niemi S, Sievänen H, Vuori I, Järvinen M (1999):
An early life femoral shaft fracture and bone mineral density at adulthood. Osteoporosis Int 10: 337-342.

V. Leppälä J, Kannus P, Natri A, Sievänen H, Järvinen M, Vuori I (1998):
Bone mineral density in the chronic patellofemoral pain syndrome. Calcif Tissue Int 62: 548-553.

VI. Leppälä J, Kannus P, Sievänen H, Järvinen M, Vuori I (1998):
Adhesive capsulitis of the shoulder (frozen shoulder) produces bone loss in the affected humerus, but long-term bony recovery is good. Bone 22: 691-694.

2. ABBREVIATIONS

ACL	Anterior cruciate ligament
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMC	Bone mineral content, g
BMD	Areal bone mineral density, g / cm^2
BMI	Body mass index, kg / m^2
CI	Confidence interval
DXA	Dual energy X-ray absorptiometry
PBD	Peak bone density
PBM	Peak bone mass
PFPS	Patellofemoral pain syndrome
SD	Standard deviation

3. INTRODUCTION

Osteoporosis is a cause for worldwide concern and it is now recognised as one of the major public health problems facing postmenopausal women and aging individuals of both sexes (Riggs and Melton 1995). Osteoporosis is characterized by low bone mass and microarchitectual deterioration of bone tissue, leading to enchanced bone fragility and a consequent increase in fracture risk (Consensus Conference on Osteoporosis 1996). Low bone mineral density (BMD) is a well-known risk factor for osteoporotic fractures among elderly people (Riggs and Melton 1992, Dempster and Lindsay 1993, Johnell 1996, Lau and Cooper 1996). For example, the risk of a hip fracture is approximately doubled for every standard deviation reduction in BMD (Hayes et al. 1996).

Hip fracture is perhaps the most devastating manifestation of osteoporosis and falls and results in increased morbidity and mortality in both men and women (Cooper et al. 1993, Baudoin et al. 1996, Johnell 1997, Slemenda 1997). Hip fracture with other osteoporotic fractures (fractures of foot, ankle, knee, pelvis, spine, ribs, proximal and distal humerus, and distal radius) also generates huge health-care costs (Dolan and Torgeson 1998, Oden et al. 1998). The number and incidence of osteoporotic fractures have increased in Finland and other developed countries during the recent decades, and they are expected to rise further especially as the population ages (Kannus et al. 1996a, 1996b, 1997a and 1997b, Parkkari et al. 1996, Johnell 1997, Lips 1997, Melton 1997, Seeman 1997, Dolan and Torgerson 1998, Palvanen et al. 1998a and 1998b, Kannus et al. 1999b).

Two well-known risk factors for osteoporosis and osteoporotic fractures are insufficient bone mass by the time of skeletal maturity (low peak bone mass) and subsequent age-related loss of bone that occurs rapidly in women especially at menopause (Dempster and Lindsay 1993, Johnston and Slemenda 1994, Cooper et al. 1995, Haapasalo et al. 1996). However, there are also some other risk factors for osteoporosis that, in contrast to generalized osteoporosis, result in a loss of bone only in certain regions of the skeleton and are usually caused by a specific event or reason. This kind of local bone loss can, for example, be seen in transient osteoporosis associated with pregnancy, after radiation therapy, and in conjuction with rheumatoid arthritis (both local and generalized bone loss), physical inactivity, and musculoskeletal injuries (Deodhar and Woolf 1996, Järvinen and Kannus 1997).

The purpose of this research project was to examine the effects of various, previously but scarcely studied musculoskeletal injuries and disorders on bone mineral density (BMD) of the human skeleton.

4. REVIEW OF THE LITERATURE

4.1. Bone biology

Bone has both stuctural and metabolic tasks. Its three main functions are: 1.) to support the body against gravity and act as a rigid lever system for muscular action; 2.) to protect the soft tissues of vital organs and bone marrow; 3.) to act metabolically as a reserve of ions, especially calcium, for the entire organism. There are two different types of bone tissue: the cortical bone, which is very dense; and the trabecular bone, which has approximately twenty times more surface area per unit volume than does the cortical bone (higher porosity). Therefore, the main function of the trabecular bone is metabolic, whereas the cortical bone fulfills mainly the mechanical and protective tasks.

The most external part of a bone is a fibrous membrane called the periosteum. Under the periosteum the bone is formed by a dense layer called the cortex. The cortex is thickest in the diaphysis of long bones. The cortex becomes gradually thinner towards the bone epiphyses, where the space surrounded by the cortical bone is filled with trabecular bone. Similarly to ephiphyseal areas, the majority of short and flat bones have a core of trabecular bone surrounded with a relatively thin cortex. The internal portion of bone cortex is called the endosteum. The two surfaces of bone (periosteum and endosteum) are in contact with soft tissues (Martin and Burr 1989, Baron 1996).

The bone tissue is formed by three types of bone cells (osteoblasts, osteocytes and osteoclasts), organic matrix and inorganic mineral. The bone cells are responsible for continuous metabolic turnover in the bone tissue. Bone tissue consists of 76% inorganic salts and 24% organic matrix. The organic matrix is composed mainly of type I collagen fibers, which accounts for approximately 90% of its total protein amount, while the remaining 10% is formed by other proteins (glygoproteins, proteoglycans, osteocalcin, and osteonectin). Adult bone, whether cortical or trabecular, is lamellated. These lamellae can be parallel to each other, if deposited along a flat surface, or concentric, if deposited on the surface of a channel that is centered on a blood vessel (so called Haversian channel system). The mineral phase of bone consists of calcium, phosphate and carbonate (10:6:1) arranged as crystals, most of it in a form of hydroxyapatite. The hydroxyapatite crystals are normally oriented in the same preferential directions as the collagen fibers. The

inorganic component (minerals) basically resists compression of the bone, while the organic component, primarily collagen, gives bone its form and contributes to its elasticity. This special organization of organic and inorganic materials results in a combination of strength and lightness. In other words, these qualities provide bone with maximum mechanical support and minimal mass (Martin and Burr 1989, Kimmel 1993, Rodan and Rodan 1995, Baron 1996).

The bone tissue is constantly being turned over in order to maintain skeletal integrity and calcium homeostasis. Three biological mechanism are involved in bone turnover at tissue level: 1.) growth determining the bone size; 2.) modeling determing the bone shape; 3.) remodeling maintaining the functional competence of bone (Kanis 1994, Demster 1995, Heinonen 1997).

During growth, weight-bearing exercise and activation of muscles form a mechanical enviroment that induces cellular activity to achieve and maintain the normal architecture, shape and size of the skeleton (Kanis 1994, Demster 1995, Heinonen 1997). In humans, the growth of bone stops around 16-18 years of age, and around the age of 20 peak bone mass (PBM) and density (PBD) are achieved as a result of growth and modeling (Kanis 1994, Haapasalo et al. 1996). PBM can be defined as the maximum amount of bone an individual has in his or her skeleton during the lifetime. In healthy individuals, the suggested main determinants of PBM are race, sex, heredity, hormonal status, nutrition, and physical activity (during the growth period bone is especially sensitive to mechanical stimuli). It has to be remembered that smoking, alcohol, and certain drugs and diseases can also affect bone metabolism. Since the amount of bone tissue present in an adult skeleton is the difference between PBM and the amount of bone loss during the following years, the PBM is an important determinant of osteoporosis and subsequent fracture risk (Kanis 1994, Seeman et al 1994, Kannus et al. 1995, Haapasalo et al. 1996, Haapasalo 1998, Kannus 1999).

Bone modeling takes place during growth or in response to increased mechanical loading. Remodeling is the main process in bone turnover in adults. It is defined as the process of bone resorption followed by new bone formation in places where the former resorption has occurred. Both of these processes provide bone an important mechanism of self repair and adaption to stress which allows the mechanical integrity of the skeleton to be maintained. In a normal remodeling cycle the amount of bone resorbed is equal to that formed is. If this fails, so that resorption exceeds formation, net bone loss will occur (Kanis 1994, Dempster 1995, Baron 1996, Haapasalo1998).

In adults, the natural control of bone turnover is derived mainly from calcium regulating hormones and mechanical loading (Lanyon 1987). However, the control of bone turnover is a very complex process involving various cellular functions directed toward coordinated resorption and formation of new bone. Bone remodeling is regulated by systemic hormones (parathyroid hormone, vitamin D,

calcitonin, glucocorticoids, sex steroids, insulin, growth hormone, and thyroid hormones) and by local factors (prostaglandins, growth factors, and cytokines), which exert their effects on replication, recruitment and differentiated function of osteoblasts and osteoclasts (Kanis 1994, Rodan and Rodan 1995, Canalis 1996, Haapasalo 1998).

4.2. Effect of physical activity and inactivity on bone

The maximum amount of bone mass gained during growth (peak bone mass) is an important determinant of bone mass in later life and thereby an important determinant of fracture risk (Seeman et al. 1994). Although genetic factors appear to be primary determinants of PBM, personal factors such as physical activity also contribute. The positive effect of physical activity (especially weight-bearing activity) on human bone mass is very well documented in many cross sectional studies comparing physically active people or athletes with sedentary controls, as well as in longitudinal follow-ups of exercisers and their controls (Heinonen et al. 1996a, Heinonen et al. 1996b, Bennell et al. 1997, Dook et al. 1997, Duppe et al. 1997, Dyson et al. 1997, Edzard 1998, Haapasalo 1998, Joakimsen et al. 1998, Kelley 1998, Nguyen et al. 1998, Wittich et al. 1998, Wolff et al. 1999).

Especially in children and adolescents increased physical activity is associated with increased bone mass (Slemenda et al. 1994, Uusi-Rasi et al. 1997, Haapasalo et al. 1998). It seems that the age at which physical activity is started is important. The benefit to bone tissue is doubled if the activity is started before or at puberty rather than after it (Kannus et al. 1995, Haapasalo et al. 1998, Kannus 1999). The evidence strongly suggests that regular physical activity is an effective, safe and cheap way to prevent and treat osteoporosis and reduce propensity to fall (Kannus 1999).

Weight-bearing activity is essential for the development and maintenance of a healthy skeleton. The load on bones come from gravity and muscle action, and bone strength is normally adapted to the largest voluntary loads affecting the bone. Disuse and immobilization cause wasting of both muscle and bone, as seen during physical inactivity and prolonged bed rest (Schoutens et al. 1989, Minaire 1989, Leblanc et al. 1990, Garland et al. 1992, Palle et al. 1991, Kannus et al. 1992a and 1992b, Wilmet et al. 1995, Uebelhart et al. 1995, Zerwekh et al. 1998). Space flight and bed rest have been shown to result in a rapid loss of trabecular bone at a rate of about 1% per week, whereas the loss of compact bone occurs at a lower rate, less than 1% per month (Mazess and Whedon 1983, Whedon 1984, Uebelhart et al 1995, Bloomfield 1997). It has been suggested that after restoration of weight bearing, trabecular bone mass will increase at a rate of 1% per month, allowing either complete or incomplete bone recovery. But the period needed for recovery appears to be several times longer than that causing the loss, with a great deal of individual variation (Mazess and Whedon 1983, Sievänen et al 1994a and 1996a, Norimatsu et al 1997).

4.3. Osteoporosis

Osteoporosis is characterized by decreased bone mass with microarchitectual deterioration of bone tissue and increased susceptibility to fracture. In osteoporotic bone, there is a reduction in the amount or mass of bone tissue, but the remaining tissue appears normal in composition (Melton 1988, Christiansen 1993, Nevitt 1994, Johnell 1996). Thus, the clinical consequence of osteoporosis is bone fracture, which is most commonly seen at the wrist, the spine, and the hip. Characteristic of osteoporotic fractures is their incidence which increases sharply with age. Fractures are more common in women, and they are associated with moderate or minimal trauma at sites containing substantial amounts of trabecular bone (Kannus et al. 1996a).

In the United States alone, osteoporosis affects more than 28 million people. It is estimated that by the year 2015, more than 41 million US men and women over the age of 50 will either have osteoporosis or be at risk for having it develop. At 50 years of age, a white woman has a 15% chance on sustaining a hip fracture during her remaining lifetime. By 90 years of age, one in three women and 15% of men will have sustained at least one hip fracture (Dubey et al. 1998, Brunelli and Einhorn 1998). Furthermore, there are also many other, less serious, osteoporotic fractures so that the total risk for a 50-year-old white woman to sustain at least one osteoporotic fracture in her remaining lifetime is as high as 40-50 % (Melton 1988 and 1997).

4.3.1. Primary osteoporosis

Primary osteoporosis includes postmenopausal osteoporosis and senile osteoporosis. The senile form occurs in both men and women. The loss of bone mass affects trabecular and cortical bone and results in bone fragility most likely due in part to age-related reduction in the load carrying usage of the skeleton. According to recent World Health Organization (WHO) criteria, the term osteoporosis is also used to designate a bone mass value more than 2.5 standard deviations (SD) below the young adult mean (Kanis et al 1994).

The risk for osteoporotic fracture increases progressively with age, doubling after every 5 to 10 years. Approximately 75% of all hip fractures occur in women, in part, because of their greater bone loss and higher mean age. Women experience BMD declines of approximately 50% during their lifetime. The rate of decline in untreated women is greatest during the first 5 years after menopause.

Elderly men experience bone loss at approximately half the rate of women, and their average lifetime decline in BMD is no more than 35% (Ross 1998).

4.3.2. Secondary osteoporosis

As noted above, osteoporosis is called ”primary” if it occurs as a part of normal aging. In addition to these primary etiologies, a host of secondary causes, including a large number of medical illnesses, endocrinopathies, medications, and lifestyle factors significantly contribute to bone loss and fracture risk (Table 1). These factors may solely or partially (in concert with primary etiology) be responsible for the individual’s risk for osteoporosis and fractures (Harper and Weber 1998, Ross 1998, Melton et al. 1999). Approximately 20% of women who otherwise would seem to have postmenopausal osteoporosis have an identifiable secondary cause contributing to bone loss. The percentage of young women and men with a secondary cause is even higher. In young osteoporotic men, the reported presence of secondary etiologies for osteoporosis is as high as 64% (Kelepouris et al. 1995, Harper and Weber 1998).

Many endocrine diseases are related in osteoporosis including hypogonadism, hyperparathyroidism, thyroid disease, and endogenous hypercortisolism (Cushing’s syndrome). There are also many other causes of hypogonadism in addition to estrogen deficiency at natural female menopause. Bone loss is typical in 45, XO gonadal dysgenesis or Turner’s syndrome and its genetic variants. Females with this syndrome fail to mature sexually at puberty and are found to have low plasma estradiol and elevated gonadotropin concentrations. Hypothalamic amenorrhea occurs in women with anorexia nervosa or excessive exercise. In both of these conditions, low plasma gonadotropin and estradiol concentrations can be found (Rencken et al. 1996, Harper and Weber 1998, Cummings et al 1998). Men with abnormal pubertal development, such as those with isolated gonadotropin defiency (Kallman’s syndrome), the XXY syndromes and its variants associated with testicular developmental defects (Klinefelter’s syndrome), or with constitutional delay of puberty, have reduced cortical and trabecular bone mass. Thus, hypogonadism is one of the most frequent causes of osteoporosis and related fractures in men (Kelepouris et al. 1995, Ybarra et

Table 1. REASONS FOR SECONDARY OSTEOPOROSIS

A. ENDOCRINE DISORDERS
Hypogonadism (primary and secondary)
Clucocorticoid excess (endogenous and exogenous)
Hyperparathyroidism
Hyperthyroidism
Hypopituitarism
Insulin-dependent diabetes mellitus
B. OTHER DISORDERS AND DISEASES
Bone marrow replacement and expansion (myeloma, leukemia, metastatic disease)
Gastrointestinal disease (GI malabsorption, hepatic insufficiency)
Connective tissue diseases (rheumatoid arthritis, osteogenesis imperfecta)
Other chronic disease (chronic renal disease, hemachomatosis , chronic obstructive pulmonary disease, organ transplantations)
C. DRUGS
Corticosteroids, heparin, anticolvulsants, immunosuppressants, chemotherapy
D. LIFESTYLE AND GENETIC FACTORS
Positive family history
Ethnicity (Caucasian, Asian)
Nutritional factors (low BMI, anorexia nervosa, deficiency states: vitamin D, C, and calcium, excessive alcohol consumption)
Smoking
Sedentary lifestyle
Excessive exercise (exercise-induced amenorrhea)
E. POSTTRAUMATIC OSTEOPOROSIS AND IMMOBILIZATION

al 1996). Many other conditions associated with osteoporosis have hypogonadism as part of their pathogenic mechanism (e.g., clucocorticoid-induced osteoporosis, and chronic exposure to alcohol).

Hyperparathyroidism can be divided into primary and secondary conditions. Secondary hyperparathyroidism can be caused by gastrointestinal illnesses and renal disease and it leads to skeletal abnormatilies. A patient with high serum calcium and high PTH most likely has primary hyperparathyroidism. Clearly, cortical bone loss occurs in primary hyperparathyroidism (Parfitt et al. 1987). The primary effect of thyroid hormones is to stimulate bone resorption. Thus, patients with hyperthyroidism have reduced BMD in comparison with healthy persons. Also growth hormone deficiency has been shown to lead to reduced BMD (Rosen et al. 1996). The rare cause of osteoporosis can be Cushing's syndrome, i.e. endogenous excess of glucocorticoid.

Some gastrointestinal diseases may cause secondary osteoporosis (e.g. regional enteritis, cholestatic liver disease, and post gastrectomy). Most cases are thought to be associated with calcium malabsorption alone, or in addition to malabsorption of vitamin D. Calcium malabsorption (or lack of calcium in diet) leads to secondary hyperparathyroidism and osteoporosis.

Clucocorticoids are often used to treat inflammatory bowel diseases, and there may be a component of glucocorticoid- induced osteoporosis in some of these patients (Rao 1996).

Any abnormal process occurring in the bone marrow may alter normal bone remodeling processes and predispose an individual to both cortical and trabecular osteopenia. Thus, patients with multiple myeloma, lymphoma and leukemia, and diffuse bony metastases may present diffuse osteopenia (Mundy 1996).

Certain rheumatic conditions are associated with reduced BMD and osteoporosis. Periarticular osteoporosis is a well-recognized phenomenon of rheumatoid arthritis that seems to be mediated by local disease mechanism. Generalized osteoporosis is also often seen in rheumatoid arthritis, although its pathogenesis is less well understood. Furthermore, increased amount of oral corticosteroids correlates with decreased bone density (Sambrook et al. 1990, Kröger et al. 1994, Deodhar and Woolf 1996).

Corticosteroid treatment and several other medications including anticonvulsants, heparin, immunosupressants and methotrexate can cause osteoporosis by a variety of known and unknown mechanisms (Hahn 1996, Ishida and Heersche 1998). There is also good epidemiologic evidence from twin and other studies that smoking reduces bone mass (Seeman and Hopper 1994, Law and Hackshaw 1997). Also, chronic alcohol abuse is associated with osteoporosis and increased risk for skeletal fractures. Ethanol has direct negative effects on normal bone remodeling and other indirect effects on bone metabolism as well (Ybarra et al 1996, Harper and Weber 1998).

4.3.3. Prevention and treatment of osteoporosis

Adequate calcium and vitamin D intakes continue to be important throughout life because they are key factors and cofactors in many biologic processes. Calcium is especially important during the period when a person is attaining PBM, and in the use of vitamin D in old age when exposure to sunlight is small. Therefore, adequate calcium and vitamin D intake can be recommended to everyone. There is also good evidence from randomized trials that calcium supplements, with or without vitamin D, reduce the rate of bone loss in postmenopausal women (Nevitt 1994, Cumming and Nevitt 1997).

When discussing optimizing PBM and overall prevention of osteoporosis, we should not forget regular physical activity. The benefit of physical activity on bone is doubled if the activity is started before or at puberty rather than after it (Kannus et al. 1995, Haapasalo 1998). However, it is also

important to get older people moving since exercise is important in preventing bone loss and falls among older adults (Kannus 1999). Furthermore, abstaining from smoking and alcohol abuse would be beneficial to bones.

The most important hormone for attaiment and maintance of bone mass in women is estrogen. A great number of studies have shown that estrogen replacement therapy is beneficial in the prevention of osteoporosis and hip fractures. Estrogen has been found to be most effective when given within 5 years of menopause and continued longer than 10 years. However, additional clinical ivestigation is needed to obtain more precise information on the long-term benefits and risks of estrogen therapy (Barrett-Connor 1998, Brunelli and Einhorn 1998, Dubey et al. 1998). The newest group of medicine for treatment of osteoporosis are antiestrogens. They (e.g, raloxifene) have the same beneficial effects on bone as estrogens, but without undesirable stimulation of breast and endometrial tissues (Delmas et al. 1997, Khovidhunkit and Shoback 1999).

Calcitonin, a hormone secreted by the parafollicular cells of the thyroid gland, targets bone, kidneys and the intestine and functions to decrease serum calcium level. In bone, calcitonin reduces the number and action of osteoclasts. The human and salmon homologues of the calcitonin polypeptide have been synthesized and developed for pharmacologic patient use. In addition to the treatment of osteoporosis, calcitonin has been used as an analgesic agent in vertebral fractures.

Thiazide diuretics decrease urinary calcium excretion, and thus, can be used to prevent bone loss. Bisphosphonates are synthetic analoques of pyrophosphate that inhibit bone resorption by decreasing osteoclastic activity. Bisphosphonates (especially alendronate) have been shown to increase BMD in the spine, the femoral neck, and the trochanter area of the femur among women who have postmenopausal osteoporosis (Brunelli and Einhorn 1998, Dubey et al. 1998).

The two drugs with the strongest effect on preserving bone mass are alendronate and estrogen. Two other approaches to preventing osteoporotic fractures in older adults are preventing falls and using external hip protectors (Tinetti et al. 1994, Parkkari 1997, Dubey et al. 1998).

4.4. Effect of some muskuloskeletal diseases and disorders on bone

Many rheumatic conditions, including juvenile rheumatoid arthritis, are associated with reduced BMD and osteoporosis (Sambrook et al. 1990, Hillman et al. 1994, Kröger et al. 1994, Deodhar and Woolf 1996, Pepmueller et al. 1996), as noted in chapter 4.3.2. Also, some heritable disorders of connective tissue (e.g., osteogenesis imperfecta, homocystinuria, and Marfan syndrome) have a similar association (Shapiro 1996). Yet, many musculoskeletal diseases and disorders and their connections with BMD have scarcely been studied. The relationship between musculoskeletal diseases and disorders and osteoporosis can be explained not only via the disease process itself but also due to immobilization, inactivity, and the impaired function of the affected skeletal site.

4.4.1. Patellofemoral pain syndrome (PFPS)

Patellofemoral pain syndrome (PFPS) is a characteristic musculoskeletal pain state that is often seen in young adults (Outerbridge 1961, Fulkerson and Hungerford 1990, Kannus et al. 1992c and 1999a). Once it has begun, PFPS frequently becomes chronic, and the pain forces the patient to stop physical activities. The etiology and pathogenesis of PFPS are still unknown, but several predisposing factors have been proposed, including acute trauma, overuse, immobilization, overweight, genetic predisposition, malalignment of the knee extensor mechanism, congenital anomalies of the patella, prolonged synovitis, recurrent hemorrhage into a joint, joint infection, and repetitive intraarticular injections of corticosteroids (Outerbridge 1961, Aleman 1982, Shahriaree 1985, Fulkerson and Hungerford 1990, Kannus et al. 1992c). In many cases, however, there are no obvious factors behind the PFPS (Kannus et al. 1992c and 1999a). The classic form of PFPS, chondromalacia patellae, is characterized by macroscopic softening, fissuring, and fragmentation of the undersurface of the patella (Outerbridge 1961, Fulkerson and Hungerford 1990, Kannus et al. 1992c). The cartilage damage may also occur at the microsopic (biochemical) level only, and presents as degradation and softening of the cartilaginous matrix, with impaired lubrication of the joint (Shahriaree 1985, Kannus et al. 1992c and 1999a).

The most common symptoms of PFPS are retropatellar pain and crepitation during various activities, such as squatting, running, jumping, and going up or down in stairs. Also, patients may feel patellar pseudolocking, snapping, knee stiffness and periodical effusions. Literature provides a

wide scale of conservative and operative managements for PFPS, but so far there is no general consensus about the treatment of PFPS. Nevertheless, quadricep muscle exercises have been recommended by many authors as an effective way to correct the faulty patellar tracking and to reduce the symptoms (Outerbridge 1961, Dehaven et al. 1979, Aleman 1982, Livigstone 1982, Wise et al.1984, Shahriaree 1985, Kujala et al.1986, Fulkerson and Hungerford 1990, Kannus et al.1992c).

Before starting the current research project, literature provided no previous reports on PFPS and its association to bone and BMD.

4.4.2. Adhesive capsulitis of the shoulder (frozen shoulder)

The frozen shoulder is a general term used to describe a shoulder that is stiff and painful. The term adhesive capsulitis infers that the reason for the stiff and painful shoulder is severe, long-term capsular constriction of the shoulder joint. The etiology of the condition has not been established, nor has the best treatment (Binder et al. 1984a, Neviaser 1987, Shaffer et al. 1992, Ogilvie-Harris et al. 1995). Adhesive capsulitis typically affects women in the sixth decade of life, involves more frequently the non-dominant than the dominant extremity, and may finally occur bilaterally in as many as 30-35 percent of the patients. The condition is rarely seen in patients under 40 years of age (Reeves 1975, Binder et al. 1984a, Neviaser 1987, Neviaser and Neviaser 1987, Hill and Bogumill 1988, Shaffer et al. 1992).

Adhesive capsulitis is thus an idiopathic condition of the shoulder characterized by spontaneous onset of devastating pain in the shoulder followed by a severe restriction of shoulder movement that finally affects every movement direction (Reeves 1975). Synovitis, dense adhesions and capsular contriction are found intra-articularly, especially in the dependent fold area, and they usually cause severe restriction of motion and intense pain (Neviaser 1987, Neviaser and Neviaser 1987).

The natural history of the condition has been investigated in several studies and they indicate that with time most patients will show clinical recovery (Reeves 1975, Grey 1978, Binder et al. 1984a, Neviaser 1987, Neviaser and Neviaser 1987, Hill and Bogumill 1988, Shaffer et al. 1992, Ogilvie-Harris et al. 1995). The clinical course of the adhesive capsulitis can be divided into three consecutive stages: 1.) pain stage, 2.) stiffness stage, and 3.) recovery stage. According to Reeves, the stage 1 or pain stage lasts 2 to 9 months (Reeves 1975). The pain in the shoulder is often very severe and disturbs sleep. There is a full range of shoulder movement, at least passively. This stage

1 often mimics the impingement syndrome and rotator cuff problems of the shoulder. Stage 2, or stiffness or frozen stage, begins when the patient starts to suffer from a progressive loss of shoulder motion. In this stage, the pain often begins to gradually be relieved. The period of stiffness without improvement usually lasts 4 to 12 months. The stage 3 is then followed with spontaneous gradual recovery of the shoulder movements (5 to 26 months) (Reeves 1975). The total duration of disease is said to be between 1 and 4 years (Reeves 1975, Grey 1978, Binder et al. 1984a, Neviaser 1987, Neviaser and Neviaser 1987, Hill and Bogumill 1988, Shaffer et al. 1992, Ogilvie-Harris et al. 1995).

A careful history and physical examination are the most accurate way of diagnosing adhesive capsulitis. Usually, there is no major trauma in the patient's history. Shoulder motion is restricted both actively and passively, primarily in three planes: 1.) abduction or elevation, 2.) external rotation, and 3.) internal rotation (Binder et al. 1984a, Hill and Bogumill 1988, Neviaser 1987, Ogilvie-Harris et al. 1995). If motion is unlimited in rotation and abduction, the diagnosis of adhesive capsulitis is probably incorrect. Routine radiographs have no diagnostic value. Arthrography clearly defines the condition revealing a contracted capsule and reduced intracapsular volume. Arthroscopy has also been shown to be a valuable diagnostic tool (Binder et al. 1984a, Binder et al. 1984b, Hill and Bogumill 1988, Neviaser 1987, Ogilvie-Harris et al. 1995).

The treatment of adhesive capsulitis has been an area of great controversy (Binder et al. 1984a, Bulgen et al. 1984, Neviaser 1987, Neviaser and Neviaser 1987, Shaffer et al. 1992, Ogilvie-Harris et al. 1995). It has been recommended that the patient should be treated with nonsteroidal anti-inflammatory drugs, physical therapy, and in certain cases with intra-articular corticosteroid injections. Manipulation of the shoulder has been advocated as a safe and effective means in enabling these patients to get back the shoulder function and motion (Reeves 1975, Neviaser 1987, Neviaser and Neviaser 1987, Hill and Bogumill 1988, Shaffer et al. 1992, Ogilvie-Harris et al. 1995). In great majority of patients adhesive capsulitis is thought to be a self-limiting condition, in which symptoms gradually subside and finally full shoulder movement returns 1 to 4 years after the onset of symptoms (Reeves 1975, Grey 1978, Bilden et al 1984a, Neviaser 1987). Long-term follow-ups are, however, lacking.

Literature provides only one previous report on adhesive capsulitis and its association with bone loss (Lundberg and Nilsson 1968). In this over 30-year-old study, Lundberg and Nilsson used gamma absorptiometry to measure changes in the bone mineral content (BMC) of the proximal humerus of frozen shoulder patients. Although the precision of their method was fairly poor and the measured area small (the width of the beam and measurement area was only 7 mm), they could give

evidence that adhesive capsulitis had led to a considerable (up to 50%) mineral loss in the proximal humerus of the affected extremity. It would have been most interesting to know if this loss was indeed permanent (the situation 10 years after the clinical recovery) and whether there were mineral losses in the other bones of the affected extremity as well.

4.5. Effect of musculoskeletal injuries on bone

4.5.1. Injuries on growing bone

High amount of bone in early adulthood (high PBM) is an important protective factor against osteoporotic fractures in later life (Seeman et al 1994, Ribot et al 1995, Riis et al 1996). Adult-age fractures can have deletorious long-term consequences on bone (Järvinen and Kannus 1997), but very little is known about the effects of injuries on growing bone. We found only two detailed studies on this topic (Nilsson and Westlin 1971, Henderson et al. 1992) (Table 2). Almost 30 years ago Nilsson and Westlin (1971) studied sixteen young adults who had had a fracture of the femoral shaft eleven years earlier. They found an average 7 per cent side-to-side difference in total bone mineral content of the distal part of the femur. In the more recent study, Henderson et al. (1992) measured bone mineral density (BMD) from the proximal part of the femora in twenty-three children who had sustained an uncomplicated fracture of the tibia, and thirteen children with a fracture of the femur. On average 2.3 years after the injury, the mean BMD difference between the injured and uninjured limbs was 3.3 per cent. It would have been most interesting to know whether there were mineral losses in the other sites of the injured extremity and the spine as well, and whether the observed losses were permanent (the situation 10 years after the clinical recovery).

Table 2. CROSS SECTIONAL STUDIES ON THE EFFECT OF EARLY LIFE INJURIES ON BONE MASS OR DENSITY

Reference	**Subjects (N)**	**Mean age* (yrs)**	**Type of injury**	**Time from injury to bone measurement (mean)**	**Measured site**	**Injured-to-uninjured side difference (mean)**
Nilsson & Westlin 1971	30	8.8	14 tibial shaft fr. 16 femoral shaft fr.	11 yrs	Distal femur	0.0 % in tibial shaft fr. -7.0 % in femoral shaft fr.
Henderson et al. 1992	38	9.3	25 tibial fr. 13 femoral fr.	2.3 yrs	Proximal femur	-3.3 %

*at the time of the injury

4.5.2. Upper extremity injuries of adults and bone

Besides osteoporotic fractures at the hip and the spine, fragility fractures at the upper extremity (distal forearm, elbow and proximal humerus) form a serious public health problem (Horak and Nilsson 1975, Owen et al 1982, Rose et al 1982, Solgaard and Petersen 1985, Kristiansen et al 1987, Obrant et al 1989, Palvanen et al 1998a) and their age-specific incidences have increased during the recent decades (Obrant et al 1989, Bengner and Johnell 1985, Bengner et al 1988, Kannus et al. 1996a, Palvanen et al 1998a). In industrialized countries, a 60-year-old woman with a life expectancy of 81 years has an estimated residual lifetime risk of radial or humeral fracture of 17% and 8% (hip 14%) (Lauritzen et al 1993). However, the effect of upper extremity injuries on bone mass and density have scarcely been studied (Table 3).

Patients who sustain a Colles'fracture and have bone fragility in the involved upper limb differ from the other patients in this review in that most of them are older women who probably already had low bone mass before the fracture. However, studies in Table 3 indicate that there are still considerable posttraumatic bone loss in the injured arm.

Rotator cuff rupture of the shoulder A complete, full-thickness rupture of the rotator cuff of the shoulder is a serious soft tissue injury that characteristically occurs in middle-aged men as a consequence of an accident at work or home (Postacchini 1986, Uhthoff and Sarkar 1991). In many patients, the cuff fibers, especially those at the distal end of the supraspinatus tendon, already show degenerative changes before the injury. As a result, the actual trauma energy, typically created by a violent abduction-external rotation of the shoulder against resistance or a direct fall on the shoulder, may be only moderate to produce an injury (Uhthoff and Sarkar 1991). The preceding cuff degeneration may, in turn, be entirely asymptomatic, or combined with symptoms of the classical subacromial impingement syndrome or supraspinatus tendinitis.

The treatment for a complete rotator cuff rupture is normally surgical consisting of an open (or today also arthroscopic) anterior acromionplasty, coracoacromial ligament release, and direct cuff repair (Uhthoff and Sarkar 1991, Neer 1972). Postoperatively, depending on the size of the rupture, the quality of the tissue, and the security of the repair, the shoulder is immobilized by an "aeroplane" immobilizer, splint, wedge pillow, or firm bandage for 1-6 weeks. According to current concepts, the immobilization time should be as short as possible and the gradually increasing mobilization and rehabilitation should be started immediately after the immobilization period. In the rehabilitation program, the therapy for restoring movement is first passive (forward flexion and external rotation)

Table 3. CROSS SECTIONAL AND PROSPECTIVE STUDIES ON THE EFFECT OF ADULTHOOD INJURIES OF THE UPPER EXTREMITY ON BONE MASS OR DENSITY

Reference	Subjects (N)	Mean age* (yrs)	Type of injury	Time from injury to bone measurement (mean)	Measured site	Injured-to-uninjured side difference (mean)
A. Cross sectional studies						
Nilsson & Westlin 1974	64	63.6	Colles' fr.	1 week	Distal forearm	-7.0 %**
	contr. 64				Forearm shaft	-7.0 %**
Nilsson & Westlin 1975	74	61.8	Colles' fr.	1 month to 12 years	Distal forearm	-9.0 %
Nilsson & Westlin 1977	69	not given	Proximal humerus fr.	39 months	Proximal part	0.9 %
			Humeral shaft fr.	43 months	of the forearm	-1.3 %
			Forearm shaft fr.	29 months		-15.4 %
(Malmin et al. 1992	74	66	Colles' fr.	2 months	Uninjured distal forearm	-11 %***)
	contr. 74					
B. Prospective studies						
Westlin 1974	19	64	Colles' fr.	4 months to 1 year	Distal forearm	-18 % after 4 months; no recovery after 1 year

*at the time of the injury
**fractured forearm was compared with the forearm with the controls
***uninjured distal forearm was compared with the controls. BMD of the injured extremity was not measured.

and then, after 4-6 weeks, active assisted motion is permitted, progressing to fully active motion at 6 weeks. Active abduction is the last of the movements allowed. Following this, rotator cuff strengthening exercises are started using theraband rubber tubing first. Isotonic dynamic exercises may be performed initially at the side of the body and progressing to 90 degree elevation by week 12. The use of isokinetic or other type of rehabilitation devices may be started during the next month. Gentle swimming may be started around 6 months while throwing activities should be avoided for 9 months.

The long-term effects of a complete rotator cuff rupture on the mineral density of the injured extremity were completely unknown before onset of the current research project.

4.5.3. Lower extremity injuries of adults and bone

A major difference between the bones of the lower extremity and those of the upper extremity is the amount of weight that they bear. With the exception of the patella, the bones of the lower limbs bear much greater weight than those of the upper limbs. Thus, a fracture or other major injury of the lower limb with the associated disability, reduction in use, reduction in weight-bearing, and immobilization may lead to a more prominent loss of bone than that found after an injury of the upper limb (Järvinen and Kannus 1997). In fact, most of the studies of the effect of injuries on bone density have focused on the injuries of lower extremities (Tables 4 and 5). As seen in Tables 4 and 5, among the fractures of the lower limb that cause osteoporosis, tibial fractures are associated with the most prominent bone loss, especially during the first year after the injury. Although some of the bone loss may be restored, there is still substantial loss ten years or more after the tibial fracture. The most important determinants of the development of post-traumatic osteoporosis seem to be the duration of immobilization and the impaired function of the injured extremity (Järvinen and Kannus 1997). Since the effect of adults' lower extremity injuries on bone had been studied rather extensively (Tables 4 and 5), the current research series included only one study (work I) from this category.

Table 4. CROSS SECTIONAL STUDIES ON THE EFFECT OF ADULTHOOD INJURIES OF THE LOWER EXTREMITY ON BONE MASS OR DENSITY

Reference	Subjects (N)	Mean age* (yrs)	Type of injury	Time from injury to bone measurement (mean)	Measured site	Injured-to-uninjured side difference (mean)
Femur						
Finsen et al. 1988	26	not given	Femoral shaft fr.	3.5 yrs	Distal femur Proximal tibia Tibial shaft	-12.0 % -5.0 % -3.0 %
Kannus et al. 1994a contr.	29 29	33	Femoral shaft fr.	10 yrs	Femoral neck Trochanter area Distal femur Patella Proximal tibia Calcaneus Lumbar spine	1.3 % 6.3 % -6.8 % -5.4 % -4.7 % -2.2 % -9.3 %**
Knee						
Nilsson & Westlin 1969	54	not given	Knee injury (medial mediscectomy)	0.1 to 5 yrs	Distal femur	-9.0 %
Karlsson et al. 1993	24	not given	Knee ligament injury	20 yrs	Femoral condyles	-4.0 %
Kannus et al. 1992d	42	46	A. ACL rupt (n=31) (severe) B. Rupture of medial collateral ligament (n=11) (moderate)	10 yrs	Femoral neck Distal femur Patella Proximal tibia Calcaneus	A. -0.4 % B. -0.9 % A. -6.0 % B. 1.4 % A. -9.0 % B. 0.0 % A. -3.3 % B. 0.6 % A. -1.0 % B. -0.8 %
Petersen et al. 1996	32	not given	A. Knee injury and complete menisc-ectomy (n=19) B. Knee injury and partial menisc-ectomy (n=11)	12 yrs	Proximal tibia	A. -2.8 % B. -1.3 %
Tibia						
Nilsson 1966	116	not given	Tibial shaft fr.	1 to 14 yrs	Distal femur	-25.0 %
Finsen & Haave 1987	20	37	Tibial shaft fr.	2.5 yrs	Femoral diaphysis Distal femur Proximal tibia Mid tibia diaphysis Distal tibia	-3.0 % -8.0 % -8.0 % -3.0 % -7.0 %
Karlsson et al. 1993	60	not given	A. Tibial shaft fr. (n=38) B. Tibial shaft fr. (n=22)	20 yrs 30 yrs	Trochanter area Femoral condyles Trochanter area Femoral condyles	-2.6 % -3.8 % 0.0 % -3.7 %

Kannus et al. 1994b	34	38	A. Primarily united tibial shaft fr (n=20)	9 yrs	Femoral neck	A. -2.4 %	B. -2.3 %
contr.	22		B. Primarily non-united tibial shaft fr. (n=14)		Distal femur	A. -4.0 %	B.-10.0 %
					Patella	A. -3.7 %	B.-11.2 %
					Proximal tibia	A. -5.1 %	B. -9.2 %
					Distal tibia	A. -1.5 %	B. -5.6 %
					Lumbar spine	A. -9.5 %	B.-12.3 %**
Eyres & Kanis 1995	21	not given	Tibial shaft fr.	5 to 12 yrs	Distal tibia	-47.0 %	
Petersen et al. 1997	14	38	Complicated tibial shaft fr.	3 yrs	Femoral neck	-22.0 %	
					Trochanter area	-24.0 %	
					Proximal tibia	-43.0 %	
Natri et al. 1999	1	26	Tibial shaft fr.	11 months	Femoral neck	-14.3 %	
					Trochanter area	-17.8 %	
					Distal femur	-26.0 %	
					Patella	-25.2 %	
					Proximal tibia	-31.8 %	
					Distal tibia	-22.1 %	
Miscellaneous							
Van der Poest	19	81	10 Ankle fr.	9.3 yrs	Femoral neck	-2.9 %	
Clement et al. 1999			6 Tibial shaft fr.		Trochanter area	-4.7 %	
			3 Other fractures of lower leg				

*at the time of the injury
** compared with the controls

Table 5. PROSPECTIVE STUDIES ON THE EFFECT OF ADULTHOOD INJURIES OF THE LOWER EXTREMITY ON BONE MASS OR DENSITY

Reference	Subjects (N)	Mean age* (yrs)	Type of injury	Follow-up time (mean)	Measured site	Bone loss
Hip						
Dirschl et al. 1997	49	77	Hip fr.	1-year follow-up	Contralateral femoral neck Lumbar spine	-5.4 % after 1 year -2.4 % after 1 year
Neander et al. 1997	25	82	Femoral neck fr.	6-month follow-up	Distal femur Proximal tibia	-11 % after 6 months -19 % after 6 months
Zerahn et al. 1998	41	71	Hip fr.	1-year follow-up	Contralateral femoral neck and trochanter Proximal tibia (fractured limb) Proximal tibia (non-fractured limb)	-4.6 % after 1 year -3.8 % after 1 year -16.4 % after 1 year -0.1 % after 1 year
Knee						
Andersson & Nilsson 1979a	44	not given	A. Knee lig. injury Partial rupture (n=22) B. Knee lig. injury Complete rupt. (n=22)	0, 5, 12 and 52 weeks	Proximal tibia	A. -10.0 % B. -18.0 % after 12 weeks and no recovery during 1 year
Sievänen et al. 1994a and 1996a	1	26	Complete ACL rupture of the knee	2-year follow-up	Lower limbs	maximum decrease about 20 % after 15 weeks; after 1 year about 10 %; further improvement after 2 years
Tibia						
Andersson & Nilsson 1979b	27	not given	Tibial shaft fr.	1-year follow-up	Proximal tibia	-45 % after 5 months; -25 % after 1 year
Ulivieri et al. 1990	7	19.5	Tibial shaft fr.	10 to 120 days	Distal tibia	about -50 % after 120 days
Van der Wiel et al. 1994	16	60	Tibial shaft fr.	1-year follow-up	Femoral neck Trochanter area	-5.1 % after 1 year -12.5 % after 1 year
Eyres & Kanis 1995	5	not given	Tibial shaft fr.	6-month follow-up	Distal tibia	about -50% after 3 and 6 months
Petersen et al. 1997	12	38	Tibial shaft fr.	6-month follow-up	Femoral neck Trochanter area Proximal tibia	3 mo / 6 mo -1.1 % / -0.5 % -3.4 % / -6.9 % -22.1 % / -18.6 %

					Lumbar spine	-1.1 %	-0.5 %	
Van der Poest Clement et al. 1999	11	not given	Tibial shaft fr.	5-year follow-up	Femoral neck	-2.9 %	after 5 years	
					Trochanter area	-4.7 %	after 5 years	
Ankle								
Finsen & Benum 1989	57	not given	Ankle fr.	2-year follow-up		18 wk	52 wk	104 wk
					Femur diaphysis	-1.0	-4.0	-3.5 %
					Distal femur	-9.0	-5.0	-5.0 %
					Proximal tibia	-8.0	-6.5	-9.0 %
					Midtibia	-8.0	-5.5	-6.0 %
					Distal tibia	-11.0	-5.0	-6.0 %
Petersen et al. 1992	12	34	Ankle fr.	3-year follow-up	Proximal tibia	-18 %	after 6 months	
						-10.7 %	after 3 years	

*at the time of the injury

5. AIMS OF THE STUDY

The aims of this study were:

1) to determine the effect of an adulthood ACL injury on BMD in surgically treated patients (group A) and conservatively treated patients (group B) for 1-year period following the trauma.

2) to investigate the long-term effect of an adulthood upper extremity injury (rotator cuff rupture) on BMD.

3) to investigate the long-term effect of early life fractures (tibial and femoral) on BMD, and to find out whether the fracture had an effect on the attainment of PBM of the patients.

4) to examine the long-term effect of a chronic PFPS on BMD of the affected limb.

5) to examine the short-term and long-term effects of an adhesive capsulitis on BMD and to compare the relative BMD results between patients with an acute, ongoing adhesive capsulitis (group A) and patients with a previous (fully recovered) adhesive capsulitis (group B).

6) to clarify, as the second objective of all these studies, whether any background or clinical follow-up variable would predict the possible BMD deficit in the affected extremity.

6. MATERIAL AND METHODS

6.1. Adulthood injuries and bone

6.1.1. Anterior cruciate injury of the knee (I)

In this one year follow-up study, we invited 21 patients (15 men and 6 women) with a surgically treated complete rupture of the ACL of the knee (group A), and 12 patients (8 men and 4 women) with a conservatively treated ACL injury of the knee (group B) to participate. They all had to fulfill the following criteria for inclusion into the study: 1. Healthy men or women with no medication affecting bone metabolism; 2. No previous serious injuries or surgery of lower extremities; 3. A complete ACL rupture of the knee treated surgically (group A), and a complete or partial ACL rupture of the knee treated nonoperatively (group B), in both groups the injury occurring with or without a partial medial collateral ligament rupture, partial meniscal tear, or their combination; 4. The baseline BMD measurements done before the surgery, latest four weeks after the ACL injury.

The mean age of the patients at time of the injury was 27±8 (SD) years (group A) and 31±11 years (group B). For all patients in group A, the reconstruction of the ACL was done using the central third of the patellar tendon as the graft (Clancy et al. 1982, Johnson et al. 1992, Shelbourne and Gray 1997). No immobilization of the knee was used after the surgery. The postoperative treatment consisted of gradually increasing intense quadricep muscle exercises. The non-weight-bearing time averaged 1.9±0.6 weeks followed by partial weight-bearing time of 2.4±0.8 weeks. In 6 patients of group B, the ACL tear was complete and in the remaining 6 patients only partial. No immobilization was used after the injury. The treatment consisted of gradually increasing intense quadricep muscle exercises. The postinjury non-weight-bearing time averaged only 0.2±0.4 weeks, followed by the partial weight-bearing time of 1.4±1.0 weeks.

The interview and subjective evalution, functional tests, clinical evaluation and muscle strength measurements were done by the same physician at study entry and after 4, 8, and 12 months. The study protocol was the same at every check-up point. BMD (g/cm^2) was measured by the same experienced laboratory technician from the femoral neck, trochanter area of the proximal femur,

distal femur, patella, proximal tibia, and calcaneus of both lower extremities, and the lumbar spine (L2–L4) and dominant distal radius using a Norland XR-26 DXA scanner (Norland Inc., Fort Atkinson, WI) (Fig. 1).

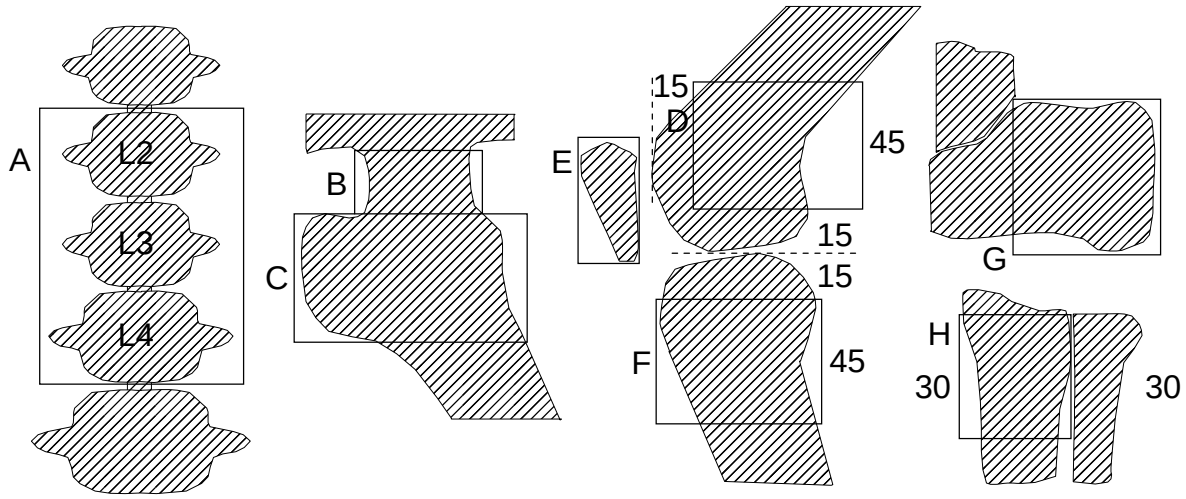

Fig. 1. Anatomic sites of the BMD measurements. The number refer to millimeters. (A) Lumbar spine, (B) femoral neck, (C) trochanter area of the femur, (D) distal femur, (E) patella, (F) proximal tibia, (G) calcaneus, and (H) distal radius.

Statistical analysis. Mean and standard deviation are given as descriptive statistics. To estimate the mean interlimb changes (and their 95% confidence intervals) during the 12-month follow-up, an analysis of covariance (ANCOVA) for repeated measures was performed using the baseline values as covariates. Changes in BMD during the follow-up were expressed as percentages of the baseline values.

In analyzing the variables that would predict the interlimb difference in BMD at 12 months, the association between sex, limb dominance, level of physical activity, ability for one-leg jumping and duck-walking, and subjective and objective overall assessments of the knee and the interlimb BMD difference was first examined by an analysis of variance. Correspondingly, the associations between age, weight, height, body mass index, pain assessment, muscle strength, the two functional knee scores, and the interlimb difference of knee BMD at 12 months were analyzed by simple regression analysis. A multiple stepwise regression analysis was decided to be the way of further analysis in the case that more than one predictor or independent variable would show significant ($p<0.05$) association with the outcome or dependent variable (the interlimb difference in BMD) in the individual comparisons.

The given significance levels refer to two-tailed tests. An alpha level (type I error) of less than 5% ($p<0.05$) was considered significant.

6.1.2. Rotator cuff rupture of the shoulder (II)

In this cross-sectional study, we invited all of the 34 adult men (≥40 years of age at the time of the injury) with a complete rupture of the rotator cuff of the dominant limb who had been treated surgically 9±2 years earlier (during 1980–1987) at the Tampere University Hospital to participate. Patients with previous or simultaneous other injuries were excluded. Also, a patient was not included if he was not previously healthy and without any known disease or medication affecting bone metabolism. The patient's mean age at the time of the follow-up was 61±6 (SD) years.

To obtain adequate control values for patients' BMDs, we recruited 34 age-, weight-, height-, and profession-matched healthy men for the study. Since in normal human population the dominant upper extremity shows about 3% higher BMDs than its nondominant counterpart (Kannus et al.1994c and 1995), care was taken that patients' side-to-side (dominant-to-nondominant) BMD values were compared with those of the controls and that the subject distribution according to the work load history of the dominant arm was the same in both groups.

The interview and pain assessment, clinical examination and functional testing of the upper extremities were carried out in a standardized manner(II). The isometric abduction strength was separately measured from the injured and healthy extremity at 90 degrees of abduction using an isokinetic dynamometer (Cybex II, Lumex Inc., Ronkonkoma, NY). Finally, each patient gave a subjective overall assessment of his injured shoulder (excellent, good, fair, or poor). The examining physicians (PK and JL) gave a similar objective assessment. BMD (g/cm^2) was measured by the same laboratory technician from the lumbar spine (L_2-L_4), and the proximal humerus, humeral shaft, radial shaft, ulnar shaft, distal forearm, and hand of both upper extremities using DXA scanner (XR-26, Norland Inc., Fort Atkinson, Wisconsin) (Fig. 2).

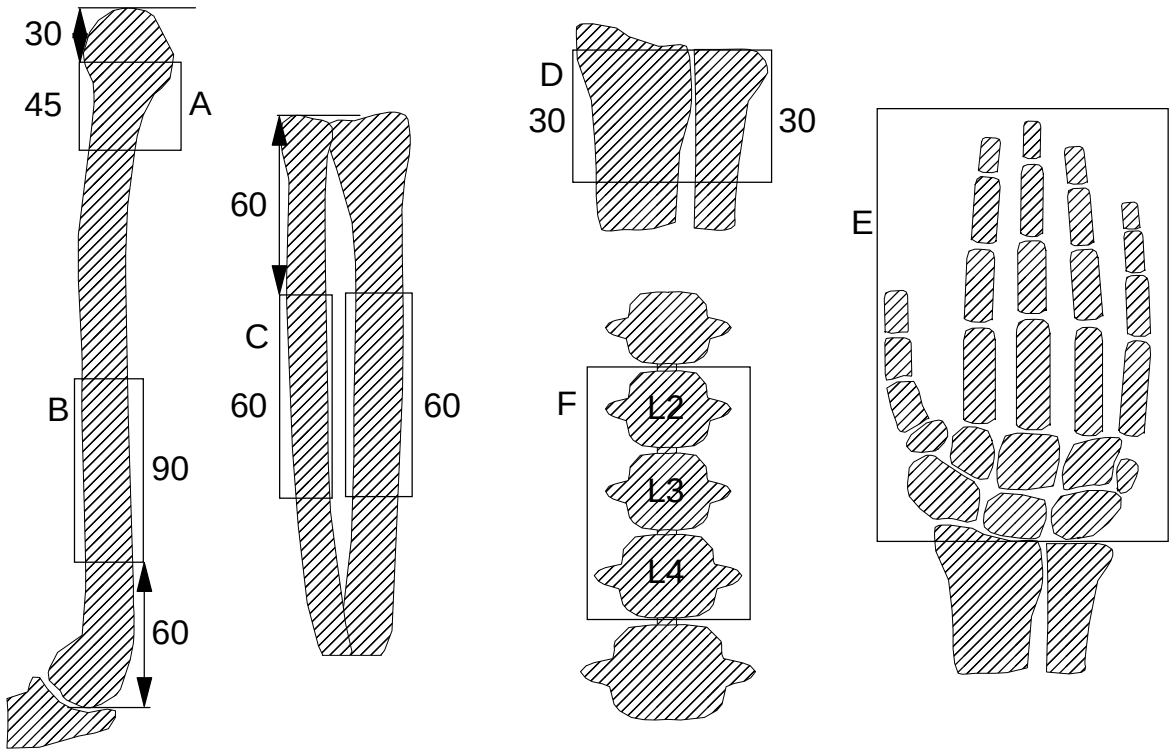

Fig. 2. Anatomic sites of the BMD measurements in the study. The number refer to millimeters. (A) Proximal humerus, (B) humeral shaft, (C) radial and ulnar shafts, (D) distal forearm, (E) hand, and (F) lumbar spine.

Statistical analysis. The relative BMD of the injured (dominant) extremity was calculated by dividing the injured-to-uninjured (dominant-to-nondominant) side difference by the absolute value of the uninjured (nondominant) side and multiplying the outcome by 100. Comparison of the BMD of the injured and uninjured sides (dominant vs. nondominant sides in the controls) was performed first by analysis of variance (Hotelling t^2 test) and then with the matched, paired *t*-test. In the comparison of the patients and controls with regard to the relative BMD of the injured side, the Hotelling t^2 test and Student's unpaired *t*-test were used. In the spine, the absolute BMDs between the patients and controls were compared with Student's unpaired *t*-test.

In patients, the effect of the size of the rupture, time delay between the injury and the surgery, type of surgery and postoperative rehabilitation, and subjective and objective overall assessments of the shoulder on the relative BMD in the injured extremity was determined by an analysis of variance. The associations between age, postoperative immobilization time, follow-up time, muscle strength, pain assessment, subjective assessment of the shoulder function, and the relative BMD in the injured extremity were determined by the regression equations and corresponding Pearson product moment correlation coefficients (r). A multiple stepwise regression analysis (forward stepping) was

decided to be the way of further analysis in the case that more than one predictor (independent variable) would show significant ($p<0.05$) effect on the outcome (dependent variable = side-to-side difference in the BMD) in the individual comparisons. In such a case, the 5% significance level was determined to be the criterion to include any additional predictive variable in the model.

In this study and also in following studies (III-VI), the results are expressed as the mean ± standard deviation (95% confidence interval) throughout the study. The given significance levels refer to two tailed tests. An alpha level (type I error) of less than 5% ($p<0.05$) was considered significant. Using this alpha level and regarding 5% difference in BMD between the patients and controls as clinically important finding, the sample size of the study was calculated to give 80% statistical power (beta level or type II error 0.20) for decision to accept the null-hypothesis if no difference could be found.

6.2. Chilhood injuries and bone

6.2.1. Tibial and femoral shaft fractures (III, IV)

In these cross-sectional studies, forty-five patients (34 men and 11 women) agreed to participate in a study of early life tibial shaft fracture (III), and forty-one (28 men and 13 women) to a study of early life femoral shaft fracture (IV). The patients were treated at the Tampere University Hospital during 1980-1990. Each subject had to fulfill the following criteria for inclusion in the study: 1. Age between 7 and 15 years and the growth plates open at the time of the injury, 2. No previous, simultaneous or later other injuries of lower extremities, 3. No disease or medication affecting bone metabolism.

The mean age of the tibial shaft fracture patients at the time of the injury was 11±2 (SD) years. The mean age of these patients at the time of the follow-up was 23±2 years. They had had 11±1 years earlier a unilateral shaft fracture of the tibia treated with a long plaster cast. The total immobilization time of the injured limb was 10±3 weeks. The non-weight-bearing time averaged 8±3 weeks followed by partial weight-bearing time of 2±1 weeks.

The mean age of the femoral shaft fracture male patients at time of the injury was 12±2 (SD) and female patients 11±4 years. Their mean age at time of the follow-up was 25±4 in men and 23±4 years in women. The male patients had had a unilateral shaft fracture of the femur 13±2 years earlier and the female patients 12±5 years earlier . Eighteen male and eight female patients had had conventional fracture treatment using skeletal traction followed by cast application, while the remaining 10 male and five female patients underwent surgery. In the male patients, the total immobilization time of the injured limb (i.e., no joint motion allowed) was 12±2 weeks. The non-weight-bearing time averaged 9±2 weeks, followed by partial weight-bearing time of 3±1 weeks. In the female patients, the total immobilization time of the injured limb was 12±2 weeks. The non-weight-bearing time averaged 9±4 weeks followed by partial weight-bearing time of 3±1 weeks.

To obtain adequate control values for the tibial shaft fracture patients' spinal and radial BMDs we obtained data from 30 age-, height- and weight- matched healthy men and 15 similarly matched women for the study.

Also, to obtain adequate control values for the femoral shaft fracture patients' spinal BMD, we recruited, with a case-control design, 28 age-, weight-, and height- matched healthy men and 13

women for the study. The controls were obtained from our institute and the Medical School of the Tampere University.

The interview and subjective evalution, functional tests, clinical evaluation and muscle strength measurements were carried out in a standardized manner (III,IV). BMD (g/cm^2) was measured by the same experienced laboratory technician from the femoral neck, trochanter area of the proximal femur, distal femur, patella, proximal tibia, and distal tibia of both lower extremities, and the lumbar spine (L2–L4) and dominant distal radius using a Norland XR-26 DXA scanner (Norland Inc., Fort Atkinson, WI) (Fig. 3).

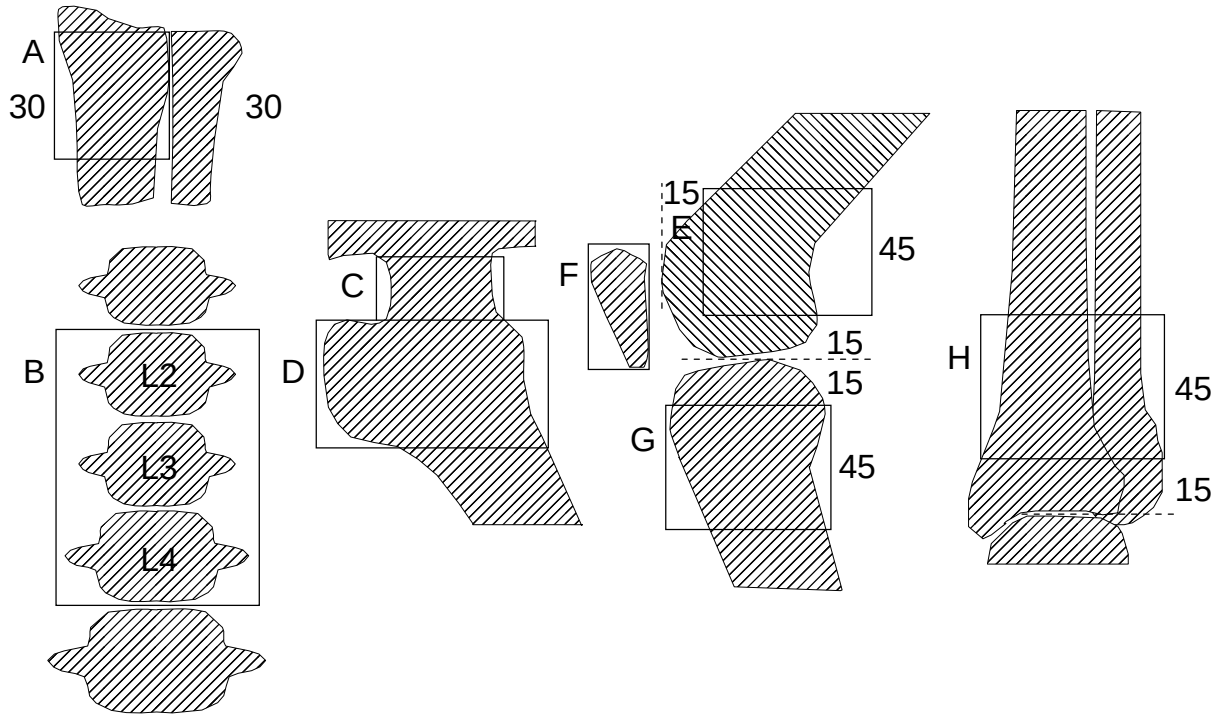

Fig. 3. Anatomic sites of the BMD measurements in the works III and IV. The number refer to millimeters. (A) Distal radius, (B) lumbar spine, (C) femoral neck, (D) trochanter area of femur, (E) distal femur, (F) patella, (G) proximal tibia, and (H) distal tibia.

Statistical analysis. The relative BMD of the injured extremity was calculated by dividing the injured-to-uninjured side difference by the absolute value of the uninjured side and multiplying the outcome by 100. Comparison of the BMD of the injured and uninjured sides was performed first by analysis of variance (Hotelling t^2 test) and then with a matched, paired t-test. In the comparison of the patients and the controls with regard to the spinal and radial BMD, the Student's unpaired *t*-test was used. The effect of gender, side of injury, limb dominance, fracture type, fracture level, level of physical activity, smoking, ability for one-leg jumping and duck-walking, and subjective overall assessments of the limb on the relative BMD in the injured extremity was determined by an analysis

of variance. The associations between age at the time of injury, age at the time of the follow-up, weight, height, body mass index, immobilization time, follow-up time, pain assessment, muscle strength, the two functional performance scores, and the relative BMD in the injured extremity were determined by regression equations and corresponding Pearson product moment correlation coefficients (r). A multiple stepwise regression analysis was decided to be the way of further analysis in the case that more than one predictor (independent variable) would show significant ($p<0.05$) effect on the outcome (dependent variable = side-to-side difference in the BMD) in the individual comparisons. The 5% significance level was also used as a criterion to include any additional predictive variable in the model.

6.3. Nontraumatic musculoskeletal disorders and bone

6.3.1 Patellofemoral pain syndrome (V)

In this cross-sectional study design, forty-nine consecutive patients with a characteristic symptomatic PFPS in one limb were initially treated in our clinic by nonoperative methods, the treatment including intensive quadricep muscle rehabilitation for 6 weeks (Kannus et al.1992c). Forty of these 49 patients (92%) attended the current 7-year follow-up visit.

The mean age of the 40 patients at the time of the follow-up was 33±6 (SD). The mean duration of the disease at the time of follow-up was 7.6±1.8 years. Each patient was examined by the same physicians at study entry and after 6 months (Kannus et al.1992c), and now after 7 years.

The interview and subjective evalution, functional tests, clinical evaluation and muscle strength measurements were carried out in a standardized manner (V). BMD (g/cm^2) was measured by the same laboratory technician from the femoral neck, trochanter area of the proximal femur, distal femur, patella, proximal tibia, and calcaneus of both lower limbs, and the lumbar spine (L2–L4) using a Norland XR-26 DXA scanner (Norland Inc., Fort Atkinson, WI) (the measured sites can be seen in the Fig. 1).

Statistical analysis. The relative BMD of the affected limb was calculated by dividing the affected-to-unaffected side difference by the absolute value of the unaffected side and multiplying the outcome by 100. Comparison of the BMD of the affected and unaffected sides was performed with matched, paired t- test. The effect of sex, limb dominance, level of physical activity, ability for one-leg jumping and duck-walking, and subjective and objective overall assessments of the knee on the relative BMD in the affected limb was determined by an analysis of variance. The associations between age, weight, height, body mass index, duration of symptoms, pain assessment, muscle strength, the two functional knee scores, and the relative BMD in the affected limb were determined by the regression equations and corresponding Pearson product moment correlation coefficients (r). A multiple stepwise regression analysis (forward stepping) was then performed, starting with the predictor (independent variable) that had the strongest (significant at least in 5% level, $p<0.05$) association with the dependent variable (= side-to-side difference in the BMD of the distal femur, patella, and proximal tibia) in the individual comparisons. The 5% significance level was also used as a criterion to include any additional predictive variable in the model.

6.3.2. Adhesive capsulitis of the shoulder (VI)

In this cross-sectional study, we invited 22 consecutive patients (8 men and 14 women) with a unilateral symptomatic acute adhesive capsulitis (group A) initially treated in the Tampere University and City Hospitals during 1995-1997 to participate. Patients with previous or simultaneous adhesive capsulitis in the opposite shoulder or with any serious injuries of upper extremities were excluded. Also, a patient was not included if he or she had any known disease or medication affecting bone metabolism.

The mean age of the patients at time of the examination was 51±5 (SD) years. The mean duration of disease at the time of the examination was 16±6 months. The dominant arm was affected in 8 patients and the nondominant in 14 patients. Before the examination all the patients had received a varying number of corticosteroid injections, oral non-steroidal anti-inflammatory drugs, and various forms of physical therapy. Nineteen of the twenty-two patients had been treated (under anesthesia performed) with manipulation of the shoulder and three patients had been operated on (anterior acromionplasty and coracoacromial ligament release).

As a second group, we studied the 31 patients (9 men and 22 women) with a previous unilateral adhesive capsulitis (group B) treated at the Tampere University Hospital during 1980-1990. All patients had fulfilled the previously described diagnostic criteria of adhesive capsulitis (that is, the pain stage followed by a severe restriction in shoulder movements with other pathologic conditions of the shoulder excluded). Patients with previous or later adhesive capsulitis or any serious injury, such a fracture of the upper extremities, were excluded from the study. Also, a patient was not included if he or she had any known disease or medication affecting bone metabolism.

The mean age of the patients in the second group at time of the follow-up was 59±5 years. They had had the unilateral adhesive capsulitis on an average 9±2 years before the measurements. The mean duration of symptoms in the affected shoulder (pain, discomfort, weakness, stiffness), had been 5±3 years. The dominant arm was affected in 10 patients and nondominant in 21 patients. During the active phases of the disease, all the patients had received a varying number of steroid injections, oral non-steroidal anti-inflammatory drugs, and various forms of physical therapy for the affected shoulder. Twenty-six of the patients had been treated (under anestesia performed) with manipulation of the shoulder and five patients had been operated on (anterior acromionplasty and coracoacromial ligament release).

The interview and pain assessment, clinical examination and functional testing of the upper extremities were carried out in a standardized manner (VI). BMD (g/cm^2) was measured by the

same laboratory technician from the proximal humerus, humeral shaft, radial shaft, ulnar shaft, and distal forearm of both upper extremities using a Norland XR-26 DXA scanner (Norland Inc., Fort Atkinson, WI) (Fig.4).

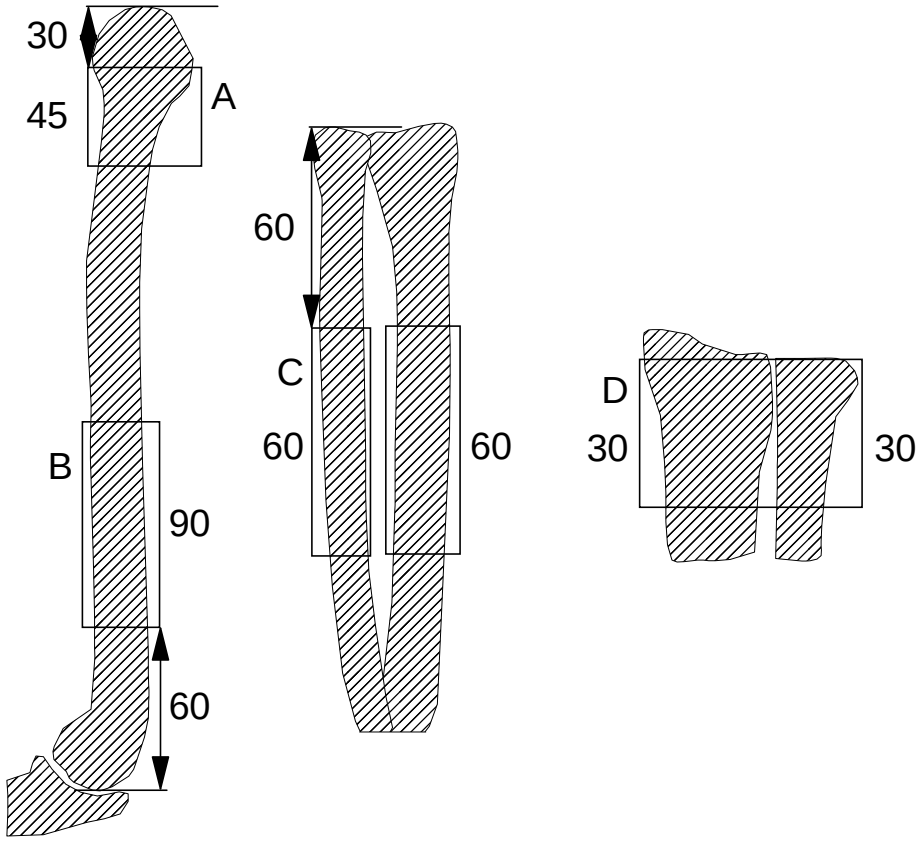

Fig. 4. Anatomic sites of the BMD measurements in the study. The number refer to millimeters. (A) Proximal humerus, (B) humeral shaft, (C) radial and ulnar shafts, and (D) distal forearm.

Statistical analysis. The relative BMD of the affected extremity was calculated by dividing the affected-to-unaffected side difference by the absolute value of the unaffected side and multiplying the outcome by 100. Comparison of the BMD of the affected and unaffected sides was performed first by analysis of variance (Hotelling t^2 test) and then with matched, paired t-test. In the comparison of the patients with the acute adhesive capsulitis (group A) and the patients with the previous adhesive capsulitis (group B) with regard to the relative BMD of the affected side, the Hotelling t^2 test and Student's unpaired *t*-test were used. The effect of sex, side of affection, level of physical activity, subjective and objective overall assessments of the shoulder, humeral rhythm, and stage of the adhesive capsulitis (group A) on the relative BMD in the affected extremity was

determined by an analysis of variance. The associations between age, weight, height, body mass index, duration of symptoms, follow-up time, pain assessment, functional assessment, muscle strength, and degree of restriction in external rotation and abduction of the shoulder, and the relative BMD in the affected extremity were determined by the regression equations and corresponding Pearson product moment correlation coefficients (r). A multiple stepwise regression analysis was decided to be the way of further analysis in the case that more than one predictor (independent variable) would show significant ($p<0.05$) effect on the outcome (dependent variable = side-to-side difference in the BMD) in the individual comparisons.

7. RESULTS

7. Adulthood injuries and bone

7.1.1. Anterior cruciate ligament injury of the knee (I)

For 21 patients with a surgically treated complete rupture of ACL of the knee (group A) the mean interlimb BMD change (in disfavor of the injured limb) was significant in the distal femur (-21%; $p<0.001$), patella (-17%; $p<0.001$), and proximal tibia (-14%; $p<0.001$). There were also small but statistically significant interlimb changes in the femoral neck (-3%; $p=0.003$), trochanter (-5%; $p<0.001$), and calcaneus (-1%; $p=0.001$). The changes were insignificant in the lumbar spine (-1%; $p=0.299$) and distal radius (0%; $p=0.170$). In the 12 patients with a conservatively treated ACL injury (group B), the interlimb change was small but statistically significant in the patella (-3%; $p=0.005$) and proximal tibia (-2%; $p=0.022$), while in the other sites the changes were insignificant (distal femur -2 %, and femoral neck, trochanter and calcaneus all 0 %; each NS). The BMD change was small in the lumbar spine (2%; $p=0.005$) and no change occurred in the distal radius (0%; $p=.223$). In contrast with many previous studies on post-traumatic osteoporosis (Järvinen and Kannus 1997), we could not find any significant background factors (I) predicting the amount of bone loss in the injured knee.

7.1.2. Rotator cuff rupture of the shoulder (II)

For the 34 patients with the formerly operatively treated rotator cuff rupture, the mean BMD of the injured extremity was significantly lower in the proximal humerus (-3.5%; $p=0.0035$) and humeral shaft (-2.6%; $p=0.0063$). In the other sites, the mean BMD of the injured extremity was at the same level (radial shaft -0.4%, ulnar shaft -0.2%, and distal forearm -0.2%, all NS) or higher (hand +2.3%, $p=0.0000$) than that in the uninjured extremity. In the control subjects, the dominant-to-nondominant side BMD difference was in every measured site positive and with the exception of the ulnar shaft (+0.2%) statistically significant (range, +1.6% to +4.0%). Compared with the

controls, the patients' relative side-to-side BMD difference was significantly lower in every measured side except ulnar shaft.

In patients, the relative humeral BMDs of the injured extremity strongly associated with the objective assessment of the shoulder function: the better the observed function of the shoulder, the less bone loss caused by the injury. In proximal humerus, the side-to-side BMD difference averaged +2.0% in the patient group with "excellent" shoulder function, -3.3% in the "good" group, -5.3% in the "fair" group, and -11.5% in the "poor" group ($p=0.0012$).

7.2 Childhood injuries and bone

7.2.1. Tibial shaft fracture (III)

The femoral neck BMDs in the uninjured (1.029±0.105) and injured (1.032±0.099) limbs of the male patients were somewhat higher than the manufacturer's age-adjusted reference value for Western European men (1.010±0.140). In women, the femoral neck BMDs in the uninjured (0.920±0.101) and injured (0.930±0.097) limbs were very near the manufacturer's age-adjusted reference value for Western European women (0.930±0.120)

For the 45 patients with the early life tibial shaft fracture, the mean BMD of the injured limb was significantly lower in the proximal tibia (-1.7%; p=0.014) and distal tibia (-2.6%; p=0.011). In the other sites, the mean BMD of the injured extremity was slightly lower or at the same level (femoral neck +0.1%, trochanter area -1.0%, distal femur -1.3%, and patella -1.1% all NS) as that in the uninjured extremity.

In order to find out whether any of the background or clinical variables would explain the above noted side-to-side results, prediction analysis was done for the BMD of the proximal and distal tibia. Muscle strength correlated significantly with the relative BMD in the proximal tibia (r=0.51; p<0. 001): the better the muscle strength in the injured lower limb (as compared to that in the opposite limb), the higher the relative BMD in the same limb. Also, the Lysholm score (r=0.32; p=0.034) had a significant association with the relative BMD of the injured proximal tibia. Smoking had a signicant association with the relative BMD in the injured distal tibia (mean side-to-side BMD difference: smokers -6.1% vs. nonsmokers -0.6%, p=0.016). Also, age at the time of injury correlated significantly with the relative BMD in the distal tibia (r = -0.35; p<0.048): the younger the patient at the time of the injury, the higher the relative BMD in the injured limb.

7.2.2. Femoral shaft fracture (IV)

Lower extremities. For the 28 male patients with an early life femoral shaft fracture, the mean BMD of the injured extremity was significantly lower in the distal femur (-3.7%; p=0.000), patella (-3.1%; p=0.002), proximal tibia (-2.0%; p=0.008) and distal tibia (-3.4%; p=0.004). In the proximal femur,

the mean BMD of the injured side was comparable to that in the uninjured side (femoral neck +1.4% and trochanter area -0.9 %, both NS).

In the 13 female patients with an early life femoral shaft fracture, the mean BMD of the injured extremity was significantly lower in the distal femur (-3.9%; p= 0.014), patella (-5.9%; p=0.009), proximal tibia (-4.6%; p=0.010) and distal tibia (-5.2%; p=0.015). In the proximal femur, the mean BMD of the injured extremity was comparable to that in the uninjured extremity (femoral neck -1.2% and trochanter area -3.1%, both NS).

In order to find out whether any of the background or clinical variables would explain the above noted significant side-to-side results, a prediction analysis was done for the BMD of the distal femur, patella, proximal and distal tibia (separately for men and women). In neither men nor women, age at the time of injury, age at the time of the follow-up, weight, height, body mass index, immobilization time, follow-up time, pain assessment, muscle strength, or the two functional performance scores (Lysholm and Tegner) had clear and systematic association with the relative BMDs in the injured limb. Furthermore, neither the side of injury, limb dominance, fracture type, fracture level, level of physical activity, smoking, surgery (vs. conservative treatment), ability for one-leg jumping and duck-walking, nor subjective overall assessments of the limb were associated with the outcome.

Spine and distal radius. Compared with normal men, the spinal BMDs were lower in men with an early life femoral shaft fracture (mean -7.9%), and the difference was statistically significant (p=0.034). In the distal radius (the nonloaded control site), the average BMD difference between the male patients and controls was -5.9% (p=0.054).

In women, the spinal BMDs were comparable between patients and controls (mean -1.6%; p=0.908). In the distal radius (the nonloaded control site), the average BMD difference between the female patients and controls was +2.7% (p=0.502).

7.3. Nontraumatic musculoskeletal disorders and bone

7.3.1. Patellofemoral pain syndrome (V)

For the 40 patients with the PFPS, the mean BMD of the affected limb was significantly lower in the distal femur (-3.3%; p=0.002), patella (-2.5 %; p=0.016), and proximal tibia (-1.9%; p=0008). In the other sites, the mean BMDs of the affected limb were also lower than those in the unaffected side, but the differences were not significant (femoral neck -1.0%, trochanter area -1.1%, and calcaneus -0.1%, all NS).

Muscle strength correlated highly significantly with the relative BMDs in the distal femur, patella and proximal tibia (r=0.58, 0.56 and 0.57 with $p<0.001$ in all sites): the better muscle strength in the affected lower limb (compared to the other limb), the higher was the relative BMD in the same limb. Also subjective overall assessment (p=0.004), objective overall assessment (p=0.038) and duck-walking test (p=0.028) had a signicant association with the relative BMDs of the affected patella. In the proximal tibia, only subjective overall assessment showed a significant association (p=0.023). In the distal femur, these above noted three variables showed tendency for association with the relative BMD, but none of the associations was significant.

According to these results, the forward-stepping regression analysis started by fixing the muscle strength as the predictive variable, muscle strength alone (r^2) accounting 34%, 31%, and 33% for the variation seen in the relative BMD of the distal femur, patella and proximal tibia , respectively. In the distal femur, inclusion of body weight (11%) and physical activity level (6%) in the model significantly improved the overall prediction so that together with muscle strength these predictors accounted 51% for the variation seen in relative BMD of the distal femur . In the patella, subjective overall assessment (15%), body mass index (9%), and limb dominance (6%) were additional independent predictors, all predictors accounting 61% for the variation. In the proximal tibia, body weight (13%) and duration of symptoms (8%) were such additional predictors, all the predictors together accounting 54% for the variation.

7.3.2. Adhesive capsulitis of the shoulder (frozen shoulder) (VI)

For 22 patients with the acute adhesive capsulitis of the shoulder (group A), the mean BMD of the affected extremity was significantly lower in the proximal humerus (-5.6%; p=0.001) and humeral shaft (-3.0 %; p=0.008). In the other sites, the mean BMD of the affected extremity was at the same level (radial shaft -0.1% ulnar shaft -0.4% and distal forearm -1.1%, all NS) as that in the unaffected extremity. In the 31 patients with the previous adhesive capsulitis (group B), the affected-to-unaffected side BMD differences were statistically insignificant (proximal humerus -1.5 %, humeral shaft - 0.8 %, radial shaft -0,2 %, ulnar shaft -0.7 %, and distal forearm -1.2 %, all NS).

Compared with the 31 patients with previous disease (group B), the relative side-to-side BMD difference of the 22 patients with acute phase of the disease (group A) was significantly lower in the proximal humerus (-5.6 % vs. -1.5 %; p=0.009). There was small group difference in the humeral shaft also, but this difference was not significant. In the other sites, groups A and B showed no differences.

8. DISCUSSION

We preferred to use the areal BMD in all our studies, since it is the conventionally used measure of bone integrity. Also, by showing the reader the relative change in each anatomic site we provided him/her understandable data to evaluate the potential severity of our findings [(i.e. we felt that a 21% decrease in the distal femur is more informative than 0.32 g/cm^2 (I)].

In these studies (I-VI) the observed 2-21% bone losses in different anatomical sites have clinical importance since the total bone loss of humans after the age of PBM is estimated to be 40% (1% per year) (Riggs and Melton 1986, Mazess 1982, Davis et al. 1991) and since prospective studies have demonstrated that a decrease of 1 SD in BMD (about 10-12%) is associated with an increase of 50-100% in the incidence of fractures (Gardsell et al 1990, Johnston et al. 1991). In other words, in a 25-year-old patient who has experienced a shaft fracture of the femur 10-15 years earlier (IV), the injured limb is 2-6 years ahead of its normal counterpart in the osteoporotic process. This circumstance, in turn, may be crucial in the development of osteoporotic fractures in later life, especially in female patients after menopause.

Because the original BMDs at various skeletal sites were not determined in the patients before the rotator cuff rupture (II), lower limb fracture (III, IV), PFPS (V), and adhesive capsulitis (VI) , two factors should be considered in interpreting the results of a side-to-side comparison. First, there may be natural BMD differences between the dominant and nondominant limbs. In the upper limbs of healthy men never involved in unilateral activities, the BMDs in the dominant side are on average 2.5% higher (Kannus et al. 1994c); however, according to literature (Lilley et al. 1992, Faulkner et al. 1993) and our own findings (Vuori et al. 1994) such a difference does not exist in the lower limbs. For this reason we used the age-, height-, weight- and profession-matched normal men as controls in the rotator cuff study (II); that is, the controls were used to find out what our patients' side-to-side BMD difference would have been in each anatomic site without the injury.

Second, one may suspect that the observed side-to-side differences were caused more by bone hypertrophy in the unaffected limb than by bone atrophy in the affected limb. Previous follow-up studies, however, have shown that after the injury and disuse bone atrophy occurs not only in the injured limb but also slightly in the uninjured limb, most probably because of the decreased general activity level of the patient (Nilsson 1966, Andersson and Nilsson 1979, Finsen and Haave 1987, Ulivieri et al. 1990). Our prospective ACL-injury study (I) confirms this result. Thus, bone

hyperthophy in the unaffected limb was very unlikely in our cross-sectional studies. Since many previous studies reveal that normal subjects without any injury do not have any side-to-side BMD differences in the lower limbs, the best possible reference point to the affected limb is the same person’s unaffected limb.

8.1. Adulthood injuries and bone

Our prospective 12-month follow-up study (I) showed that a surgically treated complete ACL rupture (group A) created considerable bone loss to the affected knee (distal femur -21%, patella -17% and proximal tibia -14%), while the other sites remained clearly less affected. The study also showed that patients with a conservatively treated complete or partial ACL injury (group B) had a small bone loss at the patella (-3%) and proximal tibia (-2%) of the injured knee, while the other sites remained unchanged. In this context it has to be remembered that groups A and B were not comparable (the injury in the group A was more severe requiring an entirely different treatment regimen than that in group B), and therefore we avoided any comparison or conclusion concerning surgical or conservative treatment of a patient with a ruptured ACL.

A major strength of our study was that in these group A and B patients we had the baseline BMDs from both limbs, and thus we were able to reliably follow the development of the BMD and the other parameters caused by the injury. A second advantage was that, all the DXA investigations were performed by the same experienced laboratory technician (Sievänen et al. 1992 and 1996b), the scanner performance was properly controlled (Sievänen et al. 1994b), and that all the repeated clinical examinations were performed by the same experienced physician, who had studied knee injuries and disorders for many years. A third advantage was that within both groups the patient material was quite homogenous with regard to the background factors, such as physical activity and anthropometry, and the treatment of the injury. Most likely all these issues accounted for the rather consistent BMD findings with small intragroup variation. The study limitation was the somewhat small number of patients in group B. However, since we found no signs of any important bone loss in this group of patients, it is unlikely that a larger number of patients would have markedly changed the results of this group.

One could suspect that the surgery removed some bone from the knee in the patients of group A that might otherwise be included in the BMD measurement site. And in fact, a surgeon had to drill narrow channels (10 mm in diameter) into a femur and tibia to be able to fix the graft. Theoretically speaking, this reduces BMC slightly (and also BMD), but given the large bone volume of the distal femur and tibia as compared to the volume of those channels, the effect of those channels on BMD remain negligible.

Post-traumatic bone loss is best described as a high-turnover condition; that is, both bone formation and resorption are increased, but the latter overcomes the former, resulting in net loss (Sievänen et al. 1994a, 1994b, 1996a). There are at least three factors in the process. First, the

trauma itself, with increased levels of catabolic stress hormones, such as corticosteroids, may turn the mineral balance in the negative direction. Secondly, in severe traumas, the associated surgery as such may interfere with the bone structure, not to mention the catabolic effect of the surgical stress on the mineral metabolism of bone. Last but not least, the post-traumatic immobilization and following (often long-term) disuse of the injured limb are known to result in rapid bone loss after injury (Nilsson 1966, Andersson and Nilsson 1979, Sievänen et al. 1994a, Järvinen and Kannus 1997). The obvious group differences in these factors may well explain the different BMD results in the groups A and B of this study.

As noted above, surgically treated complete ACL rupture (group A) resulted in significant bone loss in the injured knee and it was alarming that we could not observe any bony recovery during the one-year follow-up. Perhaps, the postoperative non-weight-bearing and partial weight-bearing times were still too long (although much shorter than in 1980s), a finding that strongly suggests even an earlier start of weigth-bearing in the future practice. Also, the surgical stress was likely to cause some bone loss to the injured limb of the group A patients, but this problem is much more difficult to avoid when treating ACL injuries of athletes and other physically active subjects.

The conservatively treated ACL injury (group B) created a statistically significant bone loss in the patella (-3%) and proximal tibia (-2%), but not in the other sites. As such, however, this amount of bone loss is not very much. One explanation for the small bone loss could be that patients with a conservatively treated ACL injury never suffered from complete immobilization of the injured limb, and the non-weight-bearing and partial weight-bearing times were short. In other words, despite pain and discomfort the patients with a conservatively treated ACL injury still had to bear the body weight and this was likely to have a considerable bone-preserving effect in the injured limb.

In contrast with many previous studies on post-traumatic osteoporosis, we could not find any significant background factor predicting the amount of bone loss in the injured knee of the group A patients. In post-traumatic osteoporosis, functional outcome of the injured extremity seems often to determine the long-term bony recovery in the same so that with excellent limb function the likehood of considerable post-traumatic osteoporosis is small while with poor limb function permanent bone loss can be expected (Järvinen and Kannus 1997). Our patients in group A were quite homogenous with the background factors, and in all these patients the functional recovery of the knee was also good. These facts could partly explain the non-existing association between the knee function and the amount of bone loss in the injured knee. Also, it has to be remembered that a longer follow-up may change the results of this kind of prediction analysis.

In conclusion, this 12-month follow-up study indicates that a surgically treated complete ACL rupture results in remarkable bone loss in the knee region of the injured extremity. In the femoral neck, trochanter area of the proximal femur, and calcaneus, the bone loss is clearly smaller whereas the lumbar spine and distal radius are not affected. In the conservatively treated ACL injuries, injuries in which weight-bearing and knee function is returned to normal very quickly after the injury, the bone loss in the knee region of the injured limb is minimal and other sites are not affected.

To our knowledge, the long-term effects of rotator cuff ruptures (or other rotator cuff problems such as supraspinatus tendinitis or subacromial impingement syndrome) on the BMD of the affected extremity have not been studied previously although the rotator cuff is one of the most common sites of musculoskeletal injuries and inflammations.

Our study (II) showed that a complete, full-thickness rupture of the rotator cuff caused significant mineral loss in the proximal humerus and humeral shaft of the affected extremity and, to a lesser extent, in the distal radius of the same extremity. The observed changes are very likely to be permanent because the follow-up time of our study averaged 9 years, and the previous short-term lower extremity studies have shown that a great part of the restoration process takes place within the first post-traumatic year after which no significant change can be expected (Järvinen and Kannus 1997).

Perhaps the most important and interesting finding in our study was that objective (physician made) assessment of the injured shoulder was the only reliable determinant of the bone status in the injured extremity. It was somewhat surprising that patients' pain assessment and self-made assessment of the shoulder function did not significantly associate with the outcome. It may be that patients with a surgically treated rotator cuff rupture gradually accommodate their activities to a lowered level so that the activities they voluntarily perform do not cause pain and other problems and they thus falsely estimate the condition of the injured shoulder better than it actually is. The more objective estimate of the condition of the shoulder is then received via a detailed clinical examination and functional testing.

We feel that the above mentioned result has two clinical implications. First, to obtain normal shoulder function physicians should use as short an immobilization period as possible in the treatment of shoulder injuries and they should prescribe early, intense rehabilitation for every patient (Lanyon 1987, Kannus et al. 1992a). Second, since patients' subjective assessment of the shoulder was not a reliable predictor of the injury-induced osteoporosis, physicians should

personally follow their patients until the objectively determined shoulder function has returned to normal.

Along with our previous findings with knee ligament injuries (Kannus et al. 1992d), tibial fractures (Kannus et al. 1994b), and femur fractures (Kannus et al. 1994a), the present study reveals an important aspect of post-traumatic osteoporosis: functional outcome of the injured extremity largely determines the long-term bony recovery in the same so that with excellent limb function the likelihood of post-traumatic osteoporosis is negligible while with poor limb function considerable permanent bone loss can be expected. This observation was consistent in each of these four studies and emphasizes the need for high quality rehabilitation in all types of musculoskeletal injuries.

The BMD measurements in the spine showed no significant differences between patients and controls. This finding, and also the finding of the above discussed ACL-injury study, support the current concept that osteoporosis after an extremity injury is in great part a local process induced by the trauma, surgery, and immobility (lack of mechanical strain) without severe, permanent disturbance in general bone metabolism of the subject (Lanyon 1987, Kannus et al. 1992a). Generalized post-traumatic osteoporosis has been seen only after severe traumas, such as complete paraplegic and quadriplegic spinal cord injuries (Garland et al. 1992) .

In conclusion, an operatively treated rotator cuff rupture results in permanently reduced BMD in the injured extremity, the reduction being greatest in the proximal parts of the extremity. The observed mean decreases (6% in the proximal humerus, 4% in the humeral shaft, and 3% in the distal forearm of the injured limb) are clinically important with respect to age-related bone loss of 1% per year after the age of PBM. Recovery of normal shoulder function seems to be crucial for good bone recovery, and therefore avoidance of immobility and early intense rehabilitation can be recommended.

8.2. Childhood injuries and bone

As pointed out before, adult-age fractures can have deletorious long-term consequences on bone (Järvinen and Kannus 1997), but very little is known about the effects of injuries on growing bone. Therefore, we conducted these two studies on the long-term effects of early life tibial and femoral shaft fractures on BMD of the injured extremity and the spine.

Our study (III) showed that tibial shaft fracture sustained in childhood or adolescence had created a statistically significant adult-age side-to-side BMD difference to the injured tibia only (proximal tibia -1.7%, and distal tibia -2.6%). However, this amount of BMD decrease is not very much, especially when compared with the side-to-side differences we have seen after a tibial shaft fracture sustained in adulthood (Järvinen and Kannus 1997, Kannus et al. 1994b).

In our previous adult tibial fracture study (Kannus et al. 1994b), a clear bone loss in the injured extremity could be seen an average nine years after the injury. For the 20 adult patients with the primarily united tibial shaft fracture, the mean BMD of the injured limb was significantly lower in the femoral neck (-2.4%), distal femur (-4.0%), patella (-3.7%), and proximal tibia (-5.1%). Accordingly, for the 14 patients with the primarily nonunited tibial fracture, the mean BMD of the injured limb was significantly lower in the distal femur (-10.0%), patella (-11.2%), proximal tibia (-9.2%), distal tibia (-7.9%), and calcaneus (-5.6%). The patients of our current study had quite a long immobilization time (10±3 weeks), although it was shorter than that in the adult study. Most probably, the small side-to-side BMD differences seen in our patients with an early life fracture was, at least in part, due to the generally more rapid fracture healing and greater potential for remodeling of the immature skeleton.

It was interesting to find out that the greater muscle strength in the injured lower limb (as compared to that in the other limb), the higher the relative BMD in the proximal tibia. Also, the functional Lysholm score had a signicant association with the relative BMDs of this site. These results confirm our other findings that good muscle strength and limb function are of great importance for good post-traumatic BMD (Works II and V). Smoking had a significant negative association with the relative BMD at the injured distal tibia, and this is in agreement with findings of the negative effect of smoking on the skeleton (Seeman and Hopper 1994, Law and Hackshaw 1997). Age at the time of injury also correlated significantly with the relative BMDs in the distal tibia: the younger the patient at the time of the injury, the higher was the relative BMD in the injured limb. This is also a logical connection, since the more immature skeleton is, the greater is the potential for bone remodeling and healing of fractures than its more mature counterpart.

As pointed out before, an insufficient amount of bone by the time of skeletal maturity (low PBM or PBD) is a very important risk factor for osteoporosis. Compared with normal men, the spinal BMDs have been shown to be significantly lower in men with a primarily nonunited adult-age tibial fracture (-12.3%) and with a similar but primarily united fracture (-9.2%) (Kannus et al. 1994b). In the current study, a small difference in the spinal BMD of the subjects and controls was also observed; however, the difference was not statistically significant, and compared with the above noted findings with the adult patients, not very large. The same concerned the subjects' and controls' radial BMD. Furthermore, compared with the manufacturer's age-adjusted reference values, we found no decrease in the femoral neck BMDs of the patients, indicating that with respect to general bone health our patients were comparable to Western European men and women.

In conclusion, this study (III) indicates that early life tibial fracture results in a small long-term BMD deficit in the fractured bone while the other sites of the skeleton seem not to be affected. Thus, the tibial shaft fracture sustained in childhood or adolescence seems to only marginally interfere with attainment of PBD, the important predictor of the osteoporotic fractures in later life.

This study (IV) showed that a femoral shaft fracture sustained in childhood or adolescence had led to a statistically significant adult-age side-to-side BMD difference (-2 to -6%) between the injured and uninjured limbs. Also, the male patients' spinal BMD was significantly lower than that of the controls, while in female patients the spinal BMD did not differ significantly from the controls.

A potential source of concern is the limited number of patients (especially women) available for this study. This may become a problem at sites where a clear difference is seen but due to relative small number of subjects the difference is not statistically significant. Fortunately, in our study, there were no more than two such sites (men's distal radius and women's trochanter area) and we want to emphasize that all interpretations at these sites must be suggestive rather than conclusive.

In our previous adult femoral fracture study, a considerable bone loss in the injured extremity could be seen an average ten years after the injury (Kannus et al. 1994a). For the 29 adult patients with a femoral shaft fracture, the mean BMD of the injured limb was significantly lower in the distal femur (-6.8%), patella (-5.4%), proximal tibia (-4.7%), and calcaneus (-2.2%). Compared with normal men, the spinal BMDs were also significantly lower in men with this adult-age femoral fracture (-9.3%) (Kannus et al. 1994a). The patients of our current study had quite a long immobilization time (12±3 weeks); in fact, it was longer than that in the adult study. Perhaps, this was one reason for the finding that the BMD decrease in the injured limb of our patients was comparable with the BMD decrease in the previous adult study. In the current study, a small

difference (-1.6%) in the lumbar spine BMD between the female subjects and controls was also observed. However, the difference was not statistically significant, and compared with the above noted findings with the adult patients, not very large. On the contrary, the spinal BMD difference between the male subjects and controls was statistically significant (-7.9%). However, there was also difference between the male subjects' and controls' radial BMD (-5.9%) indicating that at the time of the follow-up the general BMD level of the male patients seemed to be lower than that in the controls. Precise reasons for this could not be estimated, but it may partly be due to the injury, or, due to patients' lower BMD values already initially (at the time of the fracture).

As pointed out before, low PBM or PBD is a very important risk factor for osteoporosis. The above discussed study of patients with an early life tibial shaft fracture showed only a small long-term (11 years after the injury) BMD deficit in the fractured bone (proximal tibia -1.7%, and distal tibia -2.6%) and the other sites of the skeleton were not affected (III). Thus, the tibial shaft fracture sustained in childhood or adolescence did not seem to interfere with attainment of peak bone density. The current study indicates, however, that an early life femoral fracture results in a larger BMD deficit distal from the fracture site, and seems also to affect the spinal BMDs. The most probable reason for this difference is that the early life femoral fracture is a more serious injury than an early life tibial fracture, especially if judged by the immobilization time, which was longer after the femoral shaft fracture (12 ± 2 weeks) than the tibial shaft fracture (mean 10±3 weeks).

In conclusion, this study indicates that an early life femoral shaft fracture results in a moderate (-2% to -6%) long-term side-to-side BMD difference distal from the fracture site. Patients' spinal BMDs also tend to be lower than those of the controls, especially in men. Thus, the femoral shaft fracture sustained in childhood or adolescence seems to somewhat disturb the attainment of PBD, the important predictor of the osteoporotic fractures in later life.

8.3. Nontraumatic musculoskeletal disorders and bone

The effects of different types of acute knee injuries on BMD at various skeletal sites have been studied previously (Tables 4 and 5), but effects of various chronic knee disorders, such as PFPS, on BMD have scarcely been investigated. Our study (V) showed that PFPS had created a statistically significant bone loss to the affected knee (distal femur -3.3%, patella -2.5% and proximal tibia -1.9%). As such, however, this amount of bone loss is not very much, especially if compared with the side-to-side deficits seen after acute knee injuries (Tables 4 and 5). One explanation for the difference could be that patients with PFPS never suffer from complete immobilization of the affected limb, while patients with acute injuries often do. In other words, despite pain and discomfort the patients with PFPS still have to bear the body weight and this may have a considerable bone-preserving effect in the affected limb.

In every anatomic site of the affected knee, the relative BMD showed most consistent and greatest correlation with the muscle strength of the same knee: the better the muscle strength in comparison with the healthy knee, the higher the relative BMDs ($r=0.56$-0.58 with $p<0.001$ in the distal femur, patella, and proximal tibia). In the stepwise regression analysis, low body weight or low body mass index, high level of physical activity, good subjective overall assessment of the affected knee, and short duration of the symptoms were also independent predictors of the good BMD in the affected knee so that along with the muscle strength these variables could account for 51% of the variation seen in the relative BMD of the femur, 61% in the patella, and 54% in the proximal tibia. The high body weight of the patients as a risk factor for low relative BMD in the affected limb could, perhaps, be explained by increased biomechanical loading of the affected limb, resulting in pain increase and decrease in activity. Also, the other independent predictors were in close association with the usage and function of the knee. These observations are consistent with those of our previous studies: the better the strength and function of the affected extremity the better the bone recovery (Kannus et al. 1992d). For this reason, we recommend early intense rehabilitation in all types of musculoskeletal disorders (Järvinen and Kannus 1997).

In conclusion, this study (V) indicates that chronic patellofemoral pain syndrome results in moderate bone loss in the knee region of the affected limb. The spine, proximal femur and calcaneus are not affected. Further analysis of the bone loss predicting factors reveals that good muscle strength and knee function are of great importance for good BMD, and therefore, quadricep muscle exercises can be recommended for PFPS patients.

Our study (VI) showed that in the active stages adhesive capsulitis created a significant bone loss to the affected humerus (proximal humerus -5.6% and humeral shaft -3.0%) while the BMD was normal in the other sites of the same extremity. We also showed that bone recovery in patients with previous adhesive capsulitis was good with no significant residual bone loss in the affected extremity 9 years after the disease (proximal humerus -1.5 % and humeral shaft -0.8 %).

Thus, these findings indicated that adhesive capsulitis-induced bone loss is a local process, most probably initiated by the severe immobility of the affected shoulder joint. Also, the inflammatory nature of the adhesive capsulitis may create a direct bone resorbing effect on the proximal humerus without causing any major disturbance in the general bone metabolism of the subjects (Kannus et al. 1992a, Johnell 1996).

In contrast with many previous studies on post-traumatic osteoporosis, we could not find any significant background factor predicting the capsulitis-induced bone loss in the affected humerus. Perhaps, the complex and largely unknown etiology and pathogenesis of the adhesive capsulitis did not allow us to focus our prediction analysis on the most relevant predicting factors. In post-traumatic osteoporosis, functional outcome of the injured extremity largely determines the long-term bony recovery in the same so that with excellent limb function the likehood of post-traumatic osteoporosis is negligible while with poor limb function considerable permanent bone loss can be expected (II, III). In all the patients with a previous adhesive capsulitis, the functional recovery of the shoulder was good and this could be one reason for the non-existing association between the shoulder function and BMD in the affected humerus.

In conclusion, this study (VI) indicates that adhesive capsulitis of the shoulder results in significant bone loss in the proximal humerus and humeral shaft of the affected extremity. The radial shaft, ulnar shaft, and distal forearm are not affected. However, in long-term (that is, years after the clinical recovery of the patient) the adhesive capsulitis-induced bone loss seems to disappear from the affected humerus, the BMD values not differing from those in the unaffected extremity.

8.4.Prevention of post-traumatic and musculoskeletal disorder-induced osteoporosis

It seems that injuries and disorders-induced changes in bone vary depending on factors such as location and severity of the injury and the type and duration of the immobilization. Also, the bones of children can tolerate better injuries, disorders and immobization, since the more immature skeleton is likely to have more potential for bone remodeling and healing than its more mature counterpart. Weight-bearing is considered to be an important stimulus of bone formation, and non-weight-bearing is associated with bone resorption (Järvinen and Kannus 1997). Several factors, such as changes in the stucture of the injured or affected limb as a consequence of injury or disease, possible subsequent surgical treatment, persistant pain, a decreased level of activity, and atrophy of the musculoskeletal tissues, may also impair the function of the injured or affected extremity. All these factors are likely to contribute to the development of osteoporosis.

Concerning prevention of post-traumatic or disorder-induced osteoporosis, the above noted findings support the concept that treatment of injuries and diseases of the extremities should involve as short a period of immobilization as possible, early weight-bearing, and a well planned program of rehabilitation. The patient should also be strongly encouraged to increase their level of general physical activity in order to minimize age-related bone loss and the subsequent risk for osteoporotic fractures. In the future, it would also be interesting to investigate the effect of bisphosphonate or other specific bone medication in preventing post-traumatic or disorder-induced osteoporosis.

9. SUMMARY AND CONCLUSIONS

As an answer to the original research hypothesis (p.36) the summary and conclusions of this study are:

1) A surgically treated complete ACL rupture (group A) results in remarkable bone loss in the knee region (distal femur -21%, patella -17% and proximal tibia -14%; $p<0.001$ in each) of the injured extremity. In the femoral neck, trochanter area of the proximal femur, and calcaneus, the bone loss is clearly smaller whereas the lumbar spine and distal radius are not affected. In the conservatively treated ACL injuries, injuries in which weight-bearing and knee function is returned to normal very quickly after the injury, the bone loss in the knee region of the injured limb is minimal and other sites are not affected. The obvious differences between the groups A and B in the severity of the injury itself (complete or partial tear), its treatment (surgical or conservative), and subsequent rehabilitation (longer non-weight-bearing times in group A) well explain the different BMD results, and the forthcoming years will show whether the considerable post-traumatic osteoporosis in the affected knee of group A patients will finally recover, and if so, to what extent.

2) The rotator cuff patients' mean side-to-side BMD difference is significantly lower in the proximal humerus (patients -3.5% vs. controls +2.4%, p=0.0002), humeral shaft (-2.6% vs. +1.6%, p=0.0005), radial shaft (-0.4% vs. +1.9%, p=0.0311), distal forearm (-0.2% vs. +2.4%, p=0.0158), and hand (+2.3% vs. +4.0%, p=0.0047). In the ulnar shaft, this difference is almost the same as in the patients (-0.2%) and controls (+0.2 %) (NS). Also, the lumbar spine BMD does not differ significantly between these groups.

3) An early life tibial fracture creates a small but statistically significant injured-to-uninjured side BMD difference (proximal tibia -1.7%; p=0.011, and distal tibia -2.6%; p=0.014), while the other sites show no significant side-to-side differences. There are neither significant differences in the spinal or radial BMDs between the patients and their age-, height- and weight- matched healthy controls. This study thus indicates that early life tibial fracture leads to a small long-term BMD deficit in the fractured bone while the other sites of the skeleton seem not to be affected. Thus, a

tibial shaft fracture sustained in childhood or adolescence seems to only marginally interfere the attainment of peak bone density.

The early life fracture results in a statistically significant injured-to-uninjured side BMD difference distal from the fracture site (men / women: distal femur -3.7% / -3.9%; patella -3.1% / -5.9%; proximal tibia -2.0% / -4.6%; and distal tibia -3.4% /-5.2%), whereas the proximal femur did not show such differences. The male patients' spinal BMD showed to be significantly lower (-7.9%) than that in their age-, height- and weight- matched healthy controls. The female patients' spinal BMD tended to be fairly comparable (-1.6%) to that of the controls (NS). This study indicates that early life femoral shaft fracture results in a moderate (-2% to -6%) long-term side-to-side BMD difference distal from the fracture site. Patients' spinal BMDs also tend to be lower than that of the controls. Thus, a femoral shaft fracture sustained in childhood or adolescence seems to somewhat disturb the attainment of peak bone density, the important predictor of the osteoporotic fractures in later life.

4) In chronic PFPS, the mean BMD of the affected limb (compared with the unaffected side) is significantly lower in the distal femur (-3.3% ; p=0.002), patella (-2.5%; p=0.016), and proximal tibia (-1.9%; p=0.008). The femoral neck, trochanter area of the femur, and calcaneus show no significant side-to-side differences, and the spinal BMDs of men and women with the PFPS are comparable with the manufacturer' s age-adjusted reference values for Western European men and women.

5) In the acute phase of the adhesive capsulitis of the shoulder, the mean BMD of the affected extremity, as compared with that of the unaffected side, is significantly lower in the proximal humerus (-5.6%; p=0.001) and humeral shaft (-3.0; p=0.008). The radial shaft, ulnar shaft, and distal forearm show no significant side-to-side differences. In contrast, in patients with a previous capsulitis, the affected-to-unaffected side BMD differences are small and statistically insignificant. Compared with the patients with the previous disease, the relative side-to-side BMD difference of the patients with the active-phase disease is significantly lower in the proximal humerus (-5.6% vs. -1.5%, p=0.009). In the other sites, groups show no significant differences. This study thus indicates that adhesive capsulitis of the shoulder results in significant bone loss in the humerus of the affected extremity, but in long-term, capsulitis-induced bone loss shows good recovery.

6) In studies II, III and V, we were able to find several background or clinical follow-up variables which predict the BMD deficit in the affected extremity:

In patients with surgically treated rotator cuff rupture (II), the relative BMDs of the injured extremity strongly associates with the objective assessment of the shoulder function: the better the observed function of the shoulder, the less bone loss caused by the injury. In proximal humerus, the side-to-side BMD difference average +2.0% in the patient group with "excellent" shoulder function, -3.3% in the "good" group, -5.3% in the "fair" group, and -11.5% in the "poor" group ($p=0.0012$).

In patients with an early life tibial shaft fracture (III), a further analysis of the data showed that the better the muscle strength in the injured lower limb, the lower the side-to-side BMD deficit in the proximal tibia of the same limb ($r=0.51$; $p<0.001$). Smoking has a signicant association with the relative BMD in the injured distal tibia (mean injured-to-uninjured side BMD difference: smokers -6.1% vs. nonsmokers -0.6%, $p=0.016$). Also, patient's age at the time of the injury showed an association: the younger the patient at the time of the injury, the lower the side-to-side BMD deficit in the injured distal tibia ($r= - 0.35$; $p=0.048$).

In patients with a chronic PFPS (V), the relative BMDs of the affected knee show strongest correlation with the muscle strength of the same knee: the better the muscle strength in comparison with the healthy knee, the higher the relative BMD ($r=0.56$-0.58 with $p<0.001$ in each anatomic site of the knee). In the stepwise regression analysis, low body weight or low body mass index, high level of physical activity, the patient's good subjective overall assessment of his/her affected knee, and short duration of the symptoms are also independent predictors of the high relative BMD in the affected knee so that along with the muscle strength these variables can account for 51% of the variation seen in the relative BMD of the femur, 61% in the patella, and 54% in the proximal tibia.

Thus, recovery of normal muscle strength and limb function seems to be of great importance for good BMD in the affected extremity.

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12. ORIGINAL PUBLICATIONS