Exercise in Youth and Long-Term Effects on Bone and Joints

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Abstract

Partly due to an ageing population, the number of osteoporosis-related fractures and osteoarthritis (OA)-related hip and knee arthroplasty procedures is increasing. The individual suffering and the burden on society for these conditions is immense. Genetic contribution for the variance in bone mineral density (BMD) is estimated at around 60–80%, and for OA 50%, leaving a considerable proportion to environmental factors of which exercise is known to influence both. Most intervention studies have shown exercise-induced BMD benefits in young, mid, and old age groups, though all have been short-term. Most studies that have followed changes in BMD with up to ten years of reduced activity level have shown a higher BMD loss than expected by age. Retrospective studies of fracture incidence and OA prevalence have been inconclusive. Little is known about the association between types of exercise in youth and prevalence of total hip arthroplasty (THA) or total knee arthroplasty (TKA) in old age.

We evaluated bone traits in two studies. The first was a 39-year prospective cohort study that followed 46 active male athletes into a mean 29 years of retirement and 24 age-matched controls. The second used a cross-sectional mixed model design that included 329 measurements in 193 active and former male soccer players and 450 measurements in 280 controls, all aged between 18 and 85 years. The first study measured BMD by single-photon absorptiometry (SPA) on both occasions, and with dual energy X-ray absorptiometry (DXA), peripheral computed tomography (pQCT) and quantitative ultrasound (QUS) at follow-up. The second study used DXA. Fracture incidence was evaluated in two retrospective cohort studies, one including 397 former male soccer players and 1368 age-matched controls and the second 709 former male athletes in a variety of sports and 1368 age-matched controls. The prevalence of hip and knee OA and arthroplasty was also evaluated in the second study.

In the first study we found no changes in relative leg BMD levels [Δ Z-score 0.0 (95% CI –0.4, 0.4)] in athletes from activity into retirement. At follow-up, former athletes still had 0.5 to 1.2 standard deviations (SD) higher BMD, bone size, and strength index than controls (all $p<0.05$). In the second study, total body BMD, leg BMD, and femoral neck area were 0.3 to 0.5 SD higher in 30 or more years retired athletes than in controls (all $p<0.05$). Former male athletes had a 50% [RR 0.5 (95% CI 0.3, 0.9)] and former soccer players had a 60% [RR 0.4 (95% CI 0.2, 0.9)] lower risk respectively of any fragility fracture incidence than controls (both $p<0.05$), and two times higher age-adjusted risk of a hip and/or knee OA [OR 1.9 (95% CI 1.5, 2.3)], as well as a hip and/or knee arthroplasty [OR 2.2 (95% CI 1.6, 3.1)]. After adjustment for differences in BMI, occupational load, and previous soft tissue knee injury, there was no increased risk of knee OA in former impact athletes while the risk remained in non-impact athletes [OR 3.2 (95% CI 1.5, 6.9)].

This thesis infers that exercise-associated benefits in BMD and bone size remain long-term after sports, and that former athletes are at lower fracture risk than controls. In contrast, the risk of hip and/or knee OA and THA and/or TKA is higher in former athletes than in controls. The higher risk of knee OA in former athletes is associated with a knee injury in impact but not in non-impact athletes.

Key words:

arthroplasty, BMD, bone mass, bone geometry, bone size, exercise, former athletes, fracture, fragility fracture, knee injury, osteoarthritis, osteoporosis, hip injury, runners, soccer, total joint replacement

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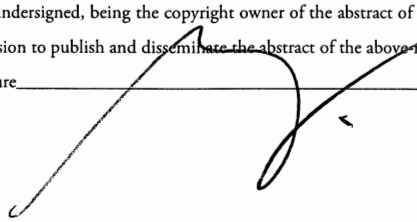

Exercise in Youth and Long-Term Effects on Bone and Joints

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Cover illustration: A fractured tibia in one of the study participants during a game at the Malmö idrottsplats between IFK Malmö and Jönköping Södra (Sydsvenska Dagbladet, 17 November 1952)

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To Linda, Ludvig, and Vilma

The whole problem with the world is that fools and fanatics are always so certain of themselves, and wiser people so full of doubts.

– Bertrand Russell

Contents

List of papers

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

I. **Tveit M, Rosengren BE, Nilsson J-Å, Ahlborg HG, Karlsson MK**

Bone mass following physical activity in young years: a mean 39-year prospective controlled study in men

Osteoporosis Int 2013 Apr;24(4):1389–97

II. **Tveit M, Rosengren BE, Nilsson J-Å, Karlsson MK**

Former male elite athletes have a higher prevalence of osteoarthritis and arthroplasty in the hip and knee than expected

Am J Sports Med 2012 Mar;40(3):527–33

III. **Tveit M, Rosengren BE, Nyquist F, Nilsson J-Å, Karlsson MK**

Former male elite athletes have lower incidence of fragility fractures than expected

Med Sci Sports Exerc 2013 Mar;45(3):405–10

IV. **Tveit M, Rosengren BE, Nilsson J-Å, Karlsson MK**

Exercise in youth is associated with high bone mass, large bone size, and low fracture risk in old age

Submitted

Thesis at a glance

Is exercise-associated high bone mass in youth maintained three decades after detraining? (Paper I)

Subjects: 46 male athletes and 24 age-matched controls were followed for a mean 39 years – from activity to a mean 29 years of retirement.

Methods: Bone mineral density (BMD) was measured on both occasions with single-photon absorptiometry (SPA), at baseline in femoral condyles and at follow-up in distal radius. At follow-up, additional regions were evaluated with modern scanning techniques (DXA, pQCT, QUS). Data are presented as means with 95% confidence intervals (CI) in parentheses.

Conclusion: At baseline, active athletes had a mean BMD Z-score of 1.0 (0.7, 1.4) in the femoral condyles. No relative change was seen in leg BMD [Δ Z-score 0.0 (–0.4, 0.4)] during the study period. At follow-up, former athletes had a BMD Z-score of 0.5 to 1.2 depending on the measuring region and the technique used (all $p<0.05$). Also, tibial cortical thickness and strength index were higher in former athletes with a mean Z-score of 0.8 (0.5, 1.2) and 0.7 (0.4, 1.0) respectively. Thus, benefits in BMD and geometry seem to be maintained three decades into retirement.

Is exercise in youth associated with a high risk of developing hip and knee osteoarthritis (OA) later in life? (Paper II)

Subjects: 709 former male impact and non-impact athletes aged a mean 69 (range 50–93) years and retired a mean 34 years (1–63) were compared with 1368 age-matched controls.

Methods: A self-reported questionnaire on anthropometry and lifestyle, including exercise and medical history with special reference to hip and knee OA and arthroplasty in these joints, was used. Data are presented as mean odds ratios (OR) with 95% CI in parentheses.

Conclusion: The age-adjusted risk of developing hip or knee OA was two times higher in former athletes [OR 1.9 (1.5, 2.3)], as was the risk of having an arthroplasty in either of these joints [OR 2.2 (1.6, 3.1)]. In absolute OR values the risk of OA and arthroplasty tended to be higher in the hip than in the knee, and driven by a higher

risk in former impact athletes. After adjustment for confounders such as previous soft tissue knee injury, no increased risk of developing knee OA was seen in former impact athletes compared with controls, while the risk was three times higher in non-impact athletes than in controls [OR 3.2 (1.5–6.9)]. Thus, hip and knee OA and hip and knee arthroplasties are more commonly found in former male athletes than expected. A previous knee injury is associated with knee OA in former impact athletes but not in non-impact athletes.

Is exercise in youth associated with low fracture risk in old age? (Paper III)

Subjects: 709 former male athletes aged a mean 69 (range 50–93) years and retired a mean 34 (1–63) years were compared with 1368 age-matched controls.

Methods: A self-reported questionnaire on anthropometry and lifestyle, including exercise and medical history with special reference to fractures, was used. Data are presented as mean rate ratios (RR) or hazard ratios (HR) with 95% CI in parentheses.

Conclusion: Former athletes after active career had a 30% lower risk of sustaining any fracture [RR 0.7 (0.5, 0.9)], 50% for a fragility fracture [RR 0.5 (0.3, 0.9)], and 70% for a distal radius fracture [RR 0.3 (0.1, 0.7)] compared with controls. After adjustment for differences in lifestyle, the lower risk remained and at similar magnitudes in former athletes, although for fragility fractures now with a non-significant difference [HR 0.6 (0.3, 1.2)]. Thus, vigorous exercise in youth seems to be associated with low fracture risk in old age.

Are exercise-associated benefits in bone traits maintained decades after a soccer career, and do former male soccer players have lower fracture risk than expected by age? (Paper IV)

Subjects: Two sub-studies were performed: (i) in a cross-sectional controlled mixed model design, we compared BMD and bone size of 329 measurements in 193 active and retired male soccer players and 450 measurements in 280 controls, all aged between 18 and 85 years, (ii) lifetime fracture rates were retrospectively registered in 397 former male soccer players a mean 69 (range 53–93) years and retired a mean 33 years (1–63) and in 1368 age-matched controls.

Methods: A self-reported questionnaires on anthropometry and lifestyle, including exercise and medical history with special reference to fractures, was used in both the sub-studies. Bone traits were evaluated with dual X-ray absorptiometry (DXA) in sub-study I. Data are presented as means (SD, RR, or HR) with 95% CI in parentheses.

Conclusion: More than 30 years after retirement from active soccer career, former athletes had a mean 0.3 to 0.5 SD higher total body BMD, leg BMD, and femoral

neck area than controls (all $p<0.05$). The risk of having sustained any fracture after career-end was 40% lower [RR 0.6 (0.4, 0.9)] and for a fragility fracture 60% lower [0.4 (0.2, 0.9)] in former soccer players than in controls. After adjustment for differences in lifestyle, the lower risk remained and at similar magnitudes in former athletes, although for fragility fractures now with a non-significant difference 0.5 (0.2, 1.2)]. Thus, soccer training in youth seems to be associated with long-term benefits in bone traits and low fracture risk in old age.

Abbreviations

ACL	anterior cruciate ligament
ANCOVA	analysis of covariance
BFR	bone formation rate
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BML	bone marrow lesion
BMU	basic multicellular unit
BSI	bone strength index
BUA	broadband ultrasound attenuation
CI	confidence interval
CSA	cross-sectional area
csmi	cross-sectional moment of inertia
CV	coefficient of variance
dGEMRIC	delayed gadolinium-enhanced MRI of cartilage
DXA	dual-energy X-ray absorptiometry
EQ-5D	the five-dimension self-assessment tool from the EuroQol-group
FCD	fixed charge density
FRAX	Fracture risk assessment tool
GAG	glycosaminoglycan
HOOS	the Hip Injury and Osteoarthritis Outcome Score
HR	hazard ratio
HR-QCT	high-resolution quantitative computed tomography

HRQoL	health-related quality of life
HSA	hip structural analysis
KOOS	the Knee Injury and Osteoarthritis Outcome Score
MES	minimal effective strain
MJS	minimal joint space
MRI	magnetic resonance imaging
OA	osteoarthritis
OR	odds ratio
PBM	peak bone mass
PCL	posterior cruciate ligament
Peak BMD	peak bone mineral density
pQCT	peripheral quantitative computed tomography
PROM	patient-reported outcome measure
PTH	parathyroid hormone
QUS	quantitative ultrasound
RCT	randomized controlled trial
ROI	region of interest
ROM	range of motion
RR	rate ratio
SD	standard deviation
SF-36	the 36-item Short-form Health Survey
SI	stiffness index
si	strength index
sm	section modulus
SOS	speed of sound
SPA	single-photon absorptiometry
THA	total hip arthroplasty
THR	total hip replacement
TJR	total joint replacement

TKA	total knee arthroplasty
TKR	total knee replacement
vBMD	volumetric bone mineral density
WOMAC	Western Ontario McMaster Universities Osteoarthritis Index

Prologue

The human body is physically built to be in motion, enabling each individual to seek nutrition and remain on the alert for danger. As standards of living have improved and modern society has developed, we have gradually adopted a more sedentary lifestyle. This, together with changes in dietary patterns, has contributed to an increase in chronic conditions such as obesity, diabetes, musculoskeletal disorders, and cardiovascular diseases.

Currently there occur around 70,000 fragility fractures per year in Sweden, rendering a number of days in hospital that falls in-between the numbers for the care of stroke and ischaemic heart diseases.[122] Due to this burden, we must search for prophylactic interventions that reduce the number of fractures. The level of physical activity could be such an intervention as exercise has a direct effect on bone remodelling and since the skeleton constantly adapts to the current load. Although bone loss and structural skeletal deterioration are normal processes of ageing, caused by a negative balance between bone formation and bone resorption, the rate of bone loss could be reduced through physical activity. Exercise may also influence the growing skeleton. To a large extent, bone formation takes place in and around puberty,[129] and, together with genetic predisposition, physical activity is one of the major factors that not only influences the accrual of bone mineral and probably even the level of acquired peak bone mass,[36] but also the improvement of bone geometry. However, it is unknown whether exercise-associated bone trait benefits remain in old age.

Yet, physical activity may also exert negative effects on the musculoskeletal system. For example, physical activities that have proven beneficial for bone formation, including high-magnitude and high-intense loadings together with loadings from different directions, may exert negative effects on joints. When exposed to intense long-term stress and micro injuries, it may eventually lead to failure, i.e. osteoarthritis (OA).[116] OA also causes a huge burden on society since the combined number of primary hip and knee arthroplasty procedures in Sweden is around 30,000 per year.[264, 265] There is an association between impact-type exercise such as soccer and OA, especially if accompanied by a soft tissue knee injury.[156, 208] Existing studies that have evaluated whether there is any association between non-impact-type exercise, such as long-distance running, and degenerative joint disease are inconsistent.[179, 254] Furthermore, little is reported as regards the need for hip and knee arthroplasty surgery in those with a high level of physical activity in youth.

The first of two general aims of this thesis was to in men study whether exercise-associated benefits in bone characteristics are maintained long-term after detraining and, if so, whether this also is associated with fewer fractures. The second aim was to in men study the long-term risk of developing OA and need for total joint replacement if having been on a high level of physical activity in youth.

The following chapter presents a review of published literature within these two research fields. A description of study design and methods applied in the dissertation is presented in the *Subjects and methods* section. The obtained data are reported in the *Results* section and discussed in connection with previously published data in the *Discussion* section.

Background

Bone

Morphology and metabolism

The skeleton is a type of dense connective tissue with a wide range of purposes within any of its principally three functionalities: mechanical, synthetic, and metabolic. Typically, bone serves as a locomotive apparatus to the human organism and provides protection for vital internal organs, it is the origin of red and white marrow where blood is synthesized, and it serves as mineral storage, mainly for calcium and phosphorus.

Morphology

The skeleton is composed of two different types of tissues, the cortical (outer, compact, dense) and trabecular (inner, cancellous, porous) bone. The former accounts for 80% of the total bone mass of an adult and comprises the outer casing of long bones – from a thin lining of the epiphysis (before the growth plates have merged during growth) at the end, past the metaphysis, and is predominantly found at the mid section of long bones called the diaphysis. Cortical bone consists of cylindrical units called osteons with both biomechanical and metabolic features. They are arranged in an overlapping brick-like manner and embrace the longitudinally arranged Haversian canals where the blood and nerve vessels run (Figure 1). The Haversian canals can also communicate stimuli and nutrition perpendicularly, from the endosteal to the periosteal surface, through Volkmann's canals.[157] Cortical bone with its dense and tubular structure enables it to withstand bending forces, yet it is brittle, and has a slow annual turnover rate of around 5%, which is why it takes a long time to heal in case of fracture. Trabecular bone accounts for the remaining 20% of the total bone mass in an adult skeleton and is primarily found at the end of long bones (epiphysis/metaphysis), in vertebrae, and pelvis. The area of trabecular bone is nearly ten times that of the cortical bone, and is the more susceptible of the two to external stimuli, whether it is hormonal, pharmacological, or mechanical.[4, 217] The three-dimensional branching of rods and plates makes trabecular bone light, elastic,

and suitable to withstand axial compression forces.[187] Because of its porosity, it is more fragile than cortical bone, but has a higher annual turnover rate of around 25%, and thus heals faster in case of fracture.

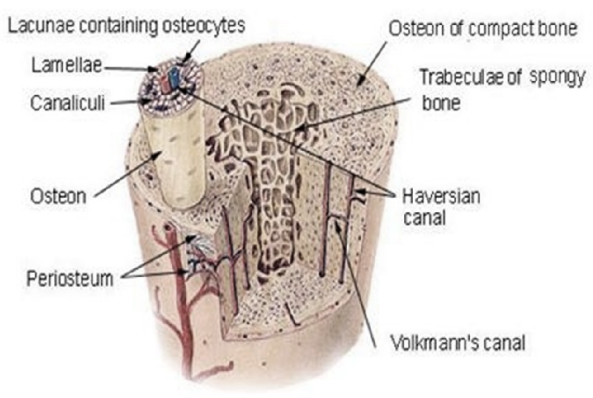

Figure 1. Illustration of a typical long bone. (Gray's Anatomy, Elsevier, www.elsevier.com)

On a cellular and molecular basis, the skeleton can be divided into 75% of non-organic bone matrix, mainly formed of calcium and phosphate into crystalline hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). Twenty per cent consists of organic materials, most of which is made up of type I collagen fibres while only a fraction is bone cells. The remaining 5% is water. Osteocytes are the most common and the longest living cells within the skeleton, with a half-life of around 25 years. They are large stellar-shaped cells, embedded deep into the bone matrix in so-called lacunae, whose extended network of canaliculi guards the integrity of the bone tissue by providing mechano-sensor function which regulates the activity of osteoblasts and osteoclasts in response to mechanical stimuli (Figure 2). The intricate cellular interplay which makes bone turnover is referred to as a basic multicellular unit (BMU). The BMUs include bone forming osteoblasts, resorptive osteoclasts, and monitoring osteocytes (for details, see section *Modelling and remodelling*).[80, 82, 216, 218] The "fourth" type of cells, called *bone lining cells*, are essentially inactive osteoblasts and covers all available bone surfaces.

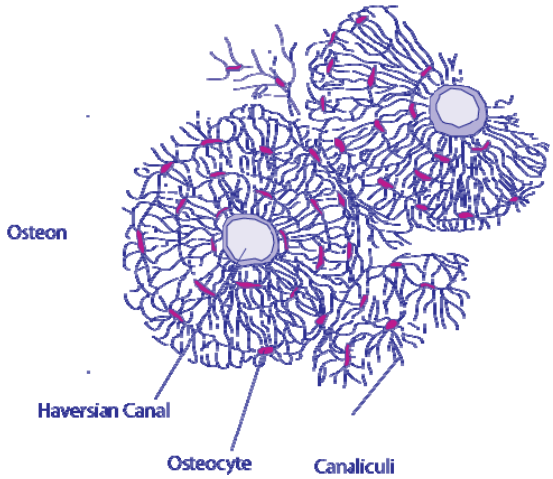

Figure 2. Illustration of an osteon. (Gray's Anatomy, Elsevier, www.elsevier.com)

Biomechanical markers

The intensity of bone turnover can be detected by bone markers in serum of which osteocalcin and bone-specific alkaline phosphatases (ALP) are examples of bone formation markers produced by osteoblasts, and crosslinked C- (CTX) and N- (NTX) telopeptides of type 1 collagen are resorption markers.

Hormones

Since the skeleton is the body's calcium reservoir, it will respond to low calcium levels in serum by releasing calcium. The calcium homeostasis is mainly regulated by interplay between vitamin D and parathyroid hormone (PTH). PTH is secreted by the parathyroid gland to stimulate the osteoclasts to mobilize calcium when serum calcium levels are low. In order to keep the bone tissue mineralized, an adequate supply of dietary calcium and sufficient access to vitamin D is vital. Vitamin D, which in effect is a hormone, is accessible to the human body through two different pathways: (i) it can be synthesized in the skin when exposed to solar ultra-violet light B (UVB), and (ii) as a dietary intake, especially from fatty foods such as salmon, dairy products, and liver. Chemically, the most important types for the human body are ergocalciferol (D_2) and cholecalciferol (D_3), both of which can be ingested from diet and the latter can be synthesized in the skin from 7-dehydrocholesterol and UVB. Calciferol (D_2 and D_3) is hydroxylated in two stages, first in the liver to calcidiol, then to the biologically active calcitriol in the kidney, and is thereafter transported to targets throughout the body attached to a vitamin D binding protein (DBP). As exposure to sunlight is required for maintaining adequate vitamin D levels, people in

the northern hemisphere are at higher risk of deficiency. The main function of vitamin D is to enhance calcium absorption in the intestines and to stimulate the osteoblasts to mineralize the skeleton. PTH increases calcium levels by stimulating the osteoclasts to mobilize calcium from the skeleton, and the kidneys to increase calcium resorption and vitamin D activation.[108] Hyperparathyroidism can ultimately lead to rachitis with soft, deformed bones in the growing skeleton, or osteomalacia in adults. The condition can be caused by a wide range of conditions such as renal failure, insufficient access to vitamin D, or insufficient intake of calcium.

Calcitonin is another hormone affecting bone remodelling and calcium levels. It is secreted by the thyroid gland and acts as an antagonist to PTH.

Among the naturally occurring hormones in the body, oestrogen probably has the strongest impact on bone tissue. Although it becomes particularly obvious in women after the menopausal hormonal transition when oestrogen levels drop and the porosity of bone accelerates, oestrogen is of great importance for bone regulation in both men and women. Even if not fully understood, the main effect of oestrogen is generally considered to suppress remodelling by maintaining the balance between osteoblasts and osteoclasts.[118, 224]

Modelling and remodelling

Historically, bone was regarded as an inert tissue largely seen solely as a reservoir for calcium that would expand by osteoblasts and erode by osteoclasts, depending merely on the serum level of calcium. It was not until 1963, when the American surgeon Harold Frost first discovered the close relationship between osteoblasts, osteoclasts, and osteocytes, that the complexity of bone and its constant adaptation to mechanical stimuli was understood. His thoughts are captured in his theories of "Mechanostat" in which the *remodelling* process is carried out by a team of two cells where an osteoblast closely follows and fills the gap made by an osteoclast, closely monitored by a highly differentiated osteocyte, to form an osteon (one of an infinite number of "bricks" that makes up the cortical bone) (Figure 3). It is this temporary team effort that is referred to as a basic multicellular unit (BMU).[80, 82, 216, 218] After having synthesized an osteoid and mineralized it (osteon), an osteoblast can become a mechano-sensoring osteocyte ready to respond to new mechanical stimuli.[146] In the adult skeleton, this well-organized (BMU-based) bone turnover, or even net removal of bone if not needed, takes place at the bone surface. This means for cortical bone the outer (periosteal) and inner (endosteal) layer of the cortex, as well as the intracortical surfaces (walls of the Haversian canals).

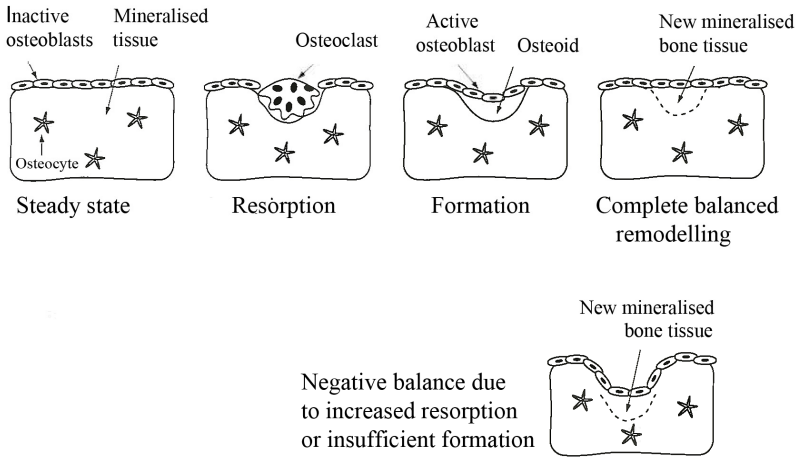

Figure 3. Illustration of bone turnover at cellular level. (The Swedish Council of Technology Assessment in Health Care, www.socialstyrelsen.se)

The *modelling* process, or formation drift, is believed to involve independent action of osteoclasts and osteoblasts (non-BMU-based). During growth, modelling is primarily driven by genetic factors but also by external stimuli (e.g. exercise),[80, 81, 218] and is characterized by mineral accrual and net increase of the cortical thickness and bone size in both boys and girls.[13, 57, 61, 129, 164, 288] In adulthood there is a net formation of the periosteal cortex and net resorption of the endosteal cortex,[3, 227] but whether this age-related widening of the skeleton is a form of modelling (non-BMU-based) or remodelling (BMU-based) is debated.[210]

Schematically, Frost first defined four different elastic states of bone deformation, or strain intervals; *disuse, adaptive state, overload,* and *fracture*. Second, depending on which state, the bone either models or remodels (Figure 4). Third, to make these load-adaptations possible, he suggested that bone cells can monitor bone usage (peak bone strains), and adjust bone strength and rigidity accordingly by changing their mass, geometry, and material properties. Also, the skeleton would be pre-programmed with a strain set point or minimal effective strain (MES). This set point could either initiate modelling (formation drifts which are non-BMU-based) when subjected to overloading and the peak bone strain is above a certain MES, or initiate remodelling (BMU-based) in order to execute bone turnover in a steady state environment or to remove bone when subjected to low load and the peak bone strain is below a certain MES.

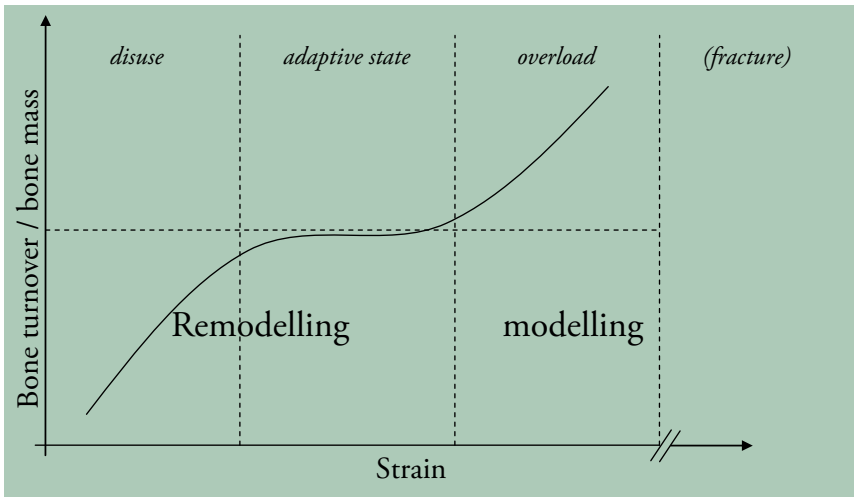

Figure 4. A scheme for bone response to mechanical loading according to the "Mechanostat" theory proposed by H Frost.

In other words, constant replacement of bone is of lifelong importance for the skeleton to withstand strains,[67, 218] and to maintain appropriate conditions for the calcium homeostasis.[31] Modelling is generally referred to as an enlargement of bone, whereas remodelling refers to turnover or removal of bone. Although the former is predominantly involved in growth and adaptation to stimuli and the latter in the lifelong renewal of the skeleton, they often occur simultaneously and may therefore be impossible to discriminate.[29]

Biomechanics – form follows function

Mechanical properties of bone are governed by the same principles as those of any man-made load-bearing structures with the fundamental difference that bone can adapt in response to changes in demands. Another fact also applicable to bone is that any type of external force will result in an equally high magnitude of internal stress in opposite direction. These estimates can be calculated from a combination of three basic components: *compressive*, *tensile*, and *shear* stresses.[66, 280] Strain, in turn, is a descriptive of the elasticity of a material. Typical stress-strain curve shows linearity between the two until the yield point where the elastic material turns plastic. The area under the curve represents the stored energy, the slope within the elastic interval represents the rigidity of the material, and at the end of the plastic interval the failure point is reached. Since stress is force per area and strain is deformation of a solid due to stress, a "solid" such as an entire bone is usually presented as a load-deformation

curve (Figure 5). Translated into orthopaedic vocabulary, the yield point has typically occurred in a childhood bend fracture or a compression fracture in elderly. The more dramatic failure point, or brake-point, has typically been reached when a splitter fractures occurs.

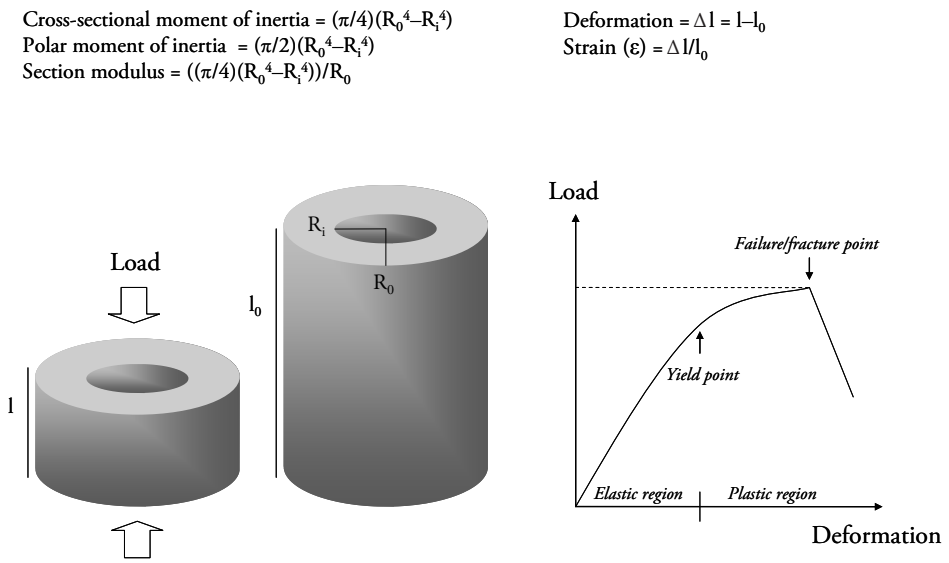

Figure 5. Cross-sectional moment of inertia and section modulud describes a tubualr structure's resistance to bending forces and polar moment of inertia its resisance to torsional forces, all independent of material properties. The tubular structure is here extrapolated to bone where R_0 represents the outer (periosteal) layer and R_i represents the inner (endostral) layer of the cortex. The unloaded bone segment (l_0) and the loaded bone segment (l). The load-deforamtion curve is used to characterize the mechanical property, in this case of bone. The linear slope within the elastic region represents the stiffness of the bone and is dependent on material properties.

The porous lattice-like micro architecture of trabecular bone and its relatively large cross-sectional area of the metaphysis at the end of long bones is a suitable arrangement for the human body to withstand tensile and compression loads as it elastically deforms under axial weight-loads and adjacent soft-tissue forces around the joint when standing/walking upright. Cortical bone with its dense overlapping brick-like micro architecture is, on the other hand, more resistant to bending and torsional loads and is thus more suitable in the diaphysis located in the mid-section of long bones.

Bone strength can be defined as *"the force required to produce a mechanical failure under a specific loading condition."*[14] Each of the above-mentioned principal stresses on

bone – compression, tensile, and shear – can be estimated mathematically. *Axial load* will produce a compression stress, so that the bone becomes shorter, and the opposite will lead to a tensile stress. The axial strength of the bone depends on its cross-sectional area. A bone that is subjected to *bending load* will produce compression stress on one side and tensile stress on the other. The bending strength of the bone depends on its inner and outer diameter and can be expressed as section modulus (sm) and is calculated using a key biomechanical parameter called cross-sectional moment of inertia (csmi) (Figure 5). It explains how very small changes in the outer diameter have a profound effect on the strength. *Torsional load* will produce shear stress, and the bone's resistance to torque can be expressed as polar moment of inertia (Figure 5).[168, 180, 280] Consequently, the further away from the neutral axis mass (cortex) is distributed the higher is bone strength; this applies to both bending and torsion situations.[66]

It has also been shown that if the shape of bone is assumed to be tubular/cylindrical, the cross-sectional area (CSA) is a more important variable to bone strength in bending or torsion situations than is its mass or density.[66] Nevertheless, the above estimates of strength are all based on structural parameters alone and do not take material properties into account. Biomechanically, bone can be described at two levels: *material* and *structural*.[66, 280] Generally speaking, the strength, or the nature, of the skeleton would then depend on both structure such as shape, and material (tissue) properties such as mineralization. The material properties reflect how the stress-strain or load-deformation curve is drawn. Translated into bone characteristics, the more mineralized/rigid/stiff the steeper the curve becomes and the more non-mineralized and saturated with collagen-weave/elastic, the flatter it becomes. In an attempt to incorporate both structural and material (tissue) variables into the equation of estimating the biomechanical nature of a bone, strength index (si) or bone strength index (BSI) can be used. This is calculated as the product of both the section modulus and the volumetric bone mineral density (vBMD) (for detail, see section *Non-invasive bone assessments*).

Osteoregulatory theories – a century of evolution

In 1892, the German surgeon Julius Wolff published his main work titled "The Law of Transformation of Bone". His theory of the relationship between bone geometry and mechanical influences on bone has since then been referred to as "Wolff's law".[298] Wolff initiated the German Orthopaedic Society and his classic work on bone adaptation is considered by many the starting point of orthopaedics as an independent discipline. As Dr Wolff stated: *"As a consequence of primary shape variations and continuous loading, or even due to loading alone, bone changes its inner*

architecture according to mathematical rules and, as a secondary effect and governed by the same mathematical rules, also changes its shape."

In 1917, the Scottish biologist Sir D'Arcy Wentworth Thompson wrote the book *On Growth and Form*, where he not only suggested that strain signals adaptation, but was also first to propose that shear stresses may play a vital role in the signalling mechanism;[273] *"the very important physiological truth [is] that a condition of strain, the result of a stress, is a direct stimulus to growth itself. This is indeed no less than one of the cardinal facts of theoretical biology."*

Yet, it was not until 1963, when the American surgeon Harold Frost first described the intrinsic interactions between osteoblasts, osteoclasts, and osteocytes in the context of loading environment that we arrived at a better understanding of how mechanically complex the skeleton really is. Frost captured the following thoughts on how local strains regulate bone mass in his "Mechanostat" theory[80, 82, 216] where he proposed bone *modelling* to equal a non-organized net formation of bone, formation drift, where bone is rearranged depending on the local loading environment. In contrast, he proposed bone *remodelling*, i.e. bone turnover in a steady state loading environment or bone loss in a decreased loading environment, to be a well-organized cell mechanism in which the above cells form so-called BMUs (for details, see section *Modelling and remodelling*).

Mechanotransduction

Though not having explained how local mechanical signals are detected, nor how they are translated to bone formation and resorption in the (re)modelling process, the above qualitative theories have formed the theoretical basis for several mathematical, computional, and laboratory-based works where mechanotransduction – the transfer of mechanical stimuli into chemical signals and tissue response – has received considerable attention among researchers. It is currently believed that the stellar-shaped osteocytes within the bone matrix, featured with far-reaching interconnections by which they communicate with each other and with other bone-lining cells (osteoblasts) at the surface, favours them to be "mechanotransductors".[190] Osteocytes, when facing alteration in loads, have the ability to release mediators, of which RANKL (receptor activator of nuclear factor kappa-B ligand) is regarded as the most important to moderate bone turnover. The RANKL system either promotes or inhibits the activity of osteoblasts and osteoclasts, resulting in either bone formation or resorption.[145, 243]

It is most likely that loads which create deformations on a bone are translated to shear stresses and strains through flows of fluids within the canaliculi on a cellular level, rather than through direct deformation of the cell membrane itself,[211, 291] an idea already expressed in general terms by Thompson in 1917. These assumptions generate predictions about how bone should behave when exposed to loads,[32] many of

which been reproduced both experimentally (rat studies) and in humans. First, fluids can only be flown through bone by cyclic loading and relaxation. In a study on rats not only cyclic loading outperformed static loading but the latter even suppressed bone formation.[231] Second, it has also been shown that bone formation rate (BFR) is proportional to strain stimulus or strain rate (basically equal to change in strain and, simplified, a product of magnitude and frequency).[188, 207, 281, 282] Third, the mechanical sensitivity of bone cells and their threshold recovery period to optimize load-adapting response was first studied in a classic work by Rubin and Lanyon in 1984[239] where they could show that 36 cycles/day was as efficient as 1800 cycles/day at the same strain magnitude, a finding that have been repeated by others.[284] That is, the second assumption only seems to be valid as long as the frequency of loading cycles does not exceed time needed to recovery. In fact, one study has stated that bone needs 4–8 hours to re-establish complete mechanosensitivity.[230, 231] Furthermore, there even seems to be an optimal recovery period within each cycle in order to maximize bone formation.[32]

Non-invasive bone assessments

A bone's ability to withstand forces is dependent on several measurable features such as the size, shape, structure, quantity, and quality of the tissue. From these parameters elasticity/stiffness, energy absorption, and ultimate strength can be calculated non-invasively,[278] while estimates of fatigue, mechanical sensitivity, and threshold recovery periods often depend on animal models.[230, 231, 239, 284]

The absorptive ability of calcium hydroxyapatite is much greater than that of soft tissue. This principle is used in bone densitometry, a non-invasive method of assessing bone and body composition. The technique is based on photon absorptiometry which, unlike e.g. magnetic resonance imaging (MRI), uses an ionizing radiation source and is thus potentially hazardous, if it was not for the low dosage used. No matter whether the densitometer is based on X-ray (generated from an X-ray tube) or a gamma ray (generated from a radioisotope), both have ionizing sources but with different wavelength. Whereas the former has long made itself indispensable in everyday medical practice, the latter has also been found highly useful, e.g. in cancer therapy by so-called gamma-knives or for diagnostic purposes in PET scans.

Bone densitometry

First, bone mass is a non-specific term yet frequently used in scientific literature in general discussions of the amount of mineral in the skeleton.

Bone mineral content (BMC) is one-dimensional and refers to the total amount of mineral detected when scanned, irrespective of width and depth. Consequently, BMC is in general higher in a larger bone than a smaller bone. Historically, BMC was presented in grams per square centimetre (g/cm^2) as the first generation of densitometry, single-photon absorptiometry (SPA), measured a section 1 cm long (for details, see subchapter below). Today, BMC is presented in grams (g) or sometimes grams per centimetre (g/cm). Actually, when a standardization of terminology was needed in the 1990s, BMC had its name changed to bone mineral density (BMD) but kept its units (g/cm^2) and instead BMC was given a new unit, grams (g), more favourable in describing the growing skeleton as the results were then not obscured by changes in bone size.[20, 99, 226, 228]

BMD is still considered the gold standard unit and is produced by virtually all densitometry devices in use today. The reason for this is both historical, as neither SPA nor dual energy X-ray absorptiometry (DXA) can measure the true volumetric density (vBMD), and practical, as the world health organization (WHO) definition of osteoporosis is based on BMD measured by DXA.[46] In fact, peripheral quantitative computed tomography (pQCT) reduces its measured true volumetric results into BMD for eligible comparison with earlier work done by either SPA or DXA and to correlate the outcome to the definition of osteoporosis. Yet, the accepted definition of BMD, a term derived from the second-generation densitometry, DXA, and goes back to the 1990s, has turned out to be misleading since it is based on bone mineral detected over a projected area and does not take the depth into account. This is why "areal" soon was added in front, i.e. aBMD or BMD is calculated by dividing BMC by area (g/cm^2).

Depending on the technique used, apparent or volumetric BMD (BMAD or vBMD) are expressions used when estimates of the "true" density of bone is eligible, and is calculated by dividing BMC by volume (g/cm^3). The measure is three-dimensional and takes both bone width and bone depth into account. Only the third-generation densitometry, pQCT, is capable of measuring the bone's true volumes.

It should be clarified that *apparent* or *volumetric* BMD (BMAD or vBMD) is thus not the same as *areal* BMD (aBMD or BMD).

Independently of units used to characterise the skeleton, each method and even each apparatus has a certain degree of adequacy which also can change over time (drift). Constant revaluation of both *accuracy* and *precision* is therefore needed. Accuracy refers to how well the true value of a subject actually is reflected by the method used, and is particular important in cross-sectional studies when only one measurement is obtained. Precision, on the other hand, is more important in longitudinal studies as it refers to the degree of reproducibility, meaning how well a certain value can be repeated (provided the true value is unchanged). Precision is usually expressed in

coefficient of variance (CV) which is the ratio of the standard deviation (SD) to the mean (Figure 6).

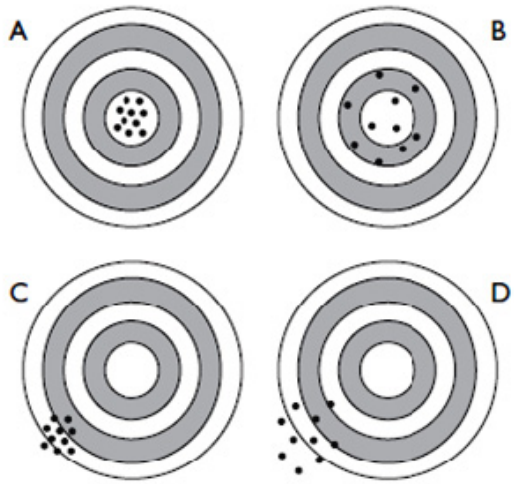

Figure 6. Illustration of accuracy and precision: A) High accuracy and high precision. B) High accuracy and low precision. C) Low accuracy and high precision. D) Low accuracy and low precision. (The Swedish Council of Technology Assessment in Health Care, www.socialstyrelsen.se)

Single-photon absorptiometry

The first ever bone densitometer is based on SPA and was constructed in the USA by Cameron and Sorenson who published their work in *Science* in 1963.[37] About the same time, at the Department of Orthopaedics at Malmö General Hospital, Bo Nilsson was developing a similar apparatus. For completion, he needed a radiation source and therefore travelled to the United States to acquire Americium. The story tells that he did not only keep the purchased piece of Americium in his chest pocket on the flight back home to Sweden but also manually carved out the proper size to fit in his very own SPA densitometer (Figure 7). The legacy of Bo Nilsson, who described his pioneering method in 1964,[202] is ever so vivid and is shown by the numerous publications in the field of bone biology that originate from this department each year.

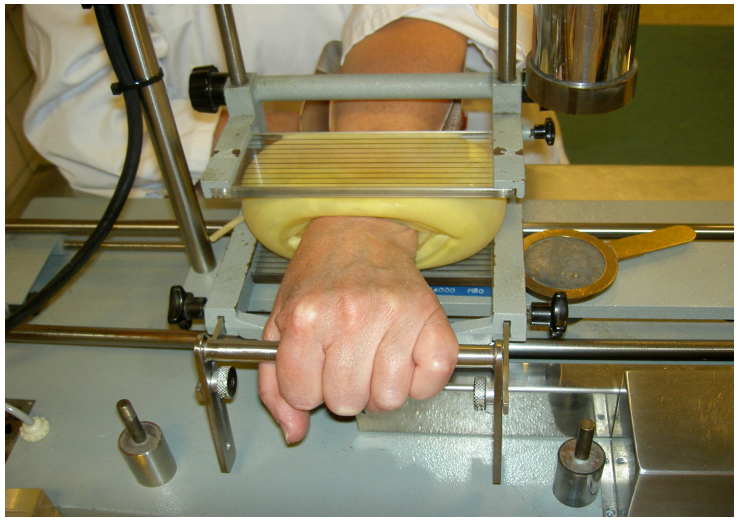

Figure 7. Measurement of bone mineral density by use of single-photon absorptiometry (SPA).

As mentioned above, the SPA technique uses gamma radiation to estimate bone traits. The setup includes a rectilinear scan (source and detector) that is moving across a peripheral bone to be measured.[37, 202, 203] Because of the generated single energy beam, the scan cannot differentiate mineralized tissue from non-mineralized tissue and is therefore most suitable in measuring appendicular skeleton with little soft tissue. The calculation of mineral thickness is dependent on the assumption that (i) non-mineralized tissue is constant and (ii) that its density can be approximated to a water-filled rubber cuff which is placed around the measured limb to compress whatever soft tissue there is surrounding the skeleton to be measured (Figure 7). The mineral thickness can then be estimated by calculating the relation of absorption between the soft and bone tissue. Finally, BMD (g/cm^2) is obtained by multiplying the thickness (cm) by the density of bone mineral (approximately $3g/cm^3$). The accuracy of the SPA method is approximately 9%[198] and the precision 1–2%.[42, 182, 191]

Dual energy X-ray absorptiometry

Since dual energy X-ray absorptiometry (DXA) first was introduced in 1987, it has become the gold standard in bone densitometry. In fact, the 1994 WHO definitions of osteopenia and osteoporosis as difference from reference BMD values in young healthy Caucasian women expressed in standard deviations (T-values) are based on DXA measurements, and still in force.[46] This second-generation densitometry has two obvious advantages compared to its predecessors: first, it does not need the measured region to be strapped in and surrounded by a water-filled cuff and, second, total body measurements are possible. Technically, DXA involves two X-ray beams with different energy. The low-energy beam attenuates soft tissue and the high-energy

beam attenuates both soft and bone tissue.[21] Subtracting the two detected beams results in BMC and divided by area in aBMD. Because of the flatter nature of DXA, no true volumetric density can be obtained. The ionizing radiation from one total body scan is less than one tenth of a chest X-ray, and even lower than the daily background radiation.[205] Primarily, lumbar spine and hip measurements are used in clinical practice, and to most accurately predict fracture, site-specific DXA measurements are needed.[178] By developing an algorithm called Hip Strength Analysis (HSA),[15, 301] additional estimates of femoral neck strength variables have resulted in even better predictions of breaking strength of the femoral neck than aBMD alone.[15, 52, 74] However, DXA measurements can be distorted with degenerative changes in lumbar spine as a recent study found a very low number of women diagnosed with osteoporosis when measured in the L2–L4 region compared with L1–L2 and the femoral neck.[268] The accuracy of DXA ranges from 3–9% and the precision 1–3%, depending on the measured region.[240]

Peripheral quantitative computed tomography

Peripheral quantitative computed tomography (pQCT) belongs to the third-generation of densitometry and has emerged from QCT, which had limited clinical use because of its high radiation dose. As the term implies, this technique enables true volumetric densities of both cortical and trabecular bone. Since pQCT has many easy-to-use features, does not take too much storage, and in combination with its capability for three-dimensional measures and low radiation dose, it has become a true competitor to DXA, at least in research. Recently, a high-resolution system (HR-QCT) has also appeared on the market, a technique that can evaluate the micro architecture down to single trabeculae in trabecular bone. Yet, DXA still earns its position in bone densitometry as it can provide total body scans with low radiation dose, and particularly as the WHO criteria for osteopenia and osteoporosis is still based on DXA values.[46] The accuracy of pQCT is 5–15% and the precision is 2–6%, depending on measured region.[240]

Quantitative ultrasound

Quantitative ultrasound (QUS) evaluation of bone is dependent on ultrasound and not on radiation. It reflects both density and to unknown extent micro architecture hence the term "bone quality" is often used in association with QUS. Yet, the term bone quality is problematic in the sense that it does not really have a solid definition other than a consensus from a National Institutes of Health conference as: *"The sum total of characteristics of the bone that influence the bone's resistance to fracture."*[83] In the context of QUS, the heel is by far the most common region to measure. The technique has a number of advantages as it is inexpensive, harmless, and portable so that it can be stored away, yet it has proven to predict both spine and hip fractures

independently of BMD.[96, 238, 240, 258] However, it has not yet been validated for monitoring therapy.

Natural course of bone – formation to fragility

Bone formation appears to be linear, with small gender differences, and primarily regulated by growth hormone (GH) and insulin-like growth factor-1 (IGF-1) until the onset of pubertal maturation.[55] During puberty both GH and IGF-1 are dramatically increased and driven by a corresponding increase of sex hormones.[181] Before puberty, enlargement of cortical area is predominantly accounted for by periosteal apposition,[13, 61, 288] i.e. the bending and torsional strength is improved as the cortex is located further away from the neutral axis.[242] The boys' skeleton turns out stronger after puberty and there are at least two reasons: (i) boys have a later onset and longer duration of puberty, and hence a longer "window" to be receptive to both endogenous and exogenous growth factors[24, 244] and (ii) from a strength point of view they have a favourable enlargement of the skeleton. Whereas oestrogens limit periosteal bone formation but stimulate endosteal formation in girls, although resulting in a net enlargement of the cortical area but with mass ending up close to the neutral axis, testosterone stimulate periosteal bone formation in boys with corresponding mass ending up further away from the neutral axis.[12, 23, 36] Pubertal maturation affects bone size much more than it does vBMD, and this applies to both sexes.[228] For this reason BMC, and not aBMD, has become the gold standard when measuring mineral accrual in the growing skeleton.[20, 99] It has been suggested that the amount of minerals accrued during two years around puberty accounts for 25% of an individual's total mineral reserve.[9, 10]

Peak bone mass

Peak bone mass (PBM), sometimes also referred to peak bone mineral density (peak BMD), equals the maximum bone mass reached during a lifetime. Peak BMD occurs by the end of the second or third decade, and from there on an annual bone loss of around 0.5–1% follows as a normal course of ageing.[25] There is an apparent sex and site difference as regards the time of skeletal maturation or so-called consolidation; in the adolescent female no further gain occurs in the lumbar spine and femoral neck within 2–4 years post-menarche whereas in the adolescent male gain can be seen in the lumbar spine and the mid-shaft of the femur until 20 years of age, though not as long in femoral neck. Gain in distal radius seems to last longer in both sexes.[272] Generally speaking, in adult men there is a linear negative relationship with age but in women the curve turns steeper at menopause.[2, 84, 87] Based on twin studies, the variance in peak BMD is genetically predetermined at around 60 to 80%.[68, 219, 246, 253] On the other hand, based on the same assumption, this leaves a "window" in pre- and

early pubertal years to influence up to 40% of the variance of peak BMD through other factors such as physical activity, dietary intake, alcohol, smoking, and other lifestyle factors.[23, 137, 244]

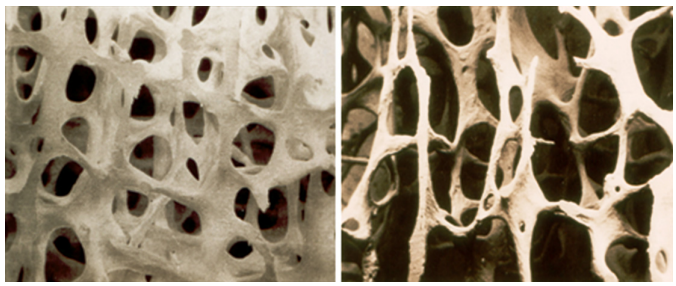

Figure 8. Normal (left) and osteoporotic (right) trabecular bone. (International Osteoporosis Foundation, www.iofbonehealth.org)

Osteoporosis

Even though structural properties have gained increased interest in recent years, peak BMD is, besides age, still regarded as being one of the single most important determinants of osteoporosis.[26, 53, 100, 105, 113, 184] The relation between age, fragility, and certain fractures was first noted in 1824 by Sir Astley Cooper,[48] while the term itself is attributed to the French pathologist Jean Lobstein (even though he most likely was referring to what today is known as osteogenesis imperfecta).[163] Osteoporosis is defined in consensus as: *"a systematic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility, and increased risk of fracture."*[47] Osteoporosis can be classified into: (i) primary (idiopathic) osteoporosis which includes both the early phase of rapid oestrogen-dependent postmenopausal bone loss in women and the slower age-related bone loss seen in both men, and (ii) secondary osteoporosis due to other conditions such as coeliac disease, renal failure, anorexia nervosa, cancers, chronic obstructive pulmonary disease, hyperparathyroidism, and Cushing's syndrome. WHO has defined operational criteria of osteopenia and osteoporosis based on spine and hip DXA measurements in young Caucasian women: ±1 standard deviation (SD) from the mean is considered to be normal, –1 to –2.5 SD is defined as osteopenia, and below –2.5 SD is defined as osteoporosis, or if combined with a fracture as manifested/severe osteoporosis (Figure 9).[46] (The absolute cut-off values for osteoporosis are 0.706 g/cm^2 for hip and 0.907 g/c m^2 for lumbar spine.) Hip fracture incidence increases exponentially with age in the elderly,[127] and in ages above 50 years the male to female ratio is between 1:2 and 1:4,[92, 162] with a much higher mortality rate within a year following a hip fracture in men.[49, 123, 128, 225]

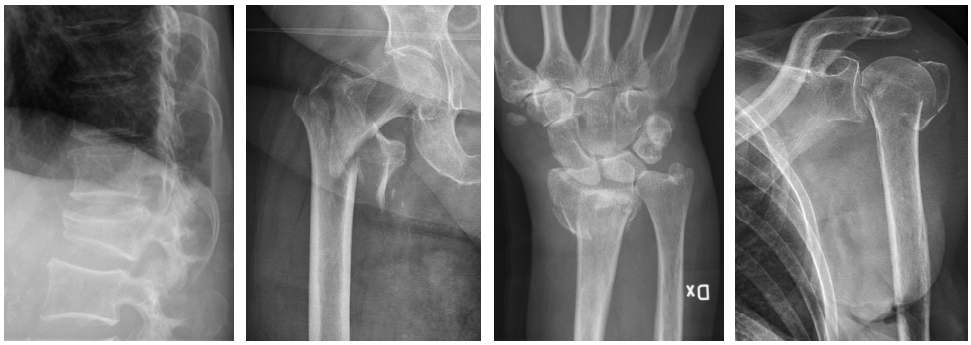

Figure 9. X-rays of typically osteoporotic fracture sites (from left): vertebrae, hip, distal radius, and proximal humerus.

Also, a number of extra-skeletal risk factors (age, fracture history, impaired vision, poor balance, smoking, and low body weight) seems to increase the risk of falling[138, 237] and these risk factors have also, independently of BMD, been shown to predict fragility fractures.[53, 126] The current working definition of osteoporosis does not take structural parameters into account, such as cortical width, which has also been shown in several studies to predict fragility fractures independently of BMD.[3, 54, 60, 245, 255, 266, 289] Last but not least, the very essence of a fragility fracture is that it is accidental by nature and often combined with an abnormal loading to which bone is not adapted, e.g. a direct hit to the hip.[89, 98, 195] For the above reasons, WHO has developed a generalized fracture risk assessment tool called FRAX® whose algorithms give a 10-year probability of fracture.[39]

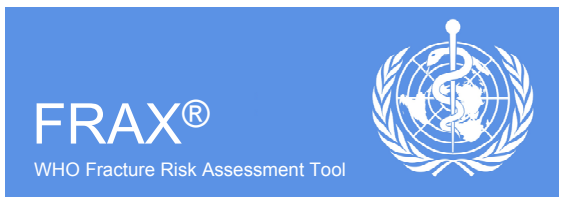

Figure 10. Fracture Risk Assessment Tool has been developed by WHO to estimate country-specific 10-year fracture probability. (WHO, www.shef.ac.uk/frax)

Joints

Articular cartilage and its constituents

Articular cartilage refers to hyaline cartilage and is one of three cartilage types found in the human body. It covers the articular surfaces of bones and is usually found in close contact with menisci and articular discs, both of which belong to a second type of cartilage named fibrocartilage. The third type is called elastic cartilage and is found in the ear and nose. All three types of cartilage are composed of specialized cells called chondroblasts or chondrocytes when caught in an extracellular matrix lying inside spaces called lacunae. Unlike other connective tissues, cartilage lacks blood vessels and is only supplied by diffusion, which is probably why cartilage has limited repair capacity. E.g., damaged hyaline cartilage is usually replaced by fibrocartilage scar tissue. Chondrocytes obtain cartilage integrity by balancing synthesis and degradation of non-cellular matrix molecules, whose relative amount differentiates the three cartilage types from one another. Type II collagen (50–60% dry weight) and proteoglycan (30% of dry weight) are the most abundant molecules.[221] In articular cartilage aggrecan is the most abundant proteoglucan to which at least one negatively charged glycosaminoglycan (GAG) is bound (Figure 11). They interact in turn with hyaluranan to form giant aggregates entrapped in type II collagen networks so that the whole cartilage becomes a tissue of high negative fixed charge density (FCD). This draws cations (mostly Na^+) into the cartilage and, through osmosis, water.

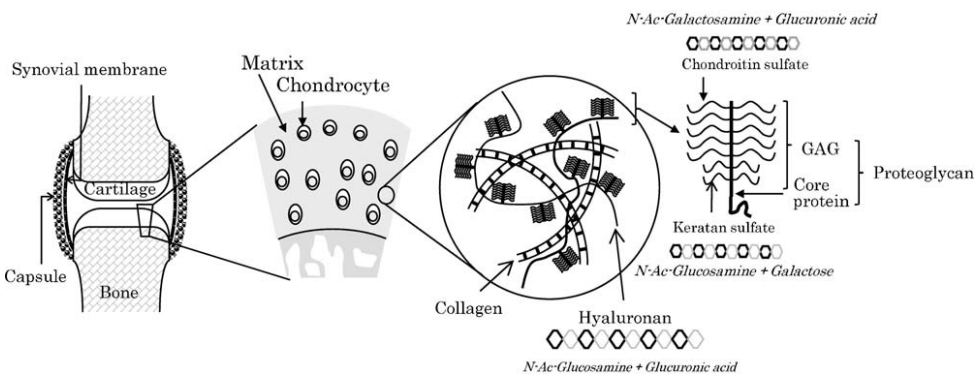

Figure 11. A schematic illustration by H Nakamura of the non-cellular matrix molecules within articular matrix. (Elsevier, www.elsevier.com)

Articular cartilage has two main purposes: (i) to provide low friction within the joint, and (ii) to interplay with adjacent ligament, muscles, menisci, and underlying trabecular bone to participate in energy absorption when the extremity is subjected to forces. The cartilage thickness differs depending on site and sex. Knee cartilage, for instance, varies from 1–6 mm in general but both the total cartilage area and thickness are lower in women.[73] The visco-elastic features of articular cartilage depend on the interaction between aggrecans and type II collagen. The cartilage is arranged in four successive zones – from the low-friction surface to the underlying subchondral bone (Figure 12).[189] Animal studies have shown a correlation between load-bearing, the amount of GAG, and stiffness of articular cartilage.[27, 170, 214] Tiderius et al have shown that exercise increases the amount of GAG in the human knee.[274]

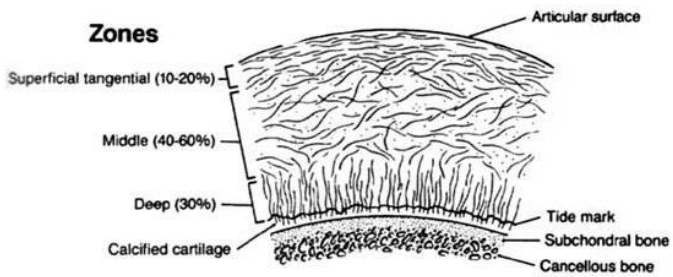

Figure 12. Illustration of the four cartilage zones. Collagen fibres in the superficial zone are oriented parallel to the joint surface indicating that the purpose of this zone may be primarily to resist shear stresses.

Osteoarthritis (OA) – "The oldest disease in the book"

OA is an ancient disease and has been found e.g. in remains of Neanderthals,[56] Egyptian mummies,[28] and Vikings.[34] Today, OA afflicts all races on all continents.[229] The term OA has been in use in English-speaking countries since the beginning of the 20th century. According to WHO, OA belongs to the top ten conditions resulting in most global disease burden and affect 50% of individuals above 65 years of age and 30% of those between 45 and 64 years of age. Yet, the aetiology of idiopathic OA remains unknown.

The inter-person presentation of OA in terms of disease onset, symptoms, joints involved, severity, rate of progress, and prognosis varies substantially; these are some of the reasons why there is neither an existing consensus classification for OA nor a

unifying algorithm for its treatment. Primary symptoms of OA include pain, morning stiffness, impaired function, crepitus, restricted motion, and bony enlargement, which lead to significantly lower quality of life.[110] Of the above symptoms, pain is particularly interesting as it is usually the reason why an individual seeks medical advice. However, the mechanism behind the pain is still unclear. Since worn-away cartilage is aneural, either bone marrow lesions,[75] raised intraosseous pressure, inflammatory synovitis, or an unidentified mechanism may perhaps be causing the pain?[18]

Diagnostics, definitions, and validations in OA

Diagnostics

Conventional radiology can detect joint defects on a macroscopic level such as cartilage loss, osteophyte formation, subchondral sclerosis, and bone cysts, characteristics typically found in OA. Magnetic resonance imaging (MRI) can detect corresponding macroscopic soft tissue defects commonly found in OA, such as ligamentous laxity, malalignment, low-grade synovitis, and degenerative meniscal tears.[18, 43] In recent years, MRI also has become useful in detecting bony defects that previously either were detected too late to treat such as osteonecrosis/osteochondritis dissecans, or not at all such as traumatic bone marrow lesions (BML) or "bone bruises", which have proven to (i) be involved in first-stage OA, (ii) cause additional pain in developed-stage OA, and (iii) to be a predictor of OA progression.[65, 115, 277]

On a molecular level, OA includes GAG loss and disruption of collagen network, starting at the superficial layer, leading to cartilage swelling and fragility,[101, 109, 177, 221] parallel to change in cartilage colour from blue to yellow. Whereas traditional MRI is limited to macroscopic cartilage defects and arthroscopy has the disadvantage of being invasive, a new quantitative technique has been developed called qMRI which enables assessments of articular cartilage on a microscopic level, i.e. molecules such as type II collagen and GAGs. One example of qMRI is a method called delayed gadolinium-enhanced MRI imaging of cartilage (dGEMRIC).[11, 33] It uses Gd-DTA^{2-}, a negatively charged contrast medium which is inversely proportionate to the negatively charged GAGs in the non-cellular matrix. The healthier the cartilage the more GAGs and less contrast medium are found in the cartilage. Low dGEMRIC values have been shown to predict knee OA.[212] dGEMRIC has also demonstrated parallel degeneration of knee cartilage and meniscus, highlighting the simultaneous pan-articular changes that occur, even at the very early stages of OA.[155]

Definition(s)

Although no universal definition exists, most authors agree that OA can be defined as a chronic, non-inflammatory joint disorder involving cartilage destruction. There are at least five ways to describe OA, all of which approach the condition from different angles:

- Histological: the progress has been categorized according to the Mankin score.[174] In short, progress is scaled from 0 (best) to 13 (worst) and describes the aggrecan degradation and ultimately even alteration in cartilage configuration.
- Self-query (self-administered questionnaire): either general (EQ5D) or joint-specific (HOOS, KOOS) symptom-based questionnaires have been used to diagnose and estimate severity of OA. In this context, patients may also be asked the straightforward question whether or not they have been physician-diagnosed with OA.
- Radiographic: the most commonly used classifications in clinical practice today are those of Kellgren and Lawrence (0–4)[140] and Ahlbäck (0–6),[1] both of which include joint-space narrowing (JSN), osteophyte formation, and subchondral sclerosis
- Arthroscopic: a direct view and feel of the cartilage, but major drawbacks, if only for diagnostic purposes, include the large inter-observer variability and the fact that the method is invasive.
- Clinical: the diagnosis of OA in clinical practice is usually based on a combination of conventional radiology, anamnesis, and examining the patient.

Validation tools

To address the main indications for arthroplasty surgery such as pain, instability (in knee OA), and impaired health-related quality of life (HRQoL), evaluation scores/outcome scores/patient-reported outcome measures (PROM) are widely used. PROMs are used not only as a basis for diagnostics and choice of treatment but, ever so important, also to determine the efficacy of the treatment chosen, in order to offer continued best clinical practice. The rationale behind the increasing use of PROM, even though it may be hard to admit, was aptly phrased by Berwick in a British Medical Journal editorial: "*Sociologically, professions tend to reserve the right to judge the 'quality' of their own work.*"[19] The most frequently used generic HRQoL tool is called the Short Form (36) Health Survey (SF-36) and consists of eight dimensions. It was originally developed and is still run by QualityMetric in USA.[290] A shortened version, consisting of five dimensions, is called EQ-5D and was originally developed and is

still run by the EuroQol Group in Europe.[270] They are both considered examples of a general generic HRQoL tools. Examples of joint-specific scores are the Harris hip score (HHS),[97] the Hip disability and Osteoarthritis Outcome Score (HOOS)[201] for the hip, and examples of corresponding scores for the knee are the Knee injury and Osteoarthritis Outcome Score (KOOS),[235] the Lysholm knee score,[169] and the Tegner activity scale,[267] and for both joints the Western Ontario and McMaster Universities Osteoarthritis (WOMAC)[16] is applicable. The Osteoarthritis Research Society International (OARSI) has proposed guidelines for the management of hip and knee OA including the importance of physiotherapy. Prompted by the findings of poor compliance with international as well as national guidelines ahead of total joint replacement as regards physiotherapy, patient education, exercise, and weight control,[45, 302] a project called "Better management of patients with Osteoarthritis" (BOA) was started in 2008 in collaboration between four healthcare councils in Sweden and has since spread nationwide.[22] The aim is to offer every patient with OA adequate information and exercise according to evidence-based recommendations, and that surgical interventions should only be considered if non-surgical treatment has been tried and failed. The goal is to reduce the need for health care and sick leave due to OA, as well as to increase the quality of life and level of independence and physical activity among patients with OA in the hip or knee. The linked BOA register is at this point in time primarily a tool for evaluating the BOA project itself by a standardized questionnaire at the first visit, after 3 and 12 months (evaluation is ongoing and therefore no data are available).

The Swedish National Board of Health and Welfare, in its guidelines for musculoskeletal diseases, has further advised against performing arthroscopic knee surgery in the form of joint lavage with a meniscectomy in the case of OA.[271] As for the hip, though promising short-term results on pain and range of motion with arthroscopic treatment of labral tears and other impingement conditions,[183, 247] there is as yet no evidence in the literature to show this procedure has any long-term beneficial effects as regards development and progression of hip OA. Total joint replacement is considered the gold standard when non-surgical treatment no longer is manageable in progressive OA. Though the overall results of total joint replacement have shown to be outstanding, there are still around 10% of the patients who do not respond or even respond negatively one year after surgery. Charnley category C, female sex, and prevalence of anxiety or depressive disorders have shown to be associated with inferior pain reduction and EQ-5D score at one-year follow-up[8, 233] and may therefore be considered, and discussed with the patient, before proceeding with surgery.

The Swedish Knee Arthroplasty Register was initiated in 1975[265] and the Swedish Hip Arthroplasty Register followed in 1979.[264] Though a number of countries now have their own registers, the Swedish registers are considered pioneers in this field with the longest-follow-up periods for many of the prosthesis designs still in use

today. Their main purposes have been to monitor the technical aspects related to surgery, such as surgical technique, the performance of different implants, prophylactic measures, and environment in the operation theatre. Through experiences drawn from the Swedish Hip Arthroplasty Register, Malchau has emphasized the importance of a stepwise introduction of new technologies, i.e. in the same manner as for the introduction of any new drug.[173]

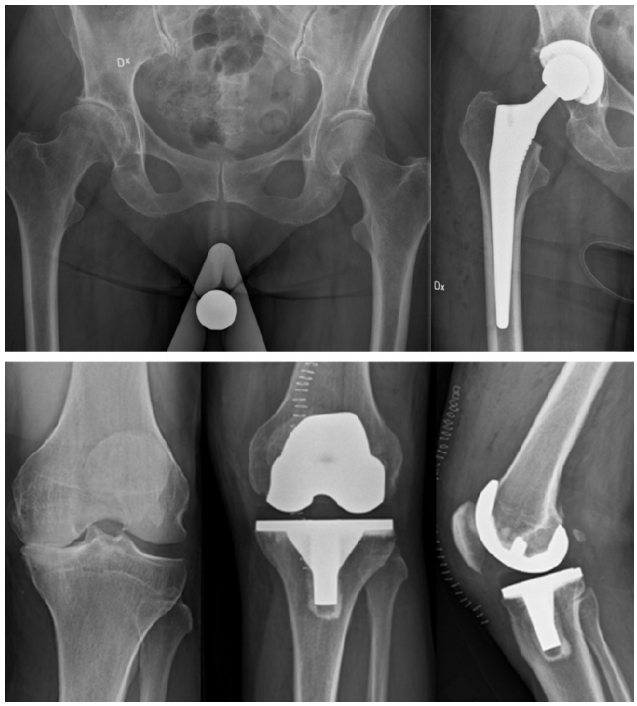

Figure 13. X-ray of hip OA treated with a THA (first row), and knee OA treated with a TKA (second row).

Mechanical theories on the "natural" course of OA

"Wear and tear" has been the most longstanding biomechanical theory in an attempt to explain the pathogenesis of OA, where ageing is simply the accumulation of joint loading cycles over a lifetime.[223] The first histological reflection of cartilage wear due to mechanical load was described by A. Ecker of Heidelberg in 1843 and it was John Kent Spender in England who in 1886 first coined the term *osteoarthritis*. It was not until the second half of the 20th century that the term OA was challenged by the term *degenerative joint disease*, which in many ways better summarizes the condition.

The expression is largely due to the work of Walter Bauer and co-workers at Harvard University in 1942, where they proposed that the disease is characterized by degeneration of cartilage but the course of degeneration is very much influenced by the response of adjacent tissues.

"The tissue homeostasis theory" was introduced by Dye in which he implies that the joint acts as a biological transmission and redirects mechanical loads.[64] When intense biomechanical long-term stress and micro injuries are added to the joint, the redirection of loads may be insufficient, and if the process continues it will lead to joint failure.[64, 116, 156, 223] Epidemiological studies support this view, reporting an association both between hip OA and heavy occupations such as shipyard work, mining, and farming and also between knee OA and occupations that include squatting and kneeling such as carpeting and floor laying.[294, 295] Football, rugby, soccer, handball, and ice hockey are all sports with high impact and torsion of the lower limb, and therefore suggested to be at high risk of developing OA.[30, 156]

"The muscle dysfunction theory" may be seen as a refined biomechanical hypothesis of the two mentioned above, in which Hurley suggests that muscles may be the main force absorbers of the joint.[116] The hypothesis may partly explain the beneficial effect of moderate exercise on lower limb joints.[236, 249, 252, 260] In this model, any type of muscle dysfunction seen, for example, with ageing, fatigue, or loss of proprioception caused by ligament tears and other types of soft tissue joint injuries would be the main local mediating factor for developing OA. Likewise, vigorous exercise has been reported to be associated with clinical or subclinical soft tissue injuries around the hip[59, 175, 248] and knee,[166, 192, 197] which may lead to either direct joint damage or prolonged joint deterioration.[116, 185, 192, 223]

In recent years, and parallel to the introduction of qMRI, there has been a shift in thinking of OA from purely an irreversible and passive degenerative disorder, for which there is no treatment, to the realization that it is indeed a highly active process where most of the radiographic signs seen in OA in fact are attempts to repair/replace damaged joint functions. Efforts have been made to modulate the disease progress through both biomechanical and biochemical interventions, of which an example of the former is the above-mentioned project called "Better management of patients with Osteoarthritis" (BOA), a habilitation programme that is under validation.

Risk factors for development and progression of OA

The cause of OA is not fully understood, but the multifactorial background and some risk factors have been highlighted, with age often being regarded as the dominant risk factor.[7] Systemic factors are often described as predisposing degenerative joint

changes, whereas local mechanical factors determine the distribution and the severity of the disease.[166, 223]

The prevalence of hip and knee OA increases proportionally with age in both sexes, though knee OA in women increases at a higher pace than in men.[209] Apart from age and female sex, there is evidence indicating that genetics contribute to around 50% of the variability in susceptibility to hip and knee OA.[117, 159, 257] There is evidence of ethnicity being a risk factor for OA. Comparative population studies in the US have indicated a ten times higher risk of hip OA among Caucasians compared with Chinese.[196] Furthermore, whereas no between-group risk difference was seen in men, Chinese women were at greater risk of knee OA than were Caucasian women.[303] However, Caucasian and African-American living in the US have shown to be at the same risk for both hip and knee OA.[5, 269]

Obesity is among the strongest risk factors for knee OA, whereas the correlation with hip OA is weaker.[76] Certain occupations have also been associated with an increased prevalence of OA, of which a classic example is that of the association seen between farmers and hip OA.[295] Kneeling and heavy lifting seem to be associated with knee OA.[294] Joint injuries of any kind are strongly associated with OA, either due to joint incongruence after fracture or soft tissue (cartilage, cruciate ligament, meniscal) damage after accidental or continuous high impact and torsional loads.[30, 156] Joint deformity such as congenital dislocation of the hip (CDH), Perthes' disease, and slipped capital femoral epiphysis (SCFE) are associated with early hip OA.[30]

Whereas risk factors for developing OA are thoroughly studied, not so much has been written about potential risk factors of disease progression. Established hip OA seems to progress more rapidly in women than in men,[58, 161] but no such gender discrepancy has been found for knee OA.[77, 241] Known risk factors for progression that apply to both sexes and both hip and knee OA include obesity, focal cartilage defects, BML, recurrent inflammation, and advanced radiographic signs of OA.[18, 51, 65, 167, 241] Malalignment and meniscal pathology are risk factors for progression in knee OA, and superolateral migration and atrophic bone response in hip OA.[41, 65]

Effects of exercise

Decreased osteogenic response with age

Bone traits

The osteogenic response to load stimuli decreases after puberty. This has been demonstrated by Sundberg et al. in a study on boys, 13 and 16 years old, with a history of moderate exercise. BMD was higher in both subject groups compared with their respective sedentary controls, but whereas a larger bone size was found in the 13-year-old subjects no between-group difference was seen in the 16-year-olds.[259] These findings of a higher BMD without enlargement of the skeleton have also been found in male military recruits,[176] supporting the view of a less favourable exercise-associated bone adaptation (i.e. endocortical/medullar contraction instead of a periosteal apposition/expansion) in terms of strength in the post-pubertal period. The need for high-level physical activity in order to obtain bone effects of biological significance in the post-pubertal period has also been show in young female soccer players.[286, 287]

The association between exercise and beneficial bone effects seems to decrease with age, as interventional studies have only shown around 3–4% gain in BMD in middle-aged men and women[139, 165] and 1–2% or in some instances even a loss in elderly cohorts.[141, 160] This low osteogenic response to mechanical stimuli has also been reproduced in an animal study which showed a 16-fold less relative overall bone formation and five-fold less relative bone-forming surface capacity in old versus young rats.[283] Kontulainen et al. have demonstrated the potential fallacy in only measuring BMD by comparing DXA measurements of the humeral shaft with strength analysis at the same site derived from pQCT in racquet-sport-playing girls. They found on average 36% lower benefits in BMD compared to BSI,[151] it has therefore even been proposed that re-evaluation of numerous longitudinal studies of moderate exercise performed in individuals in mid to old age is needed.[119] However, the potential association between exercise and improved bone geometry that has been seen in young adults does not necessarily have to be the case later in life.[200, 220, 261]

Fracture

With no falls, there are very few fractures. Also, only 5% of all falls lead to a fracture,[276] which may be why no RCTs, only observational and case-controlled studies, have been conducted that evaluate physical activity with fracture as end-point variable. Nevertheless, it seems as if fracture is inversely associated with exercise, with the highest correlation with hip fracture in women[53, 90, 213] and lowest in any fragility

fracture in men.[90, 121, 251] The explanation is of course multifactorial as exercise also affects muscle strength, reaction time, balance, and coordination, all beneficial in reducing falls and thereby fracture.[53, 186, 237, 250]

Increased joint deterioration with dose

A general conception today is that muscles play a vital role as the main force absorbers of the joint.[116] I.e., any type of muscle dysfunction seen, for example, with ageing, fatigue, or loss of proprioception caused by ligament tears and other types of soft tissue joint injuries would hence be the main local mediating factor for developing OA. Likewise, vigorous exercise, which has been reportedly associated with clinical or subclinical soft tissue injuries around the hip[59, 175, 248] or knee[166, 192, 197] may lead to either direct joint damage or prolonged joint deterioration, both of which could result in symptomatic OA.[116, 223] On the other hand, moderate exercise seems not to harm[214, 236, 249, 260] or even lowers the risk of OA.[252, 254] A recent report found a linear correlation between the extent of long-distance skiing and severe OA,[185] whereas intense running has been inferred to increase the risk,[179, 236, 296] not alter the risk,[143, 147, 158, 215] or even reduce the risk of hip OA.[254] The contradictory findings in long-distance runners may be found in differences in age as endurance-type exercise such as skiing, running, cycling, and canoeing seems dose-dependent,[154, 156, 185, 295] suggesting that long-term repeated biomechanical stress and muscle fatigue may also be critical for development of OA.[116] This view was further supported by the finding that symptomatic OA associated with these types of exercises seems to appear at a later age than does corresponding OA secondary to a macroscopic soft tissue injury such as ACL or meniscal tears which is more frequently association with team sports.[143, 156]

Different exercises exert different responses

Response

It is somewhat ironic that the types of exercise most effective in bone formation,[62, 130, 279] i.e. high-magnitude, high-intense, and odd-impact loadings from different directions such as football, rugby, soccer, handball, and ice hockey seem to be most devastating for the adjacent joint.[30, 64, 156] Although there seems to be a higher fracture risk while participating in these sports,[44, 136] the beneficial effects in bone traits are obvious compared with repetitive low-impact exercise such as cycling, and especially repetitive non-impact swimming.[62] There are even proofs in the literature of a negative effect on bone for both professional cycling[38] and swimming.[78]

In contrast, the mentioned impact/team sports are associated with high risk of soft tissue knee injuries, i.e. anterior cruciate ligament (ACL) and meniscal tears, and more so than non-impact/non-team sports.[166] Female athletes seem to be at higher risk, as e.g. Hewett et al. showed a 4–6 times higher frequency of ACL injuries in women than their male counterparts practising the same sport.[106, 107] Serious soft tissue hip injuries are rarely reported compared with soft tissue knee injuries,[59] but minor muscle sprains, ligament or labral damage are likely to accompany elite sporting activities, and underreporting may be the reason why a physician-diagnosed hip injury does not seem to be a necessary precursor of hip OA.[59, 86, 175, 248] Kostogiannis et al. divided individuals with ACL injuries into two cohorts, those who had participated in a team sport and those who had done downhill skiing[154] (in sports medicine typically examples of impact/contact vs non-impact/non-contact sports). They proposed that the former had sustained a compression-type injury and the latter a distraction-type injury, and found that having participated in impact sports led to more short- and long-term meniscal tears as well as ACL reconstructions. The finding of combined soft tissue knee injuries has been repeated in several studies.[79, 143, 194, 208]

Recovery

With the above considerations in mind, it is likely that neuromuscular function plays a critical role for bone health, on a cellular level to mediate osteogenic stimuli[91] and on a human level to reduce the risk of falling and fracture,[120] as well as for joint health to absorb and redirect forces to reduce the risk of micro and macro injuries within the low-friction articular cartilage.[106, 107, 116] It is therefore vital to obtain adequate neuromuscular function at all times, whether it is in pursuing moderate or vigorous type of exercises. While Tiderius et al. have shown the adaptive capacity of articular cartilage by increasing its GAG content,[274] it has also been shown that meniscal tear is associated with reduced muscle function.[234] Furthermore, it has been stated that every fifth injury in the industrialized part of the world is associated with recreational or sporting exercise.[275] Ekstrand et al. investigated injury patterns in professional soccer players and found that more than 90% affected the four major muscle groups in the lower limb,[69] typically resulting in thigh and knee sprain. The same research group has also clarified the hazard of muscle fatigue and overuse by showing that injuries tend to increase with time within each half of the game,[70] and that the risk of re-injury is almost tripled from one season to another, in addition to the significantly longer recovery periods compared with the corresponding initial injury.[95, 285] A meta-analysis study of recovery strategies was recently performed by Nedelec et al. in which they reviewed nutritional intake, cold water immersion, sleeping, active recovery, stretching, compression garments, massage, and electrical stimulation, and found only evidence for beneficial effect of the first three.[193]

Objectives

General aim

All interventional and prospective observational studies that have followed changes in BMD with retirement from sports have been short-term, most of them with a higher BMD loss than expected with age. Retrospective studies on fracture incidence and OA prevalence in former sportsmen have been inconclusive. Little is known about the association between types of exercises in young age and risk of prevalent hip or knee arthroplasty in old age. Therefore, the four main aims of the thesis were to investigate whether any long-terms effects of exercise in youth were to be seen in: (i) bone traits, (ii) fractures, (iii) hip and knee OA, and (IV) hip and knee arthroplasty.

Specific aims

Study I: To define bone characteristics in active male athletes and then follow them for four decades into long-term retirement from sports to determine whether any exercise-associated residual benefits are maintained in old age.

Study II: To evaluate the influence of type of exercise and the risk of developing hip or knee OA, with and without a previous soft tissue knee injury, and the risk of having a corresponding arthroplasty procedure in former male sportsmen.

Study III: To assess the lifetime distribution and risk of fracture during and after active exercise career in male sportsmen.

Study IV: To evaluate changes in bone characteristics in relation to increasing age in active and former male soccer players, and to assess the fracture risk in former male soccer players.

Subjects and methods

Subjects

Study design

Paper I

Prospective controlled cohort study; active and former male elite athletes (n=46) and controls (n=24). Level of evidence, 2.[299]

Paper II

Retrospective controlled cohort study; former male elite athletes (n=709) and controls (n=1368). Level of evidence, 3.[299]

Paper III

Retrospective controlled cohort study; former male elite athletes (n=709) and controls (n=1368). Level of evidence, 3.[299]

Paper IV

Sub-study 1: Cross-sectional controlled cohort study; active and former male elite soccer players (n=193) and controls (n=280). Level of evidence, 2.[299]

Sub-study II: Retrospective controlled cohort study; former male elite soccer players (n=397) and controls (n=1368). Level of evidence, 3.[299]

Subject selection

Paper I

At baseline, in 1968, a cohort was formed by identifying 64 active nationally or internationally ranked male athletes from southern Sweden, all of whom were Caucasian without any diseases or medications known to affect bone metabolism. A control cohort was formed by including 39 non-athletic men. They were all healthy

Caucasian volunteers, from the same geographic region, and of an age similar to the athletes. Bone mineral density was reported higher at baseline in the athletic cohort than in the control cohort.[203]

After a mean 39 years (range 38–40), we conducted a non-pre-planned follow-up. Five athletes and four controls had died, three athletes and four controls had relocated, six athletes and four controls could not be located, three athletes and one control were unable to attend due to illness, and one athlete and two controls did not want to participate for personal reasons (Figure 14). This rendered 46 former male athletes (20 runners, 12 soccer players, 8 swimmers, and 6 weightlifters) aged a mean 22 years (range 15–40) at baseline and a mean 61 years (range 53–79) at follow-up, with duration of retirement from sport a mean 29 years (range 10–58). The 24 controls were a mean 24 years (range 14–36) at baseline and 63 years (range 53–76) old at follow-up.

All athletes had started regular training before puberty, and during their competitive career they had spent on average 11 h (range 3–25) of training per week until retirement from sports. The participation rate was 72% in the athlete cohort and 62% in the control cohort.

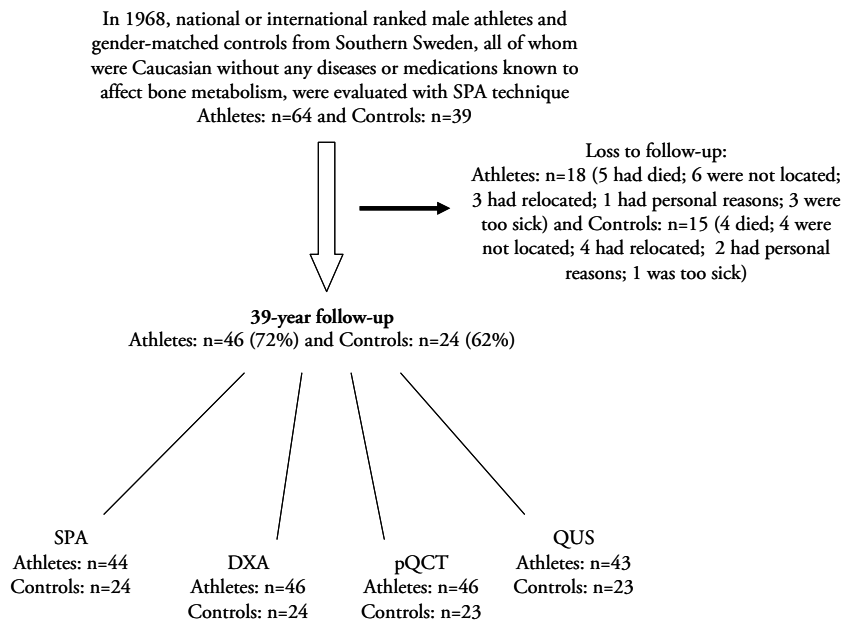

Figure 14. Flowchart detailing the inclusions and losses to follow-up (Paper I).

Papers II and III

The subjects were 709 former internationally or nationally ranked male athletes, all found in either a review book of former Swedish elite athletes (detected from enclosed trading cards of a tablet box called "Alfa pastill," which was popular in Sweden around the mid 20th century) (Figure 15), the archives of the Swedish Olympic Committee, or from a previously published study of male elite athletes.[203] The former athletes had a mean age of 69 years (range 50–93) and had retired from competitive sports a mean 34 years (range 1–63) earlier. There were 397 former soccer players, 147 handball players, and 69 ice hockey players, all classified as having participated in impact sports. There were also 43 canoeists, 20 long-distance runners, 9 weightlifters, 8 gymnasts, 8 swimmers, 6 biathletes, and 2 racing cyclists, all classified as having participated in non-impact sports. Among the 96 non-impact athletes, 64 were former Olympic competitors. From the Swedish national computerized population records, two male controls were matched to each athlete, by sex and date of birth, with their names standing closest to the former athlete in the national register. The primary response rate was 74% for the former athletes and 64% for the controls. As our aim was to include 2 controls for every athlete, we invited the second closest individual in the register in those athletes without two controls in addition to the controls from the Nilsson study.[203] This rendered 1368 control participants aged a mean 70 years (range 51–93), of whom 619 had participated in recreational exercise in their youth.

Figure 15. A tablet box with a story. From the enclosed trading cards on elite athltes came the idea to collect all of them into a review book of former Swedish elite athletes, a book from which many of the participants in this thesis were found.

Paper IV

This report included two sub-studies, first (I) a cross-sectional cohort design study that evaluated musculoskeletal features and second (II) a retrospective cohort design study that evaluated lifetime fracture risk.

In sub-study I, we invited 193 active and retired male soccer players at international or national level, aged between 18 and 85 years of age, and 280 age-matched controls to be measured with the DXA technique. All participants below age 86 years were invited to a second measurement. Among the soccer players, 136 attended a second measurement, resulting in a total of 329 measurements, while the corresponding numbers for the control cohort were 170 re-measurements, resulting in a total of 450 measurements. All examinations were performed in individuals aged between 18 and 85 years of age. The re-measurements were performed a mean 5 years (range 2–8) after the first measurement.

The mean age for termination of active soccer career in former athletes was 30 years and this age was used for cut-off when defining activity and retirement from sports. In other words, we excluded those who classified themselves as active players if they were over 30 and those who classified themselves as retired players if they were 30 years old or younger. This resulted in an exclusion of 8 players aged >30 years who still pursued their active career, 16 players aged ≤30 years who had terminated their career. We also excluded 7 players who had not given information regarding their retirement status. This left 79 active soccer players with a mean age of 23 years (range 18–30) and 219 former soccer players with a mean age of 56 years (range 31–85). The former soccer players were then stratified into four sub-cohorts by 10-year intervals of retirement from active career. For each of these strata a control cohort was set by assigning controls with an age within two standard deviations (SD) from the mean age of the retired soccer players in that particular stratum.

In sub-study II, we evaluated fracture history retrospectively in 397 former male elite soccer players with a mean age of 69 years (range 53–93 years) who had retired from regular sports a mean 33 years (range 1–63) earlier. The study protocol was identical to that in paper II and III, rendering an inclusion of 1368 controls aged a mean 70 years (range 51–93 years), of whom 619 had participated in recreational exercise in their youth.

Methods

Self-queries

A questionnaire was used to collect information about anthropometry, lifestyle, especially the amount of earlier exercise history. Though not validated, the form has been used in several previous studies.[136, 206] To the questionnaire used in papers **III** and **IV**, a detailed section to capture fracture history was added, and also validated.[125] To the questionnaire used in paper **II**, a detailed section to capture prior injury and/or prevalent degeneration (i.e., fracture, soft tissue joint injury, OA, arthroplasty) to hip and/or knee was added, but not validated (Appendix 1).

Anthropometry, lifestyle, and exercise (Paper I–IV)

Data on height and weight was measured at baseline and follow-up in papers **I** and **IV** by standard equipment. Anthropometry data was self-reported in papers **II** and **III**.

Lifestyle data on diet, alcohol, coffee, and smoking habits, as well as history of medical conditions were included in the self-query, as was data on exercise and load such as occupation, aspects of work retirement, timeline of exercise career, and weekly hours of training both when active and at the time of the study when retired. Paper **I** also included retrospectively self-reported data on more than 20 years of exercise preceding the follow-up evaluation.

Epidemiology of lifetime damage to the hip and knee (Paper II)

Eight athletes and 21 controls had sustained a hip fracture and 4 athletes and 7 controls a knee fracture – altogether 40 individuals were therefore excluded in the analyses of "Prevalent Hip or Knee Osteoarthritis and Hip or Knee Arthroplasty". Those who had not answered whether they had been diagnosed with hip or knee OA and/or whether they had undergone THA or TKA procedure were also excluded in that specific evaluation.

Excluded in the analyses of "Prevalent Hip Osteoarthritis and Hip Arthroplasty" were 29 individuals with a history of hip fracture, and, depending on the specific estimation, those who had not answered whether they had been diagnosed with hip OA and/or whether they had undergone a THA procedure.

Excluded in the analyses of "History of Soft Tissue Knee Injury and Prevalence of Knee Osteoarthritis and Knee Arthroplasty" were 11 individuals with a history of knee fracture, and, depending on the specific estimation, those who had not answered

whether they had been diagnosed with a soft tissue knee injury or knee OA and/or whether they had undergone a TKA procedure.

No validation was done in relation to the Swedish hip- and knee arthroplasty registers or medical journals.

Epidemiology of lifetime fracture distribution (Paper III and IV)

A fracture before active career was defined as occurring before age 15 years, during active career as occurring between ages 15 and 35 years, and after active career as occurring at an older age than 35 years. The limits chosen were the mean ages for initiation and termination of competitive career in papers **III** and **IV**. A fragility fracture was defined as a facture of the proximal humerus, distal radius, spine, pelvis, hip, or tibial condyle sustained after age 50 years. It was not possible through the questionnaires to evaluate whether the fracture was a low-energy-related fracture or not.

Non-invasive bone assessments

Single-photon absorptiometry (Paper 1)

In paper **I**, single-photon absorptiometry (SPA) measurements were used both at baseline and at follow-up. At baseline, the distal femur of the dominant leg was measured ten times and the estimated bone mineral density (BMD; g/cm^2) was calculated as the average value of all ten measurements.[203] At follow-up the radii and ulnae of both arms were measured, and the estimated bone mineral density (BMD; g/cm^2) was calculated as the average value of all four bones.[191] The BMD coefficient of variation (CV) was 2% with a standardized phantom and *in vivo* 4% determined by duplicate measurements after repositioning in 20 subjects. The long-term drift was 0.1%/year [95% confidence intervals (CI), –0.2, 0.4], evaluated by a standardized phantom every second week.[3] One of the authors analysed all plots.

Dual X-ray absorptiometry (Paper I and IV)

In papers **I** (follow-up) and **IV** (sub-study II), dual X-ray absorptiometry (DXA) (Lunar® DPX-L scanner, software version 1.3z; Lunar, Madison, WI, USA) was used to evaluate area as well as bone, lean, and fat mass in different regions using either of the supplied total body, spine, or hip software. Daily calibration of the apparatus was done with the Lunar® phantom. The CV evaluated in 14 individuals after repositioning was 0.4–3.0% depending on the measured region. Two technicians performed and analysed all scans.

Peripheral quantitative computed tomography (Paper I)

Peripheral quantitative computed tomography (pQCT) (XCT 2000 L scanner, software version 6.00 B 00.61; Stratec, Pforzheim, Germany) was used to evaluate volumetric bone mineral density (vBMD; g/cm^3) and structural parameters of the tibia (Paper **I**, follow-up). A scout view determined the 4% and 38% level from the ankle joint in both extremities, after which, both trabecular (4%) and cortical (38%) mean bone trait values were measured. Daily calibration of the apparatus was done with a standard phantom. The CV evaluated in 14 individuals after repositioning was 1.0–1.7% for vBMD depending on the measured region. One technician performed and analysed all scans.

Quantitative ultrasound (Paper I)

Quantitative ultrasound (QUS) measurements of the heel were performed using the Achilles InSight® (Lunar, Madison, WI, USA device (Paper I, follow-up). Two parameters were extracted from this instrument: broadband ultrasonic attenuation (BUA; dB/MHz) and speed of sound (SOS; m/s). The CV evaluated in 14 individuals after repositioning was 2.2% for BUA and 0.3% for SOS. Three technicians performed and analysed all scans.

Ethics

Each study in this dissertation was approved by the Ethics Committee of Lund University and conducted in accordance with the Helsinki Declaration. Informed written consent was obtained from all participants prior to study start.

Statistical analysis

Statistical calculations were performed with Statistica®, version 7.1 (StatSoft®, Tulsa, OK, USA) and with IBM® SPSS® Statisitics, version 20 (IBM Corporation, Armonk, NY, USA). The cohorts were considered normally distributed when being evaluated by Shapiro-Wilk test (Papers **I–IV**). Non-adjusted between-group differences were evaluated using chi-square test and Student's *t* test, whereas ANCOVA was used when adjusting for differences in anthropometry and lifestyle characteristics (Papers **I** and **IV**).

We also calculated and compared Z-scores, i.e. the number of standard deviations above or below the age-predicted mean derived by linear regression using data from the control cohort (Papers **I** and **IV**). In Paper **I**, we calculated Z-scores for the athletes at baseline by using the baseline control cohort as reference and Z-scores for

the athletes at follow-up by using the control cohort at follow-up as reference population. Pearson's correlation coefficient was used to correlate BMD at follow-up with years since retirement. In paper **IV**, we used two control references as a basis for the Z-score calculations, those stratified into either below or above 30 years of age.

Odds ratios (OR) for developing OA or having an arthroplasty surgery was estimated by logistic regression in different models adjusted for combinations of age, body mass index (BMI; kg/m^2), occupational load, and previous physician-diagnosed soft tissue knee injury (Paper **II**).

Between-group differences in time to first fracture were calculated using Kaplan Meier survival analyses and Log Rank test. The fracture rates and rate ratios (RR) were estimated using Poisson distribution. Cox proportional hazards regression was used for calculations of lifestyle-adjusted hazard ratios (HR) (Papers **III** and **IV**).

Data are presented as means with either standard deviations (SD) or 95% confidence intervals (95% CI) or as numbers with proportions (%). A $p < 0.05$ was considered a statistically significant difference (Papers **I–IV**).

Results

Paper I

There was no group difference in anthropometry either at baseline or at follow-up. At follow-up, there was a higher proportion of blue-collar workers (p=0.009) and smokers among controls (p=0.03).

The BMD Z-score in athletes at baseline was 1.0 (95% CI 0.7, 1.4) in the femoral condyles and at follow-up between 0.5 and 1.2 depending on the measuring technique and the measured region (all $p<0.05$) (Figure 16). The between-group difference remained after controlling for both anthropometry and lifestyle factors. There were no changes in BMD Z-scores during the follow-up, neither when BMD was estimated by the same SPA apparatus, at baseline in the femoral condyles and at follow-up in the distal radius [Δ Z-score −0.3 (−0.8, 0.2)], nor when BMD was estimated in the lower extremity but with different techniques, at baseline by SPA in the femoral condyles and at follow-up by DXA in the legs [Δ Z-score 0.0 (−0.4, 0.4)]. There were no correlations between years since retirement and BMD measurements at follow-up. At follow-up, the tibial cortical area was larger in former athletes than in controls with a Z-score of 0.8 (0.5, 1.2) as was the tibial strength index with a Z-score of 0.7 (0.4, 1.0).

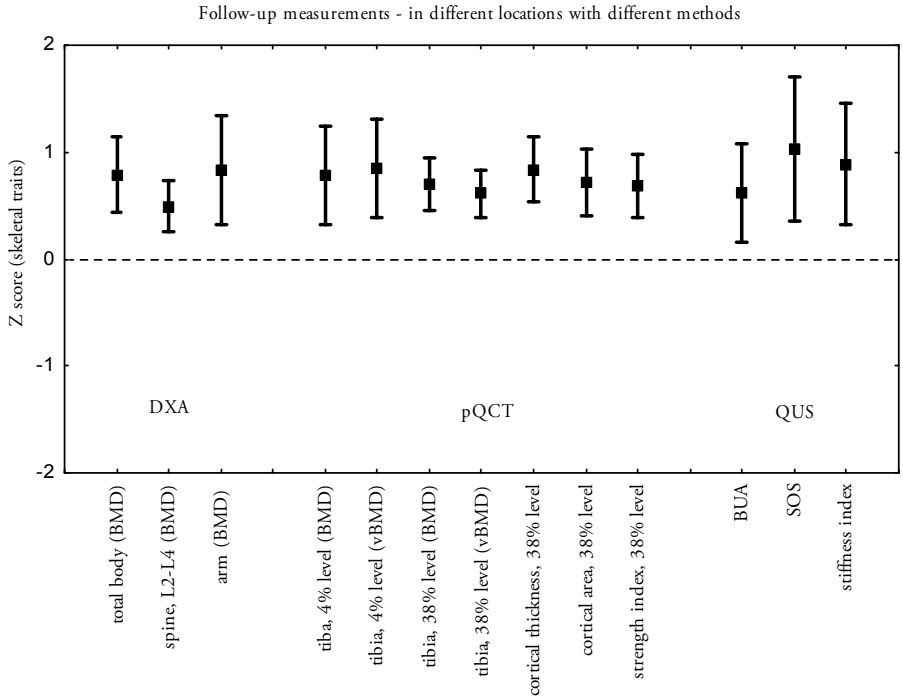

Figure 16. Follow-up measurements in Paper I of different bone traits evaluated with different techniques — BMD, vBMD, bone size, broadband ultrasonic attenuation (BUA), speed of sound (SOS), and stiffness index (si) measured by DXA, pQCT, and QUS.

Paper II

Similar anthropometry and lifestyle were found in former athletes and controls. Hip OA was found in 14.2% of former athletes and 7.9% of controls ($p<0.001$), THA in 8.3% former athletes and 3.8% of controls ($p<0.001$). Some 36.1% of former athletes had suffered a previous significant soft tissue knee injury compared with 25.2% of controls ($p<0.001$); for knee OA the proportions were 19.4% and 13.0% ($p<0.001$), and for TKA 3.6% and 2.4% ($p=0.12$).

The age-adjusted risk of developing hip OA was doubled [OR 2.0 (95% CI 1.5, 2.8)], and that of having a THA 2.5 times higher in former athletes than in controls [OR 2.5 (95% CI 1.6, 3.7)]. The higher risk of hip OA seemed predominantly driven by a higher risk in former impact athletes [OR 2.1 (95% CI 1.6, 2.9)], with a doubled risk in soccer and handball players and a tripled risk in ice hockey players, while the risk in non-impact athletes was no higher than in controls [OR 1.4 (95%

CI 0.6, 2.9)]. The results remained after adjustment for differences in age, BMI, occupational load, and soft tissue knee injury.

The age-adjusted risk of developing knee OA was 64% higher in former athletes than in controls [OR 1.6 (95% CI 1.3, 2.1)], while the 58% higher risk of having a TKA did not reach statistical significance [OR 1.6 (95% CI 0.9, 2.7)]. The higher risk of knee OA seemed to be driven by a higher risk in both former impact [OR 1.6 (95% CI 1.2, 2.1)] and non-impact athletes [OR 1.8 (95% CI 1.0, 3.1)]. However, when controlling for BMI, occupational load, and soft tissue knee injury, the higher relative risk remained only in non-impact athletes [OR 3.2 (95% CI 1.5–6.9)].

Paper III

There was no difference in fracture risk when comparing athletes and controls before an athletic career [RR 0.8 (95% CI 0.5, 1.1)], but a two times higher fracture risk during a career [2.0 (1.6, 2.6)], a 30% lower fracture risk after a career [0.7 (0.5, 0.9)], and a 50% lower fragility fracture risk after a career [0.5 (0.3, 0.9)] (Figure 17).

After controlling for differences in lifestyle (occupational load, smoking, alcohol, disease, and medication), the hazard ratio (HR) of any fracture after active career was 0.7 (95% CI 0.5, 1.0) ($p<0.05$) and the HR of any fragility fracture after age 50 years was 0.6 (95% CI 0.3, 1.2).

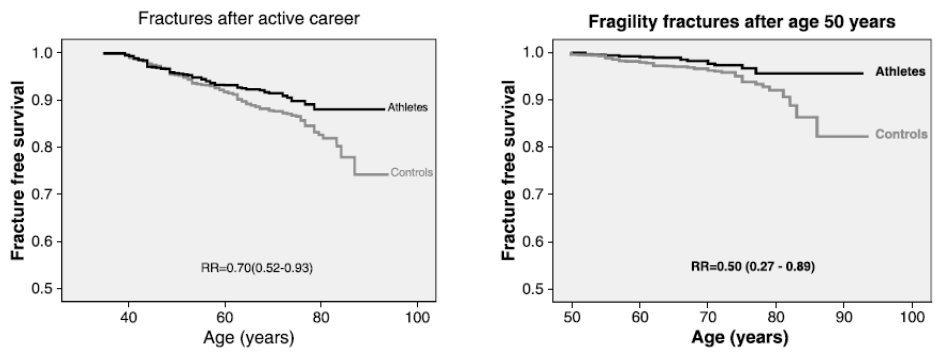

Figure 17. Fracture-free survival of any fracture after career-end (left) and any fragility fracture after career-end (right) presented as Kaplan-Meier survival curves (Paper III).

Paper IV

Sub-study I

Anthropometry and lifestyle in soccer players and controls were very similar both in active soccer career and in all strata of 10-year intervals of retirement. After more than 30 years of retirement from sports, former soccer players had a higher BMD and a larger bone size in loaded regions; 0.4 (95% CI 0.1, 0.6) SD higher total body BMD, 0.5 (95% CI 0.2, 0.8) SD higher leg BMD, and 0.3 (95% CI 0.0, 0.5) SD larger femoral neck area (Figure 18). After adjustment for group differences in BMI, occupation, smoking, and current level of physical activity, BMD remained significantly higher for leg BMD 0.5 (95% CI 0.3, 0.7) (not shown in the printed version of Paper IV).

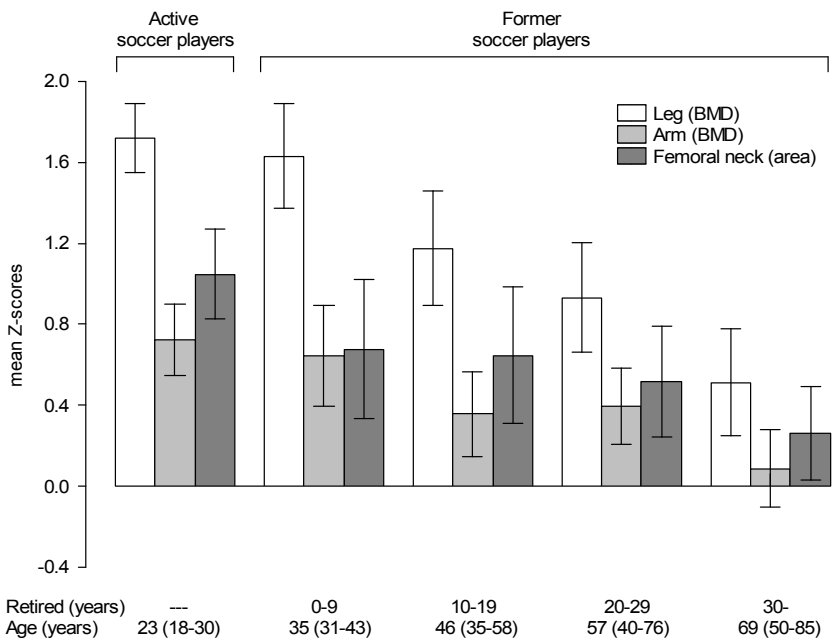

Figure 18. BMD measurements in loaded (leg) and non-loaded (arm) regions together with femoral neck area in active and former male elite soccer players in sub-study I, of which the latter were stratified into four sub-cohorts by 10-year intervals of retirement from sport (Paper IV).

Sub-study II

Anthropometry and lifestyle parameters were similar when comparing former soccer players and controls. Former male soccer players had a lower fracture risk after active career than did controls, with a RR for any fracture of 0.6 (95% CI 0.4, 0.9) and for any fragility fracture a RR of 0.4 (95% CI 0.2, 0.9). After adjustment for age, alcohol, occupation, and medication, the HR for any fracture after career was 0.6 (95% CI 0.4, 0.9) and the HR for any fragility fracture was 0.5 (95% CI 0.2, 1.2).

Discussion

More than 70,000 osteoporosis-related fractures occur each year in Sweden.[240] Half of all women and one third of all men will suffer such a fracture during their lifetime, a fracture type that increases exponentially in old age.[50] Degenerative joint disease currently renders 15,000 total hip arthroplasties and 15,000 total knee arthroplasties each year in Sweden, with a linear annual increase in THA and exponentially annual increase in TKA.[264, 265] At present, more than one in ten elderly have undergone joint replacement surgery and the prevalence is increasing.[264, 265] The individual suffering involved as well as the burden on society for these conditions are thus immense.

Physical activity may however influence the development of both conditions but, unfortunately, the same type of activities shown to be beneficial for bone formation[62, 130, 279] seem to have a detrimental effect on joints.[30, 64, 156] To gain more knowledge as regards possible associations between exercise in youth and bone traits (**I**, **IV**), risk of fracture (**III**, **IV**), and risk of having OA and arthroplasty to the hip and knee (**II**) in old age, we used male elite athletes as a model.

Exercise and bone

Exercise seems to influence the skeleton most obviously in the pre- and peri-pubertal period, corresponding to Tanner stages II and III, by enhancing both the accrual of bone mineral[9, 10] and the gain in bone size.[13, 57, 129, 164] The latter finding is of great importance as bone strength and resistance to bending forces increase by the forth power of a tubular structure.[3, 66, 232] I.e., a small increase in bone size is sufficient to render a great increase in bone strength. The former finding of a substantial amount of lifetime mineral reserve accrued during puberty[9, 10] is equally important as it affects peak BMD. Several studies have also proposed peak BMD, besides age, to be the best predictor of BMD in old age.[26, 53, 100, 105, 113, 184, 263] Exercise during growth could therefore hypothetically be used as a strategy to improve the skeletal resistance to fracture in old age as well. There are also reports indicating that there is a correlation between lifelong level of exercise and BMD,[88] and that the training needed to maintain exercise-associated bone benefits is lower than the amount needed to accrue

more bone.[102] In contrast, it is unclear whether exercise-induced skeletal benefits in young years remain with no recreational training in adulthood.

Bone adapts physiologically to loading by gain in density and width. As the age-related bone loss occurs, the skeleton gradually becomes less dense and thus more fragile. However, this is to some extent compensated by increased width of the skeleton that occurs with ageing.[3, 227, 261] Even if the foundation of bone health is laid down during the pubertal years, several studies have shown that vigorous exercise in young adulthood may insert additional beneficial musculoskeletal effects. These include studies on arm-to-arm difference of which 35% cortical thickness[124] and 25% BMC[149] gain has been found in young male tennis players. A side-to-side effect has also been shown in male Olympic fencers[40] and in male triple jumpers,[104] both of which showed a 50% difference in femoral cortical thickness. A 40% side-to-side effect has also been shown in the cortical area of distal radius in the female weightlifters.[103] Several cohort studies performed by Karlsson et al have shown beneficial BMD effects in ballet-dancers,[133] weightlifters,[134] and soccer players.[136] Our data support this view, as paper **I** reports around 1.0 SD higher BMD in active athletes compared with controls. Not only is the osteogenic response to loading site-specific,[61, 103, 111, 141, 288] there is also an indication of a subsequent redistribution mechanism of which accrued minerals are transported wherever they are needed. This was postulated in elite tennis players in that the non-dominant arm in players had a lower BMC than in controls [94, 129] and that a low skull BMD returned to normal after detrainng.[132, 172]

Detraining and bone traits

Are there any residual benefits in bone traits with detraining and, if so, are they maintained long-term? Hypothetically, according to Wolff's law it seems less likely as the skeleton is suggested to adapt to current level of mechanical loads,[298] though the later "mechanostat" theory proposed by Frost suggests a steady-state scenario but only as long as a certain minimal effective strain (MES) is applied.[80] Most short-term prospective observational studies that have followed former athletes over a period of less than 10 years, during a period when the athletes has retired from sports, have shown a higher loss than would be expected by age. These studies have shown maintenance of beneficial skeletal effects in racquet sports and high jumpers, though with only a short retirement period,[148, 149, 152] while most studies have reported that only around 50% of the exercise-associated BMD is maintained with 5–10 years of retirement from active sports career.[93, 206, 286] One five-year prospective study on female racquet sports players, however, showed good maintenance of both "young" and "old" starters, aged 22 and 39 years respectively with an arm-to-arm difference in BMC of around 20% and 10% respectively with no relative change found during the

study period.[150] Until now, the longest prospective study has been performed by Erlandson et al., who showed a remaining size-adjusted higher total body, lumbar spine, and femoral neck BMC (13, 19, and 13%, respectively) in 25 former female elite gymnasts retired 10 years compared with 22 controls, all aged 8–15 years at baseline.[72]

When prospectively evaluating the effect of retirement there are at least two different risks involved in short- to mid-term prospective follow-up studies. First, athletes who retired during the study period had first a period with active career and then a period with retirement. Bone trait could then hypothetically increase during the active period, and then decrease during the retirement period so that the net result during the entire period (and also the conclusion) would be that there were no changes during the study period.[148-150, 152] Second, with short-term studies it is impossible to draw any conclusions as to whether a high loss is transient or persistent with long-term retirement from exercise.[72, 93, 206, 286]

Paper **I** represents the hitherto longest prospective controlled cohort study that evaluates the effect of retirement from sports as it spans over four decades and includes a mean 29-year retirement period. At follow-up, the favourable effects in bone mass, geometry, and strength were between 0.5 and 1.2 SD compared with controls, depending on the measuring technique and the measured region. It is noteworthy that benefits were found despite the heterogeneity within the athlete group, also including low-impact athletes such as swimmers[17, 62, 78] and low-frequency/high-magnitude such as weightlifters.[17, 199] Also, no relative change in BMD was detected during the study period, nor any correlation with retirement years (**I**), suggesting that the benefits in bone traits would be seen for an even longer follow-up period and into ages when fragility becomes an even bigger problem.

Cross-sectional cohort studies in former athletes have been equally inconsistent in trying to answer whether there are residual benefits in bone after adopting a more leisure-time level of physical activity. Studies in former female ballet dancers have suggested that all skeletal benefits are lost long-term.[133, 144] A study in former male weightlifters showed beneficial effects in weigh-bearing regions in athletes up to 65 years of age and thereafter no differences in comparison with controls,[135] as did two studies in former male soccer players which showed no remaining exercise-associated effects after age 50 and 60 years, respectively.[136, 172] Similar results have also been shown in former female soccer players[63] as in other sporting activities of both sexes.[54, 132] However, one cross-sectional study in former female elite athletes, 12 runners and 12 swimmers, and 12 controls, all in the postmenopausal period, demonstrated bone trait benefits more than 20 years after retirement.[6] No long-term prospective study with repeated measures has ever been conducted enabling the capture of any transient loss right after detraining. In the cross-sectional cohort study conducted in paper **IV**, however, we did find a transient decline in total body BMD between the active period

and the second decade of retirement. We must however emphasize that this inference is drawn from cross-sectional comparisons. It also seemed as if geometry was more persistent than bone mass after detraining (**IV**), as has been demonstrated in former soccer players[130, 131, 286], sprinters,[153] and racquet players[112] of both sexes. This was recently also shown in moderate physical activity in women compared with sedentary controls.[262] Another finding in paper **IV** was that of a between-group difference in the femoral neck area 30 or more years after cessation of soccer, while no corresponding difference was found in the lumbar spine, supporting the view that an osteogenic effect is site-specific.[35, 61-63, 103, 111, 136, 141, 199, 204, 206, 286, 288, 292] This site-specific difference between hip and spine geometry was not reproduced with the same discrepancy in BMD, which partly can be explained by the false increase seen in lumbar spine BMD with more degenerative changes,[268] and the fact that the bone mass heritability of the spine has been reported to be more pronounced than in the hip.[293]

There is also evidence of an inverse association between benefits in bone structure and fracture risk, independently of BMD.[3, 54, 60, 245, 255, 266, 289] This could at least partly explain the lower fracture risk in former athletes found in papers **III** and **IV** than would have been expected by the BMD differences alone. But, also BMD benefits seems to be of importance for fracture risk, supported by the findings in both the longitudinal study (**I**) and the cross-sectional study in this thesis (**IV**).

Detraining and fractures

Few studies have addressed the question of whether fracture risk is reduced in men and women after a reduction or cessation of exercise. Some studies support this view,[131, 206] others do not,[136, 300] and one was inconclusive.[142] One study that included 2622 former female college athletes and 2776 controls all aged between 20 and 80 years showed no difference in between-group fracture rates.[300] However, this study did not control for potential confounders, e.g. the wide spread in age. Kettunen et al. assessed fracture risk in 2147 former male athletes and 1467 controls and found a 23% non-significant risk reduction for a hip fracture after having adjusted for occupational load.[142] They did however find a significant age-difference in time to first facture, 77 years of age in former athletes and 71 years of age in controls ($p=0.005$). Nordstrom et al. included 400 former male soccer and ice hockey players aged a mean 71 years and 943 age-matched controls in a retrospective cohort-design study in which they found an overall fracture rate of 8.9% in former soccer players and 12.1% in controls ($p<0.05$).[206] No between-group difference was seen in hip fracture rate and no adjusted numbers was presented in that study. Papers **III** and **IV** are currently the two largest retrospective matched controlled cohort studies with the aim of estimating any fracture and fragility fracture incidence in old former male athletes and old former male soccer players. The risk of any fracture after career was

30 to 40% lower in former athletes compared to controls, depending on sport practised in youth. The corresponding numbers for any fragility fracture were 50% and 60%, respectively. Different rate ratios in former athletes (**III**, **IV**) could be due to different fracture risk in low-magnitude and/or low-intense sports such as canoeists, long-distance runners, weightlifters, swimmers, biathletes, and cyclists, (**III**) and intense high-impact activity such as soccer (**IV**). This view corresponds to the notion that different types of activities exert different osteogenic responses, both in experimental studies[62, 130, 279] and in athletes.[17, 35, 38, 62, 63, 78, 199, 292]

It is also of interest to notice that after adjustment for confounders, in paper **III** occupation, smoking, alcohol, disease, and medication and in paper **IV** age, alcohol, occupation, and medication, the lower general fracture risk remained and at a similar magnitude. In other words, differences in lifestyle factors, at least those we adjusted for, seemed not to explain the group differences. The low fracture risk demonstrated in former athletes (**III**) and in former soccer players (**IV**) may thus at least partly be explained by an improved bone mass but also skeletal geometry achieved by exercise in adolescence and young adulthood, as the reduction exceeded what would have been expected when only the BMD benefit was taken into account.[3, 53, 184, 206, 263] It is also known that bone size reduces the fracture risk independently of BMD.[3, 54, 60, 289] It could also be of interest to mention that in paper **I** we observed five athletes (10.9%) and five controls (20.8%) who had sustained at least one fracture after career-end, data not reported in the original paper due to the low sample size. Due to this we report the proportions in this summary only as descriptive data. Nevertheless, these descriptive data together with the around one SD higher BMD in athletes compared with controls at follow-up (**I**) corresponds to a 50% risk reduction in fracture with one SD higher BMD, as has been reported in previous large observational studies.[3, 53, 184, 206, 263]

Difficulties in deriving data

The discrepancies in literature when reporting long-term residual skeletal effects of exercise in youth can partly be explained by variations in study design and in examined cohorts. Sample size, type of exercise during an active career and lifestyle factors after career-end could all influence any inferences. To exclude the risk of selection bias, a double-blinded RCT would have been needed, though impossible to perform with our aim, and a non-randomized interventional study with fracture as end-point is not practically feasible as training confers bone benefits at a very early age[256] and fragility fracture is not exponentially increased until old age.[50] Also, papers **I, III,** and **IV** cannot exclude the risk of selection bias, making statements about causal relationships between exercise in youth and long-term benefits on bone impossible. Inherited stronger bone and more suitable neuromuscular setup present

before the start of training, thus including individuals more prone to exercise, cannot be ruled out. However, although not reported in the printed version of paper **I**, this was less likely as the higher muscle strength in active athletes dropped during the study period to no difference versus controls with retirement (Appendix 2). Also, retrospective data of long-term leisure-time physical activity did not differ between the cohorts (**I**). In paper **III**, the risk of selection bias was also opposed by the fact that there was no significant difference in fractures incidence before active career. As for paper **IV**, the limitation includes the cross-sectional study design in the bone trait evaluation (sub-study I) where a number of individuals contributed two measurements, and the retrospective study design in the fracture evaluation (sub-study II). Prospective long-term data would have been preferable but not feasible with a measurement period spanning over six decades in addition to the power problem when using fragility fractures as an end-point variable. Furthermore, as muscle strength in **paper I** diminished in former athletes more than being expected so that there was no longer any group difference with long-term retirement and muscle mass in former athletes was no higher than in controls already within the first decade of retirement in paper **IV**, indicates that there was no selection bias at baseline that would have obscured the results.

Exercise and joints

Systemic factors are often described as predisposing degenerative joint changes, whereas local mechanical factors seem to determine the distribution and the severity of the disease.[166, 223] Compared to osteoporosis, grading OA is difficult as there is no consensus on the definition. Instead, there are several different definitions depending on focus such as patient-centred, structural, or cellular. In clinical practice, for instance, both radiographic and clinical definitions are to be considered. These varying definitions also apply to research, making comparability between studies low. In our study we focused on the association between exercise in young years and the risk of developing OA in old age by asking participants whether or not they had been diagnosed with OA by a physician, that is, we used a clinical diagnosis (**II**). As for bone evaluation, there are no RCTs to rely on when addressing whether exercise in young years increases the risk of developing OA in old age. Compared with studies on bone, there are fewer controlled cohort studies and we have to rely on knowledge from lower evidence level observational studies, typically including a meniscal or ACL injury as a starting point for the evaluation.

Type of impact

As this thesis aimed to investigate any long-term exercise effects on both bone and joints, we soon became aware of heterogeneity in the vocabulary. For example, whereas soccer often, but not always, is classified as an odd-impact or moderate-impact sport in the field of bone research[54, 199] it is often, but not always, classified as a mixed, high-impact, or just impact sport in the field of sports medicine.[30, 156] Ballet dancing is another example of the confusion as regards terminology; in bone research, it would be described as high-magnitude or high-impact exercise, whereas in sports medicine non-impact, non-contact, or a non-team sport activity. In other words, impact, contact, and team sports are often referred to in sports medicine as the same type of exercises in principle, i.e. those involving risk of sudden and high-magnitude forces, with little or no warning. In paper **II**, soccer, handball, and ice hockey were all classified as impact sports, while canoeing, long-distance running, weightlifting, gymnastics, swimming, biathlon, and racing cycling were all classified as non-impact sports.

Soft tissue injuries are commonly associated with OA. Three different joint-related structural injuries have been shown to predict OA and are likely to occur in vigorous exercise: (i) macroscopic labral,[59, 86, 175, 248] anterior cruciate ligament (ACL),[208] and meniscal tears,[71, 166] (ii) subchondral bone marrow lesions (BML),[65, 115, 277] and (iii) microscopic cartilage lesions.[212] In addition to bedside examination, all of the above may need magnetic resonance imaging (MRI), and the latter even quantitative MRI technique in order to be detected. In paper **II** we could adjust only for the first described type of injury, since the other two injuries were rarely diagnosed 40–50 years ago.

Injuries to the hip are rarely reported compared to the knee,[59] either due to lack of available techniques required to diagnose the injury or simply for not having sustained such a notable injury. Nevertheless, acute muscle tears and chronic groin conditions are common in this region. A study conducted by Manning and Hudson showed a lower range of joint motion already in professional soccer players aged 16 to 18 years, even without any prior clinically relevant hip injury, suggesting this finding to be an early signs of joint degeneration.[175] It has been proposed that joint laxity, bone bruise, and subchondral bone stiffening caused by repetitive trauma, may play an important role in development of OA by causing secondary micro injuries to the articular cartilage.[65, 115, 171, 222] We, like others, found that impact sports seem to be associated with a high risk of hip OA.[59, 86, 248] After adjusting for age, occupational load, BMI, and soft tissue injury, we found a 2.2 times higher risk of hip OA in athletes compared with controls, predominantly driven by sportsmen in impact sports (**II**).

Although few controlled studies have been performed, the risk of sustaining an ACL injury and/or meniscal tear is considered to be higher in impact athletes than in nonsporting individuals,[143, 154, 166] and that a knee injury is a risk factor for future knee OA.[71, 208] This is supported by our results in paper **II**, with an almost doubled relative risk for a soft tisue knee injury in impact sportsmen [OR 1.8 (95% CI 1.5, 2.2)] but no higher risk in non-impact sportsmen [OR 0.9 (95% CI 0.5, 1.5)] compared with controls. Furthermore, although not reported in the printed version of paper **II**, we speculate that this could possibly explain the 20 times higher risk of knee OA and 12 times higher risk of TKA in those who had sustained a prior soft tissue knee injury compared with those who had not.

Impact of fatigue

But could muscle dysfunction without a defined injury also be associated with OA? A biomechanical hypothesis referred to as "the muscle dysfunction theory" has been proposed by Hurley, in which he suggests that muscles are the main force absorbers of the joint.[116] In this model, any type of muscle dysfunction, for example, related to ageing, fatigue, or loss of proprioception caused by ligament tears or other types of soft tissue joint injuries would be the main local mediating factor for developing OA.[116] The hypothesis may partly explain some of the diversity in risk estimates reported for degenerative hip disease in long-distance runners, from a higher risk,[179, 236, 296] normal risk,[143, 147, 158, 215] or even a lower risk compared with controls.[254] It could also explain why vigorous exercise may lead to a high risk of OA,[30, 156] mediated through direct joint damage or prolonged joint deterioration, while moderate physical activity does not seem to alter the risk or even be protective against OA.[114, 236, 249, 260] Likewise, paper **II** demonstrates a roughly two times higher risk of both hip or knee OA and a similar high risk of a THA or TKA in former male elite athletes compared with controls. After adjustment for soft tissue knee injury, we found that impact athletes were no longer at higher risk of knee OA, while non-impact athletes had a three times higher risk (**II**). This makes us speculate that the pathophysiological pathway for an increased risk of knee OA may differ depending on the type of sport, so that knee OA in impact sportsmen may be more associated with a soft tissue knee injury,[71, 143, 154, 166] and in non-impact sportsmen with repeated biomechanical stress and muscle fatigue.[116, 154, 156, 179, 185, 212, 236, 295, 296]

Impact versus no impact

Osteoarthritis

Few studies have made a direct comparison of joint deterioration between different types of sports. Even fewer have taken soft tissue joint injuries into account in such comparisons. Kujala et al. compared hospital admissions for OA of the hip, knee, or ankle joints between 2049 former male elite athletes and controls.[156] After adjusting for age, occupational load and BMI, the relative risk was 2.4 times higher for both endurance athletes (long-distance runners and cross-country skiers) and mixed athletes (several different team sports) compared with controls. After exclusion of ankle OA, those who had previously participated in endurance sports had a non-significantly higher risk of both hip and knee OA than had those in mixed sports with a crude cumulative hip OA incidence of 5.3 and 2.5% respectively, and knee OA of 2.5 and 1.9% respectively. (No adjusted site-specific ORs were presented in the study.) While former endurance athletes sought medical attention for OA symptoms at a mean age of 71 years, former athletes in mixed sports did so at a mean age of 58 years.[156] In paper **II**, both impact and non-impact sportsmen had 1.6–1.9 times higher age-adjusted risk of OA in either the hip and/or knee. Another study compared the prevalence of hip and knee OA in 1321 former male elite athletes in a variety of sports with 814 controls.[143] After adjusting for age, occupational load, and BMI, a 1.5 times higher risk of knee OA was seen in those having participated in team sports compared with controls, and a 2.0 higher risk in athletes under 45 years of age, driven by a 3.4 times higher risk in team sport athletes. A higher fraction of participants in team sports had suffered soft tissue knee injuries, but this was not adjusted for in this study.[143] The low mean age in former athletes, and the fact that severe soft tissue knee injuries associated with impact sports[143, 154, 166] may initiate the deterioration process at an earlier age than in endurance sports, may have interfered with the conclusions. In paper **II** we present currently the largest retrospective matched controlled cohort study that not only compares different sports in association with OA but also controls for soft tissue knee injury. As in other studies,[71, 143, 154, 166] we also found a high prevalence of previous soft tissue knee injury in those with participation in impact sports (38%) compared with non-impact sports (24%) and controls (25%). However, despite the significantly lower incidence of a previous soft tissue knee injury compared with impact athletes, and similar to controls, non-impact athletes still had a 1.8 times higher risk of developing knee OA than controls (**II**). We speculate that the repeated monotonous motions under loads in for example long-distance runners and cross-country skiers may result in an accumulation of minor subclinical injuries or a continuous wear, finally resulting in knee OA even without a clinically significant soft tissue knee injury.[116, 154, 156, 179, 185, 212, 236, 295, 296]

Arthroplasty

Hip OA has also been associated with endurance sports,[143, 156] and Vingard et al. were able to demonstrate a two times higher risk of THA in those with high exposure to long-distance running compared with low exposure, after controlling for age, occupational load, BMI, and other sports.[296] In paper **II** we present currently the largest retrospective matched controlled cohort study that compares different sports in association with THA and TKA. While the 1.9 (95% CI 0.6, 5.9) times higher risk of THA in non-impact athletes was not significantly different from controls, the 3.1 (95% CI 1.8, 5.1) times higher risk in impact athletes was (adjusted for age, occupational load and soft tissue knee injury). We speculate that a type II error and the relatively young ages in the former non-impact athletes possibly could have influenced our results, as there is evidence of a later joint deterioration in non-impact sportsmen than in impact sportsmen.[143, 156]

Two controlled studies on participants in a variety of exercises, one in 535 men[296] and one in 503 women,[297] found that moderate physical activity was associated with 2.6 times higher risk in men and 1.5 times higher risk in women of THA, while a high-level physical activity was associated with 4.5 times higher risk in men and 2.3 times higher risk in women. In another report, Michaëlsson et al. investigated in another report almost 50,000 individuals who had participated in *Vasaloppet*, an annual Swedish ski race of 90 km during the period 1989 to 1998. They reported a 3 times higher risk of THA and 2 times higher risk of TKA after 10 years in those with five or more ski races and a fast finish time compared with those who only participated once with a slow finishing time.[116] We support the notion of long-term mechanical stress as being a potential risk factor for developing OA in loaded joints, when reporting a 2.2 times higher age-adjusted risk in former athletes of having a THA and/or TKA, and a 2.6 times higher risk after adjustment for occupational load, BMI, and soft tissue knee injury (**II**). Published studies also infer that the risk of a THA or TKA has a dose-dependent relationship to previous exercise level,[185, 296] and that the need occurs at an older age in former non-impact than in former impact sportsmen.[143, 156] Furthermore, the literature suggests that OA in impact sportsmen is more associated with a previous soft tissue joint injury than in endurance sportsmen,[143, 154, 166] results supported by our study (**II**).

Limitations in paper **II** include the study design making statements about causal relationships between exercise and joint deterioration impossible, as there was both a risk of recall bias as regard previous injuries and a risk of selection bias. However, we found only minor differences in anthropometrics and lifestyle between former athletes and controls, indicating a lower risk of selection bias. It would also have been advantageous to use a validated questionnaire, and to have had larger sample sizes in order to reduce the risk of type II errors, especially in sub-group analyses.

Clinical implications

It is well known that exercise induces beneficial bone effects, especially during growth.[13, 129, 259, 286, 287] This thesis support this notion (**I, IV**) and further indicates that such effects may remain in the long term (**I, IV**) and are associated with a low fracture risk in old age (**III, IV**). The clinical implication based on the current knowledge would therefore be to recommend physical activity during growth as a strategy to reduce the number of fragility fractures in the long term.

But exercise may also imply adverse effects. One such effect is more factures during high level of exercise, probably due to more trauma episodes.[59, 85, 166, 175, 192, 197, 248] This adverse effect was also demonstrated in our studies (**III, IV**), but could be addressed by training on a more moderate level.[57, 164] Such training has been shown to increase both bone mass and bone size, without increasing the fracture risk.[57, 164] The clinical implication based on the current knowledge would therefore be to recommend exercise strategies that improve bone traits without increasing the fracture risk.

Prolonged vigorous exercise could also in the long term have adverse effects on joint health,[116, 185, 192, 223] a notion also supported in this thesis (**II**). But also this issue could possibly be addressed by exercising on a more moderate level. Exercising on a more moderate level has been associated with beneficial quality of the cartilage,[274] and most studies suggest that there is no increased risk of hip or knee OA with moderate exercise in young years.[114, 236, 249, 252, 254, 260] The clinical implication based on the current knowledge would therefore be to recommend exercise strategies that do not increase the risk of OA but instead may possibly improve the quality of the cartilage.

Future perspective

This thesis provides us with some new and most important information. However, the thesis does not provide us with information regarding optimal age limits for training, optimal duration, levels, or types of training, nor does it provide any information regarding plausible association between exercise and long-term bone and joint health in women. Therefore, we are of the opinion that studies evaluating these issues should be performed.

It could also be debated whether we should search for information with a higher level of evidence. Double-blinded RCTs that evaluate the research questions we have addressed in this thesis cannot be performed, and a non-randomized prospective controlled study will probably never be done due to the long follow-up and the large sample size required if fractures and OA as end-point variables are to be used. Instead,

we have to rely on studies with a lower level of evidence. Lack of evidence in RCTs is not proof of lack of efficacy, and when making our inferences, we have to rely on the highest current level of evidence.

Conclusions

Vigorous exercise in youth, in men long-term after retirement from sports, is associated with:

- a larger bone mass and more beneficial bone geometry than expected by age.
- a lower fracture risk and lower fragility facture risk than expected by age.
- a higher risk of OA in hip and knee than expected by age.
- a higher risk of arthroplasty in hip and/or knee than expected by age.
- a higher risk of knee OA in non-impact athletes than expected by age, independent of any previous soft tissue knee injury.
- a higher risk of knee OA in impact athletes than expected by age, but only if previously having sustained a soft tissue knee injury.

Vigorous exercise in youth, in men long-term after retirement from sports, is not associated with:

- a larger muscle mass or higher muscle strength than expected by age.

Populärvetenskaplig sammanfattning (Summary in Swedish)

Osteoporos (benskörhet) är ett tillstånd som definieras av låg benmassa och ett tillstånd som ökar med stigande ålder. Sjukdomen i sig är symptomfri men ökar risken för frakturer. Frakturer i kota, axel, handled, bäcken, och höft efter 50 års ålder är ofta förknippade med osteoporos och ca 70 000 sådana frakturer inträffar årligen i Sverige. Även artros (ledsvikt) i höft- och knäleder är vanligt hos äldre. Artros leder till belastningssmärta, vilovärk, stelhet och svullnad. Hjälper ingen annan behandling kan man ersätta den förstörda leden med en protes och årligen utförs i Sverige ca 30 000 sådana ledprotesoperationer i höft- och knäleder. För både osteoporos och artros är det individuella lidandet stort, samhällskostnaderna höga och stora resurser läggs därför ner på att förebygga tillstånden.

Precis som för de flesta sjukdomar anses osteoporos och artros till stor del vara beroende av genetiska faktorer. Det finns dock även en mängd påverkbara riskfaktorer för sjukdomarna som graden av fysisk aktivitet, rökning för osteoporos och fetma för artros. Fysisk aktivitet i unga år leder till ett större skelett med högre benmassa, gynnsamma förändringar som är kopplade till låg frakturförekomst. Men det är oklart om dessa gynnsamma effekter kvarstår under resten av livet. Man vet inte heller om träning i unga år skyddar mot osteoporosfrakturer i hög ålder.

Hög fysisk aktivitet verkar också öka risken för att drabbas av symtomgivande menisk- och korsbandsskador i knäna. Sådana skador leder till ökad risk för artros. Om hög träningsnivå utan (symtomgivande) skador leder till ökad artros är däremot oklart. Det är också oklart om olika typer av träning ger upphov till olika risk att drabbas av artros samt vilken betydelse mjukdelsskador i knälederna har för uppkomsten av artros inom olika typer av idrotter. Syftet med avhandlingen var att hos män studera långtidseffekterna på skelett och leder efter hög fysisk aktivitet i ungdomsåren.

Figure 19. Författaren utför en knäprotesoperation tillsammans med kollegan Martin Sundberg.

I delarbete **I** följde vi benmassan och muskelstyrkan hos 46 idrottsmän och 24 kontrollpersoner under i genomsnitt 39 år. Den första mätningen gjordes när idrottsmännen var aktiva, den andra i genomsnitt 29 år efter att de hade avslutat sin idrottskarriär. Som förväntat hade idrottsmännen när de var aktiva högre benmassa och starkare muskulatur än kontrollpersonerna. Vid uppföljningen var det ingen skillnad i muskelstyrka medan benmassan fortfarande var högre hos de f.d. idrottsmännen. Det verkar alltså som om idrottsmän trots att de avslutat sin idrottskarriär tre decennier tidigare hade kvar sin höga benmassa.

I delarbete **II** undersökte vi risken att utveckla artros och behovet av ledprotes i höft- och knäleder hos f.d. idrottsmän och en kontrollgrupp. Vi undersökte 709 före detta idrottsmän med en medelålder på 69 år och 1368 kontrollpersoner i samma åldrar. Genom ett frågeformulär tog vi reda på deras längd och vikt samt om de hade fått diagnosen artros i höft- eller knäleder av en läkare samt om de hade blivit opererade med en protes i någon av dessa leder. Vi fann då att de f.d. idrottsmännen löpte

dubbelt så hög risk att drabbas av artros i höft eller knä och att ha genomgått en ledprotesoperation i jämförelse med kontrollgruppen. Efter att vi tagit hänsyn till skillnader i tidigare arbetsbörda, vikt, och mjukdelsskador i knäet så fann vi inte längre någon ökad risk hos de f.d. kontaktidrottsmännen att drabbas av knäartros medan de f.d. idrottsmännen i individuella/uthållighets/icke kontakt grenar hade en tre gånger högre risk jämfört med kontrollgruppen. Det verkar alltså som om den ökade risken för uppkomst av OA i knälederna hos f.d. idrottsmän är beroende på olika mekanismer i olika idrotter.

I delarbete **III** undersökte vi samma individer som i delarbete II men tittade på frakturrisken hos f.d. idrottsmän och kontrollpersoner, utvärderat via det frågeformulär som beskrivs ovan. Vi fann då att de f.d. idrottsmännen löpte 30 % lägre risk att drabbas av fraktur efter avslutad karriär och 50 % lägre risk att efter 50 års ålder drabbas av en benskörhetsfraktur jämfört med kontrollgruppen. Vår slutsats blev att idrottande i ungdomen hos män är kopplat till en lägre frakturrisk senare i livet.

I delarbete **IV** inkluderades i den första delstudien 329 skelett- och muskelmätningar genomförda på 193 manliga fotbollsspelare och 450 mätningar genomförda på 280 kontrollpersoner. Samtliga individer var mellan 18 och 85 år gamla och vissa individer mättes alltså två gånger. I den andra delstudien inkluderades 397 f.d. manliga fotbollspelare och samtliga 1368 kontrollpersonerna ur den grupp som beskrivits i delarbete II. Vi fann då att benmassa och muskelmassa var högre bland de aktiva fotbollspelarna än bland kontrollpersonerna men att denna skillnad också sågs hos de f.d. fotbollspelarna som hade avslutat sin karriär mer än 30 år tidigare jämfört med kontrollgruppen. Vi fann också att de f.d. fotbollspelarna löpte 40 % lägre risk att drabbas av fraktur efter avslutad karriär och 60 % lägre risk att efter 50 års ålder drabbas av en benskörhetsfraktur jämfört med kontrollgruppen. Våra slutsatser blev att de gynnsamma skeletteffekter som syns hos aktiva fotbollspelare kvarstår lång tid efter avslutad idrottskarriär och att dessa fynd även är kopplade till en låg frakturrisk senare i livet.

Sammantaget verkar det som idrottande på hög nivå hos unga män är kopplat till ett starkt skelett och låg frakturrisk senare i livet men också till mer artros och ett större behov av ledprotesoperationer i höften och knäet.

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Appendix 1

Universitetssjukhuset MAS
Ortopediska kliniken, 205 02 Malmö

REGION SKÅNE

PROTOKOLL TILL AKTIVA OCH F.D. OS-DELTAGARE

1. Namn..... 2. Pers nr.....
3. Adress.....
4. Tel/mobiltel .... 5. Längd.....cm 6. Vikt.....kg
7. Födointag
   ☐ normalkost ☐ vegetarian ☐ komjölksintolerans
   ☐ andra kostrestriktioner .....
8. Äter/dricker du något av följande regelbundet; yoghurt, filmjölk, mjölk, ost?
   ☐ Nej ☐ Ja
9. Hur många koppar kaffe dricker du per dag? .....koppar
10. Röker du idag?
    ☐ Nej ☐ < 10 cig. per dag ☐ > 10 cig. per dag
11. Dricker du alkohol? ☐ Nej ☐ Ja
12. Om "ja" - hur mycket dricker du per vecka?
    ☐ .....cl starksprit ☐ .....liter vin ☐ ..... liter starköl
13. Tidigare eller befintlig sjukdom
    ☐ magsår ☐ alkoholism
    ☐ opererad i magsäcken ☐ behandlad för cancer
    ☐ reumatiska besvär ☐ opererad gynekologiskt (kvinnor)
    ☐ njursjukdom ☐ epilepsi
    ☐ diabetes, insulinbeh. ☐ astma/kronisk bronkit
    ☐ diabetes, kostbehandl ☐ annan sjukdom .....
    .....
14. Tar du några mediciner
    ☐ Nej ☐ Ja Om "ja", vilken/vilka medicin(-er) tar du?
    .....
    .....
15. Har du någon gång haft behandlingskrävande knäskada ☐ Nej ☐ Ja
16. Hur behandlades den?
    ☐ ingen behandling ☐ bandage ☐ gips ☐ operativt
    ☐ annat.....
    .....
17. Har du någon gång haft diagnostiserat benbrott (innefattar alla delar av skelettet)
    ☐ Nej ☐ Ja

Om "ja" på fråga 17 besvaras frågorna 18-21

18. Hur många gånger har du haft diagnostiserat benbrott?
    1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ > 5 ☐ gånger

Beskriv kortfattat typ av benbrott (exempelvis axel, handled, bäcken, höft, underben, fot- och knäled etc)

19. **Benbrott 1:** I) Vad bröt du?.....
II) Hur gammal var du? .....år

20. **Benbrott 1:** I) Vad bröt du?.....
II) Hur gammal var du? .....år

21. **Benbrott 1:** I) Vad bröt du?.....
II) Hur gammal var du? .....år

Vid ytterligare benbrott - utnyttja baksidan av detta papper. Det är mycket viktigt att alla benbrott du haft noteras.

22. Har du av läkare diagnostiserad förslitning (artros) i höftleden?
☐ Nej ☐ Ja

23. Är du protesopererad i din/dina höfter?
☐ Nej ☐ Nej

24. Har du av läkare diagnostiserad förslitning (artros) i knäleden?
☐ Nej ☐ Ja

25. Är du protesopererad
☐ Nej ☐ Ja

26. Vid vilken ålder började du träna regelbundet (minst 2 ggr/vecka)? ..... år

27. Vid vilken ålder började du tävlingsidrotta? ..... år

28. Vid vilken ålder slutade du tävlingsidrotta? ..... år

29. Vid vilken ålder slutade du motionsidrotta ..... år

30. Om du fortfarande är aktiv, vilken typ av träning bedriver du idag?
☐ löpning ☐ gymnastik ☐ annat .....
☐ cykling ☐ styrketräning .....
☐ simning ☐ bollidrott .....
☐ ingen

31. Hur många timmar tränar du per vecka idag? ..... tim/vecka

32. *För lagspelare* - vilken position spelade du huvudsakligen i laget?
☐ Målvakt ☐ Forward ☐ Mittfältsspelare
☐ Försvarsspelare ☐ Alternerad position ☐ Ej lagspelare

33. Vilken typ av arbete har du i huvudsak haft/har efter avslutad idrottskarriär?
☐ Manschettarbete ☐ Tungt arbete
☐ Lättare arbete ☐ Oklart

34. Vad är/var ditt huvudsakliga arbete efter karriären?.....
.....

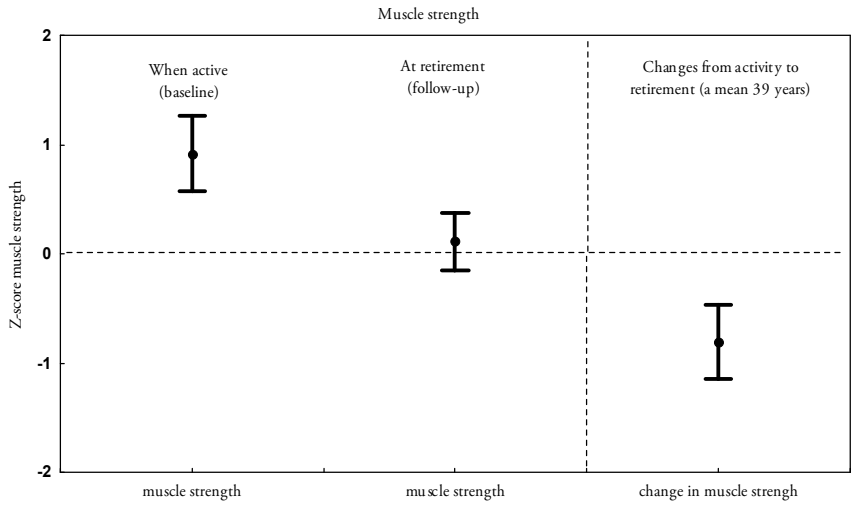
35. *För äldre* – arbetade du till ålderspensionen eller slutade du tidigare
☐ till ålderspension ☐ slutade i förtid

36. Om du slutade i förtid – vid vilken ålder slutade du? .....år

37. Om du slutade i förtid – beskriv kort varför
.....
.....

A self-reported questionnaire on anthropometry and lifestyle, including exercise and medical history with special reference to fractures and degenerative change in hip and knee was used in papers II–IV.

Appendix 2



Between-group comparisons of muscle strength expressed as Z-scores: to the left real values at baseline and follow-up, and to the right relative change during the study period (Paper I).

Papers I–IV