

3rd Baltic bone and cartilage conference

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Invited lectures

1. Mineralization—physiology, estimation and regulation

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The formation of a solid phase of Ca-P in bone represents a *phase transformation* due to homogenous nucleation without initiation of an organic nucleation agent. Calcification of collagen fibrils occurs in highly organised fashion, where it is initiated at spatial distinct nucleation sites. The additional increase in the mass of Ca-P apatite accrues principally by multiplication of more crystals and not by additional growth of more crystals. Bone mineralization is coupled to osteoblastic function and is followed by a sequential secretion of different formative osteoblastic bone markers.

In clinical situations bone mineralization rate can be measured at cellular and tissue level by *quantitative histomorphometry* after intravital tetracycline double-labeling and at organ level by *⁴⁷Ca-kinetics* employing different multicompartment models or the continuous expanding calcium pool model. A reduced mineralization rate may be due to reduced bone formation (i.e. hypothyroidism or glucocorticoid treatment) or compromised mineralization of produced osteoid (osteomalacia). During bone formation an average of 0.5–0.7 mm of osteoid is deposited per day. The osteoid mineralize after a lag time of about 10–50 days. The amount of osteoid depends on the osteoid thickness and the surface extent of osteoid seams. The average osteoid thickness increases if the osteoid appositional rate increases or the mineralization lag time is prolonged. The surface extent of osteoid is—according to common population statistics—proportional to the activation frequency and the duration of the formative period in the remodeling sequence. Osteomalacia is defined by an increased osteoid thickness due to a prolongation of the mineralization lag time.

Inhibition of the mineralization process may be due to lack of calcium and especially phosphate at the mineralization front. It is, however, uncertain whether the effect of vitamin D deficiency is explained by deficiency of these ions

due to intestinal malabsorption or to the lack of active vitamin D. Hypophosphatemia, either due to intestinal malabsorption or to inherited or acquired increased renal loss induced by phosphatonin is followed by a deficient mineralization. Furthermore, mineralization is impaired by aluminium, iron, fluorid and certain bisphosphonates.

It is concluded that bone histomorphometry after intravital tetracycline double-labeling is an essential tool to evaluate abnormalities in the mineralization process.

2. Implant mechanisms, biocompatibility and interface

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The success of non-cemented bone implants/prostheses are believed to depend on the early implant fixation which is provided by initial press fit insertion of the implant followed by bone ingrowth. Bone ingrowth to an implant depends on numerous factors which can be categorized into four main groups:

1. Implant related factors: surface chemistry and topology, implant design, etc.
2. Mechanical conditions: stability and weight-loading conditions.
3. Host bone repair and remodeling capacity: bone stock, drug therapy, metabolic dysfunction, etc.
4. Bone stimulating factors: growth factors, bone graft materials, calcium phosphate coatings, etc.

This presentation will focus on the effects of implant related factors, mechanical conditions, bone stock quality, and bone stimulating factors on bone ingrowth and mechanical fixation of non-cemented implants. It is concluded that implant surface texture (porous versus grit-blasted), calcium phosphate coatings and the presence of micromovements (150–500µm) significantly influence bone ingrowth. Moreover, it is demonstrated that implant fixation and bone in-

growth are influenced by bone allograft and bone substitutes, alone or in combination with growth factors (TGF- β and BMP-7). In addition, the revision situation is shown to be different from the primary regarding healing capacity both with and without growth factors.

4. Genetic approaches to the study of cartilage protein function

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Cartilage plays an important role in the formation and growth of vertebrate skeleton. During embryogenesis cartilaginous models of many skeletal elements are formed. The extracellular matrix (ECM) of the cartilage models is later mineralised and replaced by bone through endochondral ossification. The ECM of cartilage consists of three major components: the collagens, proteoglycans and noncollagenous glycoproteins. To understand the role of these molecules in skeletal development and diseases we generated several mouse lines carrying null alleles for genes encoding cartilage ECM proteins.

Type II collagen is found almost exclusively in cartilage where it represents more than 90% of the collagenous proteins. Transgenic mice deficient in type II collagen die at birth and develop a skeleton without endochondral bone formation. Null-mutant mice exhibit structurally abnormal cartilage and lack growth plates in long bones. Furthermore, *Col2a1*^{-/-} animals are unable to dismantle the notochord which leads to impaired intervertebral disc (IVD) development. *Matrilin-1* (mat-1) is a member of a non-collagenous glycoprotein family called *matrilins* and it is thought to bridge the large aggregating proteoglycan (aggrecan) and collagen fibrils in hyaline cartilage. Surprisingly, mice lacking mat-1 develop normally without detectable anatomical or histological abnormalities in their skeleton. One possible explanation of this result is that mat-1 function is compensated by other member(s) of the matrilin family. *Perlecan* is a heparan sulphate proteoglycan which is expressed in basement membranes and cartilage. The function of perlecan during skeletal development is unclear, although recent *in vitro* data suggest that it may have a role in chondrocyte differentiation. Ablation of the perlecan gene leads to a severe skeletal phenotype which is currently analysed and will be presented on the congress.

5. Cartilage oligomeric matrix protein—aspects of the pathogenesis of osteochondrodysplasias

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Osteochondrodysplasias are constitutional diseases of bone which manifest in a large diversity of clinical phenotypes. Their classification has been the subject of several recent revisions based on radiodiagnostic and morphologic criteria. The increasing pace of linkage analyses has allowed the identification of mutations in genes and etiopathogenetic mechanisms can now be investigated in detail.

Pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED) are autosomal dominant conditions characterised by short-limbed dwarfism.

Dwarfism is not obvious at birth but becomes evident during childhood. Early-onset arthrosis of weight-bearing joints accompanied by joint laxity is the major clinical complication for the patients. Point mutations in cartilage oligomeric matrix protein (COMP) have been analyzed as the cause for these two human diseases.

COMP is an extracellular glycoprotein expressed in cartilage and tendons, its physiological function is not known so far. Most point mutations detected in the COMP gene of PSACH and MED patients affect amino acids in the central part of COMP characterized by acidic repeats predicted to bind calcium ions.

We are currently taking a protein chemistry approach to elucidate how the mutations in COMP lead to the clinical phenotype in PSACH and MED patients.

In patient biopsies an accumulation of proteins was detected in the endoplasmic reticulum of chondrocytes. We therefore first investigated whether mutations in COMP destabilize the protein and thus cause the accumulation in the endoplasmic reticulum during folding. We expressed full-length COMP as well as the calcium-binding repeats alone in an eukaryotic expression system. We could demonstrate that calcium indeed binds to the acidic repeats of COMP and induces a conformational change. We then introduced three different mutations DD470, D361Y and D475N into COMP which are known to cause PSACH or MED, respectively. All mutated COMPs were expressed and secreted in high amounts from the used human kidney cell line.

Circular dichroism analysis showed that the conformation of the mutated COMP differed only slightly from the one of normal COMP. However, the conformation of mutated calcium-binding repeats was affected although they still bound calcium ions, indicating an only small local disturbance of the protein structure.

Patient chondrocytes in culture have been shown to secrete COMP. We could demonstrate that the mutations in COMP interfere with high-affinity binding to collagens. Thus the phenotypes of PSACH and MED seem not to be the result of an instability of COMP and its retention inside the chondrocyte but may be caused by a disturbance of the proper function of mutated COMP in the extracellular matrix. At present we examine the effects of the expression of mutated COMP on chondrocyte proliferation and differentiation to understand why growth of long bones is retarded in the patients.

6. Novel ultrasound parameters in skeletal diagnosis

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Quantitative ultrasound (QUS) is a relative new method for the assessment of bone quality. Because QUS depends not only on material density but also on properties like elasticity and structure, a refined analysis of bone strength might be possible. Nevertheless, rare data are available showing a superior performance of QUS as compared with DXA or QCT. Today, several new parameters are under evaluation which might improve the diagnostic sensitivity and the precision of QUS measurements.

A better performance of QUS measurements can be achieved by measuring properties of soft tissue, which have an impact on the QUS results. Examples are the additional measurement of heel temperature and phalanx thickness. An improved measurement of bone properties might be possible by using new techniques like ultrasound backscatter or new parameters calculated from the ultrasound signal. An example is the estimation of morphometrical and structural parameters in cortical as well as trabecular parts of the finger phalanx from ultrasound parameters.

Ultrasound is a complex, not a simple method. A variety of parameters can be extracted from the ultrasound signal, which might allow us to assess an improved analysis of bone in future.

7. Biomarkers of bone turnover

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Various enzymes and bone matrix proteins synthesized by osteoblasts and osteoclasts are transported into body fluids. Several assays measuring these biomarkers of bone turnover have been developed that can be used for rapid determination of bone turnover rate. Most commonly used bone formation markers include serum alkaline phosphatase, osteocalcin, and the type I collagen propeptides PICP and PINP. Most promising resorption markers are serum bone sialoprotein, ICTP, and TRAP 5b, and various type I collagen degradation products such as urinary deoxypyridinoline, pyridinoline, and urinary and serum CrossLaps and NTx. The urinary markers respond better to changes in bone turnover, but they are also associated with higher intraindividual day-to-day variation than the serum markers. The urinary markers must be correlated to creatinine, making them more laborious and sensitive to errors than the serum markers. It has been suggested that biomarkers may be useful in selecting and monitoring antiresorptive treatment, in identifying "rapid bone losers", and in the prediction of osteoporotic fractures. However, more studies with improved assays and with combina-

tions of formation and resorption markers are needed to find out the clinical utility of biomarkers.

8. The function of nerves in healing of bone

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Bone growth, repair and remodeling may be subject to the influence of the nervous system. In a series of six experiments we investigated the effects of peripheral nerve damage on fracture healing, posttraumatic osteopenia, and healing of structural bone allografts. Further, we studied nerve ingrowth into a bone conduction chamber during bone ingrowth and bone allograft incorporation.

Materials and methods: Rats were used as experimental animals in all studies. In the fracture studies a standardized tibial fracture was applied, stabilized with a modular intramedullary nail. Sciatic nerve resection was performed unilaterally. Bone graft incorporation was studied in a bone conduction chamber, and in a model utilizing loaded, large structural allografts in the proximal tibia. Effects of sciatic nerve resection on posttraumatic osteopenia was studied in the femur adjacent to tibial fractures. Mechanical testing of the bones were performed with a three-point cantilever bending test. Bone mineralization was evaluated using ^{85}Sr incorporation, and bone mineral measured with dual x-ray absorptiometry. Bone and callus innervation was studied with immunocytochemistry, utilizing antisera against neuropeptides as CGRP and substance P, and several nerve regeneration markers.

Results: Peripheral nerve resection impaired fracture healing, as ultimate fracture strength was lower after nerve resection, even though larger fracture calluses were generated. Also, nerve injury protected against posttraumatic osteopenia of the femur adjacent to a tibial fracture. Sensory nerves were found in rich amounts in the healing fractures, and also in the bone chamber model during bone ingrowth and incorporation of bone allografts. The mechanical strength of incorporating large allografts was impaired by nerve injury.

Conclusions: Normal fracture healing and adequate integration of bone allografts depend on intact peripheral innervation. Peripheral nerve resection induced a large, but mechanically insufficient callus during fracture healing, and protected against posttraumatic osteopenia.

9. Bone and vascularity

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Bone homeostasis and fracture healing is a multistep process coordinated by a complex cellular interaction of prolifera-

tion, differentiation, apoptosis, extracellular matrix formation and angiogenesis.

Angiogenesis in bone tissue, controlled by specific cellular interactions, is characterized by endothelial cell migration and proliferation resulting in replacement of avascular cartilage by a highly vascular bone tissue. Infiltration of the bone growth plate and fracture callus by vessels is dependent on a balance between the production of inhibiting and stimulating angiogenetic factors. Bone derived growth factors and probably also specific matrix proteins stimulate endothelial cell migration and cell division.

Proliferation of endothelial cells in mature bone tissue is a rare event, with the exception of new blood vessel growth that occurs in fracture healing and tumor formation. A deeper understanding of Angiogenesis in skeletal tissue is not only important for understanding the mechanisms behind bone growth and repair, but also fundamental in the development of novel potential targets for pharmaceutical intervention.

10. Cartilage damage and regeneration

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Cartilage damage: Cartilage degeneration after tissue damage involves activity of degrading enzymes, such as matrix metalloproteases stromelysins and collagenases, which are synthesized by the chondrocytes. Simultaneously, activated chondrocytes produce in excess both proteoglycans (PGs) and collagen trying to compensate for the enhanced turnover of matrix constituents. Degradation products of cartilage affect the synovium which contributes to tissue damage by releasing proinflammatory cytokines like IL-1 and TNF- α . These reduce synthesis of matrix molecules. Cartilage PG concentration decreases and cartilage softens. Cartilage is now prone to further damage by joint loading due to increased energy absorption. Disruption of collagen network marks the "point of no return" in cartilage degeneration. Fibrillation from cartilage surface gradually extends into depth of tissue. Subchondral bone shows concomitant sclerosis and stiffening. Accelerated damage of cartilage takes place between the stiffened bone ends. Finally complete loss of cartilage ensues.

Cartilage regeneration: As long as chondrocytes are viable and the collagen network is intact, cartilage can recover from tissue damage. Under such circumstances, PGs which are depleted during the first stages of cartilage degeneration, can be fully replenished. True cartilage defects which are restricted to uncalcified cartilage substance, do not heal spontaneously. The scar formation is far better when the cartilage damage extends to subchondral bone. The bone marrow-derived cells of scar tissue are able to create hyaline cartilage-looking tissue which usually with time, unfortunately, transforms into fibrocartilage which biomechanically is of inferior quality to hyaline cartilage.

11. Parathyroid hormone receptors

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Parathyroid hormone (PTH) is the most important peptide hormone regulator of calcium homeostasis in mammals. It mediates its biological actions through the PTH/PTHrP receptor (PTH1R), but most likely also through at least two other receptors, the PTH2R and the PTH3R. The PTH1R signals through adenylate cyclase/protein kinase A and phospholipase C/protein kinase C, and is most abundantly expressed in kidney and bone, where it mediates the endocrine actions of PTH. However, it is also highly expressed in the metaphyseal growth plate, where it mediates the autocrine/paracrine actions of PTHrP. The PTH1R thus has an important role in the regulation of endochondral bone formation and growth, and mutations in its gene were identified in two different genetic disorders in humans that present with severe skeletal defects. The PTH2R shares higher amino acid sequence homology with the PTH1R than with any other member of the secretin/PTH/CT family of G protein-coupled receptors. Unlike the PTH1R, it is activated only by PTH (and most likely a novel hypothalamic peptide), but not by PTHrP; its biological function(s) remains to be established. Recent studies in zebrafish have shown that teleost express not only the homologs of the mammalian PTH1R and PTH2R, but also a third receptor, the PTH3R. Transient expression studies in mammalian COS-7 cells showed that this novel zebrafish receptor interacts preferentially with PTHrP. Since pharmacological findings in rodents suggested the presence of a PTHrP-selective receptor in some mammalian tissues, it appears plausible that the equivalent of the zebrafish PTH3R exists also in the mammalian genome.

12. Transplantation osteopathy

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Due to advances in immunosuppressive therapies organ transplantation (TX) became a standardized therapy in several endstage diseases. Posttransplantation bone disease is one major complication in patients with successful organ TX and impairs their quality of life due to an increased risk of osteoporotic fractures. However, only few prospective data are available concerning the incidence of osteoporotic fractures and possible risk factors after different organ TXs. The bone status before TX may be impaired due to immobility and hypogonadism in severely ill patients and the underlying disease itself. After TX immunosuppressive therapy, rejection episodes, hypogonadism and immobility are major risk factors for osteoporosis. However, only few studies were able to show this association, probably due to the complex pathogenesis of post-TX osteopathy and the limited number

of observed patients. In agreement with findings of others our own data following 235 consecutive patients after cardiac or liver TX showed that about one third of these patients suffered from at least one fracture, with the highest risk during the first year after TX. Several studies showed, that the highest rate of bone loss occurs within the first 6 to 12 months after TX. After cardiac TX a decrease of biochemical bone formation and an increase of bone resorption markers was shown. A recent study found a markedly increased risk of symptomatic fractures after kidney TX, with a predominance of foot fractures.

The high incidence of fractures during the first year after solid organ TX and the limited ability to predict fracture risk reliably in a single patient, emphasize the need to evaluate whether fractures can be prevented by bone specific medications (i.e. antiresorptive agents) started before or immediately after TX.

13. Treatment of osteoporosis—antiresorptive regimes

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The effect of antiresorptive agents on bone is to decrease the rate of bone remodelling. The increase in bone density is a consequence of the infilling of the 'remodelling space' and the increase in the degree of mineralisation of bone tissue. This increase in bone mineral density is associated with a decrease in the rate of osteoporosis-related fractures, especially vertebral fractures. The change in bone density does not explain all of the decrease in fracture risk. It is likely that the reduction in bone remodelling rate itself may contribute to the reduction in the risk of fracture.

Treatment with bisphosphonates such as alendronate and cyclical etidronate results in a decrease in bone turnover, an increase in BMD at the spine and hip and a decrease in the risk of vertebral fractures. Alendronate therapy results in a decrease in wrist and hip fracture. Hormone replacement therapy results in similar changes in bone density and fracture risk; most of the supporting data for HRT comes from case-control and cohort studies. Raloxifene and calcitonin have smaller effects than bisphosphonates and HRT on bone turnover and fracture risk, but still decrease the risk of vertebral fractures. Considerations of side effects and efficacy allow us to choose the optimal treatment in an individual.

14. Anabolic osteoporosis therapies

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The ideal therapy for osteoporosis should be able to increase

bone mass to normal levels and restore normal bone structure. This demands increases in bone mass in the order of 30–40%. Several therapeutic modalities have been invoked as anabolic therapies, but so far none of these have entered clinical practice as established treatment regimens.

Fluoride (NaF) increases osteoblastic proliferation and bone mass. Unfortunately long term fluoride therapy also changes the material properties of bone matrix. The formation of fluorohydroxyapatite reduces the elasticity of bone, which predisposes to low energy fractures despite large increases in bone mass. Whether slow release formulations of NaF or lower doses can offset these negative effects of fluoride, remains to be established.

Recombinant parathyroid hormone (PTH) is the most promising anabolic agent. The mechanism behind its anabolic effects is still subject to debate. Intermittent therapy in combination with vitamin D has reported increases in spinal bone mass up to 100%, while combination therapy with estradiol or calcitonin revealed smaller increases. In one study marginal reductions in fracture has been reported. The side effects are few, and hypercalcemia a minor problem with the right dosing. Unfortunately, a recent large scale study was terminated prematurely, so the final role for PTH in future clinical practice is unknown.

Recombinant human growth hormone (hGH) exerts powerful effects on bone remodeling, but the effects on bone mass are marginal and no significant antifracture effects have been reported. Even combination therapy with estradiol was not significant better than therapy with estradiol alone. Insulin like growth factors (IGF) also stimulate bone turnover, but have not been proven effective as antifracture therapies. Growth factors like fibroblast growth factors (FGF), transforming growth factor β (TGF- β) and bone morphogenetic proteins (BMP) all exert some anabolic effects in vitro, but have only been used in animal models.

15. Vitamin D—effects on bone and muscle in relation to osteoporotic fractures

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Increasing evidence has shown that vitamin D prophylaxis is essential in prevention of hip fractures. In an overview lecture recommendations for relevant prophylactic doses of vitamin D and calcium are discussed. The mechanisms by which vitamin D mediates its anti-fracture effects are reviewed.

Hypovitaminosis D Osteopathy is very important to take into account, when the results of BMD measurements are analysed. Vitamin D + calcium treatment results in an increase in BMD of 2–4 % per year in patients with secondary hyperparathyroidism, whereas the increase in osteomalacic patients can be as high as 60% per year.

Hypovitaminosis D myopathy is a common disease in pa-

tients with serum levels of 25-hydroxyvitamin D below 25 nmol/l (10 ng/ml). Myopathy is common in vitamin D deficient patients even without biochemical signs of bone involvement. Vitamin D deficiency results in weak and slow muscles, which makes falls and consequently hip fractures more likely. Vitamin D treatment results in significant improvement in both muscle strength and kinetics. These findings could be a very likely explanation of the anti-fracture effect of vitamin D.

16. Molecular markers in osteoarthritis—progress and challenges

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OA is associated with a loss of the balance between synthesis and degradation of macromolecules that provide joint cartilage with its functional properties. The destruction or remodeling of cartilage and other joint tissues involves the degradation of matrix molecules, released as fragments to joint fluid, blood and urine. Such molecular fragments, or proteases and other molecular factors, can serve as 'biomarkers' of joint metabolism in OA. If properly validated, biomarkers could serve as surrogate measures to determine prognosis, severity; predict response to therapy, monitor response to therapy, and to identify disease mechanisms on the molecular level. Since the markers reflect dynamic changes, they are perhaps most likely to serve as surrogate measures of prognosis and response to treatment. Markers may thus complement existing measures of OA. They may also uniquely provide support for proof-of-principle in early-stage trials of new disease-modifying drugs for OA.

We have shown the increased release of fragments of aggrecan, COMP, BSP, procollagen II C-propeptide, and type II collagen C-terminal crosslinks. Further, the levels are increased of MMP-1, MMP-3 and TIMP-1 proteins in human joint fluid after knee injury and in OA. MMP-1 protease activity in joint fluid is increased in OA. MMP protein levels in synovial fluid are sensitive indicators of joint pathology. Serum concentrations of MMP-3 increase after joint injury. The changes are consistent with known alterations of *in vivo* and *in vitro* metabolism in animal models of OA and joint inflammation, and *in vitro* in human OA.

These events point to marked changes in rates of both matrix degradation and matrix synthesis in OA, and that markers can reflect such changes. We have determined between- and within-patient variability for molecular markers in different body fluid compartments in several stable cohorts of patients with OA. The availability of such data now allows calculations to determine the number of patients needed in prospective studies using these markers as surrogate outcome measures.

17. Techniques for cartilage repair

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To facilitate the repair of a cartilage defect it is important for the surgeon to deliver high densities of chondrogenic repair cells into the cartilage defect. All current clinical cartilage repair methods could be seen as cell therapies.

Most used technique have been to repair cartilage defects by opening of the subchondral plate with drilling, abrasion arthroplasty or microfracturing, allowing stem cells to migrate from the bone marrow to populate the fibrin clot of the defect. Periosteal and perichondral grafting in combination with subchondral drilling have been reported to produce hyaline-like repair through recruitment of chondrogenic cells from the bone marrow and the graft itself. Large experience exist with osteochondral allografting and interesting is also the multiple autologous osteochondral grafting technique recently introduced clinically. Transplantation of *in vitro* expanded autologous chondrocytes in combination with periosteal grafting has been tried for chondral and osteochondral lesions of human knees with promising results.

Unfortunately, there is a lack of randomized studies comparing the different cartilage repair methods and we are not yet able to tell which methods that are superior over the other to produce a repair tissue with the potential to heal the injured cartilage and maintain its function for a prolonged time.

18. Pharmacological intervention in osteoarthritis

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Therapeutic targets in osteoarthritis (OA) include the following protection: primary (remove the cause), secondary (treat the OA process), and tertiary (treat the consequences of OA). Secondary protection must consider: 1) mechanical/surgical intervention, 2) drugs, local or systematic, and 3) combination of drugs and mechanical ones. The first duty in OA management is patient education, pain relief and optimisation of functioning. Current consensus demands to distinguish drugs directed at symptoms called "Symptoms modifying drugs" and/or at pathology of OA called "Structure/disease modifying drugs". Glucosamine sulphate, hyaluronan, diarthrin, chondroitin sulphate represent a first group. Flavonoids and bone resorption inhibitors are tested. Symptomatic medications used in OA include also simple analgesics, low analgesic or higher anti-inflammatory doses of NSAID, antispasmodics, narcotic analgesics and topical capsaicin. Targets for drugs of second group are inhibition of cartilage degradation: cytokine and proteases inhibition,

stimulation of repair process and reduction of subchondral bone remodelling. Up to now there are not drugs being able to stop or reverse OA pathology, but intensively tested are glucosamine sulphate, sulphated and non-sulphated glycosaminoglycans, bone related active agents, enzyme inhibitors, stem cell grafts and cytokine/growth factors.

19. Extreme physical activity and its consequences for bone and cartilage

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The purpose of the present review was to evaluate the influence of extreme physical activity on bone and cartilage. The possible effect of extreme physical activity on bone is poorly investigated. A few prospective studies have investigated the effect of strenuous physical training on Israeli recruits. Bone mass increased with about 10% in the tibia for those who completed the 14-week training period, with a drop out rate of about 40%, mostly due to stress fractures. Other studies have found increases in bone mass of a few percent women participating in more low impact exercise training. Experimental studies suggest that the increase in bone mass is related to the magnitude of deformation of the bone. It is also suggested that the loading should be in an unusual direction and repeated regularly to result in a great osteogenic effect. Cross-sectional studies have generally demonstrated higher bone mass in athletes participating in weight bearing activities compared to controls. The effect of physical activity on bone seems to be influenced also by factors such as the age, hormone- and nutritional status.

An increased incidence of degenerative joint changes and cartilage damage has been found primarily in the knee but also in the hip in former athletes previously active in soccer, ice hockey, and track- and field. Interestingly, the increased bone density in athletes has been suggested to be associated with higher bone stiffness and less shock absorbing capacity of the subchondral bone, with the risk of developing osteoarthritis. Most previous studies have found that physical activity in the recreational athlete is not associated with osteoarthritis.

20. Cellular mechanisms of action of bisphosphonates

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The bisphosphonates (BPs) are synthetic analogs of naturally occurring pyrophosphate. BPs suppress bone resorption. Clinically they have an established role in the prevention and treatment of skeletal diseases that involve bone destruction, such as osteoporosis, bone metastases and Paget's dis-

ease. BP molecules are comprised of a carbon-phosphate-carbon backbone, to which various side chains can be attached. The backbone confers high affinity to bone mineral, whereas the side chains influence the pharmacological activity of the compounds. BPs with side-chains containing an amino-group (aminoBPs) are typically more potent than non-aminoBPs. The different groups of BPs have different mechanisms of action, but in the bone microenvironment the ultimate target of all BPs is the bone resorbing osteoclast. Depending on the BP in question, they have been suggested to affect the information, activation or apoptosis of the osteoclast. Both direct effects and indirect effects mediated by osteoblasts have been suggested. The non-aminoBPs are metabolized in mammalian cells into ATP-like compounds and at least some of their effects are mediated through these metabolites. AminoBPs are not metabolized, but effect osteoclasts by inhibiting one or more enzymes of the mevalonate pathway. Recently, the first intracellular target of aminoBPs was identified as isopentenyl pyrophosphate isomerase/farnesyl pyrophosphate synthase. After 30 years of intensive BP research, these recent findings are revealing new targets for the development of bone drugs.

Bone – genes

21. Testing adenovirus-mediated gene transfer into regenerating bone

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Osteoinductive growth factors have potential to enhance fracture healing. As bone healing proceeds relatively slowly, repetitive application of large doses of such growth factors may be required. Gene transfer provides interesting possibilities for sustained delivery of growth factors in regenerating bone. The purpose of this study is to evaluate the efficacy of adenovirus mediated transfer of growth factor genes, such as BMP-2, into regenerating bone. As the first step we tested the ability of adenovirus to infect bone cells *in vivo*.

A round bone defect, 0.9 mm in diameter, was drilled into the distal metaphysis of mouse femur. Recombinant replication-deficient adenoviruses (1.75×10^8 pfu) containing *LacZ* reporter gene under the control of CMV IE promoter (rAd-*LacZ*) were injected locally into the defect at the time of surgery. Expression of the transferred gene was detected by staining for β -galactosidase activity and by measuring the enzyme activity in bone homogenates.

After *in vivo* injection of rAd-*LacZ*, a strong staining for β -galactosidase activity was observed in the metaphyseal

bone and in the growth plate distal to the defect, whereas only faint staining was observed in the surrounding periosteum and no staining in epiphyseal or diaphyseal bone. In control bones no staining was observed. Expression of marker gene persisted for >2 weeks.

The results suggest that adenoviral vector can be used for gene transfer to regenerating bone tissue *in vivo*.

22. Regulation of OPG mRNA levels by protein kinase A and protein kinase C in human bone marrow stromal cells

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Osteoprotegerin (OPG) or osteoclast inhibitory factor is a soluble member of the TNF receptor superfamily. By binding to osteoclast differentiation factor, OPG can inhibit osteoclast recruitment, thereby blocking osteoclastogenesis.

By using RNase protection assay we have investigated the regulation of OPG mRNA levels in human bone marrow stromal cells by activators of protein kinase A and protein kinase C pathways. Stimulation of human bone marrow stromal cells with either phorbol 12, 13-dibutyrate (10 nM), or thrombin (3U/ml), both activators of the protein kinase C pathway, increased the levels of OPG mRNA. However treatment of cells with Forskolin (FSK) (10 µM) an activator of protein kinase A pathway decreased the OPG mRNA levels. The decrease in OPG mRNA levels was also seen when stimulating cells with prostaglandin E₂ (PGE₂) (1 µM). Since PGE₂ stimulates cAMP formation in human bone marrow stromal cells these data suggest that PGE₂ down regulates the mRNA levels of OPG via protein kinase A activation.

Conclusion: The mRNA levels of OPG are upregulated via the protein kinase C pathway while stimulators of protein kinase A downregulate the OPG mRNA levels in human bone marrow stromal cells.

23. Mouse cathepsin K gene overexpression in transgenic mice

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Cathepsin K, a lysosomal enzyme predominantly expressed in osteoclasts, belongs to the papain family of cysteine proteinases. Several recent studies suggest that cathepsin K plays a major role in osteoclastic bone resorption.

Materials and methods: The overexpression vector consists of the mouse cathepsin K gene (*Ctsk*) including 4 kb of

5' and 0.3 kb of 3' flanking regions. The genomic clones were retrieved from a 129SVJ mouse phage library. A silent mutation was engineered in exon 6 of the transgene for detection and monitoring of its function. The construct was microinjected into fertilized FVB/N eggs using standard protocols. The resultant transgenic mice have so far been analyzed using histological and Northern analysis.

Results: The mice overexpressing the *Ctsk* gene are viable and fertile. Northern analysis of a panel of tissues show a prominent increase in the mRNA levels of the heterozygous transgenic mice in calvarial bone and skin and to some extent in muscle compared to their non-transgenic littermates. Preliminary histological data suggest that the tibias of the heterozygous newborn mice are normal.

Conclusions: In a search for a novel osteoporosis model we have created transgenic mouse lines overexpressing the *Ctsk* gene. Further studies are required to assess the levels and activity of the cathepsin K in these mice. Additional histological data is also needed on the microarchitecture of the bone during ageing.

24. Characterization of cell type specific promoter elements and their use in targeting transgenes into skeletal tissues

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This project aims to develop techniques and vectors for the expression of engineered genes in specific cells of the mouse skeleton, chondrocytes, hypertrophic chondrocytes and osteoclasts. For this purpose we use mouse genes type II collagen (*Col2a1*), type X collagen (*Col10a1*) and cathepsin K (*Ctsk*) respectively. Precise tissue-specific regulatory elements in the *Col2a1* have been identified but not in the *Col10a1* or in the *Ctsk*.

Materials and methods: Green fluorescent protein (GFP) has been used as a reporter gene in chondrocyte-specific vectors built up from the *Col2a1*. For hypertrophic chondrocyte-specific vector we are looking for regulatory elements in more distal regions of hitherto identified 5'-flanking region of the *Col10a1*. For osteoclast-specific vector we have used GFP as a reporter gene in two different constructs of the *Ctsk*.

Results: Different kinds of positive GFP transcripts have been detected in the RNA samples of the chondrocyte-specific vectors but not at appropriate levels or sizes. The *Ctsk* gene constructs used have not revealed any GFP transcripts.

Conclusion: Further experiments are needed to establish the optimal conditions for detecting GFP in skeletal tissues, to determine why the *Col2a1* vectors are not producing expected amounts of transcripts, to find out genomic DNA clones of the *Col10a1* and to find out positive regulatory elements of the *Ctsk*.

Bone – receptors

25. Interleukin-13 and interleukin-4 inhibit proliferation and stimulate interleukin-6 formation in human osteoblasts—evidence for the involvement of receptor proteins IL-13R α , IL-13R α' and IL-4R β

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Remodeling, the continuous turnover of mature bone is influenced by several known proinflammatory cytokines. Less is known about the effects of the anti-inflammatory cytokines, interleukin-13 (IL-13) and interleukin-4 (IL-4).

The antiinflammatory cytokine IL-13 inhibits cell proliferation and stimulates IL-6 formation in isolated human osteoblasts (hOBs), previously shown by us. Comparative studies on cell proliferation demonstrated that IL-4 and IL-13 dose-dependently inhibited [³H]-thymidine incorporation into DNA of cultured hOB cells. IL-13 and IL-4 also enhanced the mRNA levels of IL-6, as measured by RNase protection assay. ELISA measured secretion of IL-6 revealed a dose response augmentation of IL-6 formation and that IL-4 was ten times more potent than IL-13 as an IL-6 inducer in hOB cells. Also the RNA expression of the four known IL-13/4 receptor proteins was investigated in hOBs. mRNA expression for IL-13R α , IL-13R α' and IL-4R β was repeatedly demonstrated by reverse transcriptase while mRNA for IL-2R γ_c was not detected.

Conclusion: Human osteoblasts express mRNA for the receptor proteins IL-13R α , IL-13R α' and IL-4R β . Finally, IL-4R β activation is involved in IL-6 formation whereas blocking antibodies to this receptor protein failed to influence the antiproliferative effect of IL13/4.

26. Analysis of phospholipase C signaling in Zebrafish PTH-receptor type 1 and type 3 receptor chimeras

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Recently, cDNAs encoding three PTH/PTHrP receptors were obtained from zebrafish. In addition to the homologues of the mammalian type I (PTH1R) and type II (PTH2R) receptors, a novel receptor designated type III (PTH3R) was isolated. Contrary to the PTH1R the agonist-stimulated zPTH3r failed to activate the phospholipase C (PLC) signaling pathway. To elucidate the structural basis for this finding we generated chimeras between the zPTH1R and zPTH3R and tested these receptor mutants for their ability to activate

the PLC pathway.

Methods: Using oligonucleotide site-directed mutagenesis we introduced two unique restriction sites without changing the amino-acid sequence and generated receptor mutants with amino acid changes in the second intracellular loop (ICL). Wild-type and mutant receptors were expressed in COS-7 cells and radioreceptor assays showed that all receptor mutants bound PTH with similar affinity as wild-type receptors. To assess total inositol phosphates (IP) accumulation cells were prelabeled with 3H-myoinositol, before challenge with PTHrP and isolation of IP by ion-exchange chromatography.

Results: A chimeric receptor containing zPTH1R sequence from the amino-terminus to the middle of transmembrane region (TM) 5 and zPTH3R sequence onwards had impaired PLC signaling capabilities whereas the reciprocal receptor signaled well. A chimera with PTH1R sequence from TM 3 to the tail showed further improvement in signaling. These findings suggest that ICL2 and the region from ICL3 to the tail in zPTH3R contain amino acid sequences that prevent PLC activation.

27. Osteocyte-like cell line MLO-Y4 expresses estrogen receptors α and β

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Osteocytes are the most abundant but also the most unknown cells in bone. MLO-Y4 osteocyte-like cell line has been isolated from long bones of transgenic mice in which the SV40 large T-antigen is expressed under the osteocalcin promoter (¹). The properties of this cell line are very similar to primary osteocytes. To test the hypothesis that osteocytes would be partially responsible for the anabolic effects of estrogen in bone, we studied the possible presence of estrogen receptors α and β in MLO-Y4 cells.

Materials and methods: RNA was isolated from two clones of MLO-Y4 cells, 3F5 and 4A6, and synthesised into cDNA which then was subjected to RT-PCR. We used primers for both estrogen receptor (ER) α and β . RNA preparation from liver was used as a control.

Results: ER α was shown to be expressed in both clones. Especially high signal was seen in 4A6. ER β was more weakly detectable but also here it could be seen at least in clone 4A6. Liver control gave a positive result for ER α .

Conclusion: The expression of estrogen receptors in osteocytic cell line suggests that estrogen may have an important function on these cells also in vivo. Estrogen levels may alter the bone adaptation to mechanical loading by sensitising osteocytes and thus be part of the interplay between hormonal and mechanical stimuli.

Reference: 1) Kato Y, Windle JJ, Koop BA, Mundy GR and Bonewald LF (1997) Establishment of an osteocyte-like cell line, MLO-Y4. *J Bone Miner Res* 12: 2014-23.

28. Effects of IL-4 and IL-13 on IL-6 formation in human osteoblasts, interactions with TNF and IL-1

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Interleukin-6 (IL-6), a cytokine known to stimulate osteoclast development, is produced by osteoblasts. The formation of IL-6 is influenced by different factors where especially the two proinflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF) strongly promote IL-6 formation. We have previously shown stimulation of IL-6 production by the antiinflammatory cytokines, interleukin-4 (IL-4) and interleukin-13 (IL-13) in human osteoblasts. Recent studies have disclosed similarities between the receptors of IL-4 and IL-13. There is evidence that these receptors, consisting of different proteins, in some way share receptor subunits. The receptor subunits IL-13R α , IL-13R α' and IL-4R β but not IL-2R γ c are expressed on the human osteoblast surface. Out of these subunits IL-4R β is involved in IL-6 formation induced by either IL-4 or IL-13.

In this study we have investigated interactive effects between the mentioned cytokines concerning IL-6 formation in human osteoblasts. By co-stimulation experiments with IL-4 and IL-13 respectively together with IL-1 or TNF- β we found a synergetic effect on IL-6 formation in human osteoblasts. However, no synergetic effect on IL-6 formation was detected when stimulating the cells with both IL-4 and IL-13. Since IL-4 and IL-13 share receptor subunits this may indicate a competition between IL-4 and IL-13 on the receptor level.

Bone metabolism

29. Serum PTH and B-Ca⁺⁺-responses to oral calcium and D-vitamins

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The immediate influence on S-PTH and B-Ca⁺⁺ of oral calcium $\pm$ vitamin-D₃ or calcitriol were studied.

Material and methods: B-Ca⁺⁺ and S-PTH were measured after an overnight fast every 5 or 15 minutes during 4 hours in 7 healthy women (30–45 years). Study 1 (control): 125 ml tap water (also given in study 2–4); Study 2: 1 g calcium; Study 3: 1 g calcium and 400IU (5 μ g) vitamin-D₃; and Study 4: 0.5 μ g calcitriol plus 1 g calcium.

Results: S-PTH (AUC) fell significantly during study 4 compared to study 1 ($p = 0.01$) but non-significantly during study 2 and 3 compared to control (study 1) ($p = 0.15$ and $p =$

0.09). B-Ca⁺⁺ increased significantly during study 4 ($p = 0.009$) and study 3 ($p = 0.04$) compared to study 1 and was higher during study 4 than during study 3 ($p = 0.03$).

Conclusion: Both calcium alone and calcium plus vitamin-D₃ increases B-Ca⁺⁺ within 4-hours but only calcitriol plus calcium suppresses S-PTH significantly. Oral calcitriol plus calcium therefore seems to inhibit the PTH secretion immediately. This could be of physiological importance for e.g. in prevention of bone loss.

30. Bone mineral density cannot be predicted accurately by clinical and biochemical variables in perimenopausal women

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Our aim was to predict spinal and femoral bone mineral density (BMD) in perimenopausal women from simple clinical and biochemical variables.

Material and methods: 2016 women 3–24 months past last menstrual bleeding. Mean age 50.1 ± 2.8 , range 43–58 years. Age, height, weight, number of full term pregnancies, number of hours of physical activity per week, sunbathing habits, daily intake of calcium and vitamin D, use of solarium, smoking habits, consumption of alcohol, coffee, and tea, history of forearm or femoral neck fractures among the parents, serum osteocalcin (S-OC), serum bone specific isoenzyme of alkaline phosphatase (BSAP), and urine hydroxyproline/creatinine ratio (U-OH/creatinine) were used as predictors. BMD of lumbar spine (L2-L4) and of femoral neck were measured by DEXA.

Results: Spine: physical activity, height, and weight were all positively related to BMD, while age, S-OC, BSAP, U-OH/creatinine, and a maternal history of forearm or femoral neck fractures were negatively associated with BMD. The regression equation explained 17.0% of the total variation.

Femoral neck: physical activity, body weight, calcium intake, and tea consumption were positively related to BMD while age, BSAP, U-OH/creatinine, coffee intake, and a maternal history of forearm or femoral neck fractures were inversely associated with BMD. The regression equation explained 20.4% of the total variation.

Conclusions: High bone turnover evaluated by biochemical bone markers was linked to low BMD. The maternal history points to an inherited lower bone mineral density. On an individual basis the prediction of BMD by simple clinical variables had limited value.

31. Longitudinal study of IGF-I and osteocalcin between 70 and 86 years of age

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Growth hormone is important for bone development and metabolism in young individuals but, so far, it has not been established whether growth hormone plays a role in common senile osteoporosis. Serum osteocalcin is considered to be a marker of bone turnover and formation.

The purpose of this study was to examine the relations between IGF-I, osteocalcin to bone mineral density and other factors in a community based population study between 70 and 86 years of age.

The present study was performed in a random sample of 619 individuals at age 70 with follow up at age, 76 and 86. Bone mineral density was measured by dual photon absorptiometry in calcaneus at the age of 70 and 76 and by DXA HOLOGIC 4500 at age 86. Serum IGF-1 was determined by radioimmunoassay, Nichols. Osteocalcin was analysed by a double-antibody radioimmunoassay, CIS.

Crosssectional (C) and longitudinal (L) data of IGF-1 µg/L, mean (SD)

Age	Women IGF-1		Men IGF-1	
	C	L	C	L
70	138.7 (55.6)	132.2 (50.8)	155.3 (62.9)	163.7 (53.6)
76	123.9 (55.2)	118.7 (49.4)	141.0 (56.0)	146.9 (47.4)
86	118.4 (51.0)	118.2 (60.5)	130.4 (47.4)	132.3 (52.6)

IGF-1 was significantly correlated to BMD in all age groups in women but not in men.

Crosssectional (C) and longitudinal (L) data of osteocalcin µg/L, mean (SD)

Age	Women osteocalcin		Men osteocalcin	
	C	L	C	L
70	6.9 (3.5)	7.1 (3.5)	6.3 (3.3)	6.2 (2.9)
76	8.5 (3.0)	8.5 (3.0)	7.8 (3.4)	7.6 (2.7)
86	9.4 (3.5)	9.3 (3.4)	8.5 (3.6)	9.0 (3.3)

Osteocalcin correlated negatively to BMD in both sexes in all age groups. Osteocalcin correlated to S-PTH ($r = 0.39$, $p = 0.0001$).

We conclude that S-IGF-1 decreases after the age of 70, more in men, compared to women. S-IGF-1 correlated to BMD in women but not in men. S-osteocalcin increased in both sexes and correlated negatively to BMD in both sexes.

32. Bone mineral density (BMD) and osteocalcin level in broiler chickens during 8 weeks of life after aluminium sulphate treatment

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The aim of the experiment was to determine the effect of aluminium sulphate on bone mineral density (BMD) and osteocalcin levels in broiler chickens.

Materials and methods: Broiler chickens were kept in a climate-controlled room with feed and water ad libitum, from the 1st day of life to 8 weeks. From the 4th day of life, aluminium sulphate was added to the drinking water. The aluminium content (g/dm³) was 2 g. At the end of the experiment the chickens were slaughtered and changes in bone mineral density, osteocalcin level in blood serum, body weight and bone mass were measured. Aluminium content in bone was also controlled.

Results: Aluminium sulphate decreased the value of osteocalcin in the blood serum of female and male broiler chickens in comparison to the control group. Aluminium sulphate decreased bone mineral density in female femur and humerus in all experimental groups in comparison to the control. The value of bone mineral density in male humeri was lower than in the control group, but in femora, aluminium sulphate increased the value of BMD. Body weight and bone mass were lower in all experimental groups in comparison to the control.

Conclusion: The obtained results present evidence of influence of aluminium sulphate on bone mineral density, body weight and bone mass and also on values of osteocalcin in broiler chickens.

33. The effect of isotretinoin on bone turnover and insulin-like growth factors during treatment of young adults for severe acne

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The vitamin A derivative, isotretinoin, is used in adolescent and young adults for treatment of severe acne resistant to conventional therapy. Major concerns are raised due to possible musculo-skeletal side-effects, related to the effect of retinoids on bone cell proliferation and differentiation.

In order to evaluate the effects on isotretinoin treatment on bone metabolism we longitudinally followed 31 patients (12F, 19M), mean age 22 (17–36) years, treated with isotretinoin 1 mg/kg body weight daily for 6 mo. Blood and urine samples were collected prior to treatment, at 3 mo, at the end

of treatment (6 mo) and at 12 mo. Assessment was made by S-osteocalcin (Oc) and pro-collagen peptide (PICP), U-deoxypyridinoline (D-pyr) and insulin-like growth factor I (IGF-I, -II) and binding proteins (IGFBP-3, -4, -5).

Results: Oc, PICP or D-pyr did not change during therapy. IGF-II was significantly increased at 3 mo ($p < 0.01$), remained elevated at 6 mo, but had normalized at follow-up. IGFBP-3 reached a maximum at 6 mo ($p < 0.05$), while IGF-I, BP-4 and -5 showed similar trends but the changes were not significant, thus, all measured IGF-components showed a similar reaction during treatment. The IGF-I and BP-5 levels were correlated at all time points ($r = 0.45-0.71$). The increase of IGF-I and BP-3 correlated during treatment. The changes in IGF-I and -II were not related to liver function.

Conclusion: In this longitudinal study of isotretinoin, we found no significant effect on bone turnover using a standard clinical treatment protocol for severe acne in young adults. These findings suggest, that short-term treatment with isotretinoin may not cause deleterious skeletal effects, and thereby allowing for a wider use of this effective treatment. The result may be specific for this vitamin A derivative. In contrast to the anticipated decrease in stimulatory IGF's from retinoids, we found an upregulation in stimulatory IGF's, which may possibly have prevented the negative skeletal effects of this derivative.

34. Fracture induces long-term effects on bone turnover in humans

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Despite the fact that fracture is known to induce long-term effects on bone mass at all ages, fracture effects are rarely considered when using biochemical markers as a tool, in the evaluation of fracture prone osteoporotic populations.

To further elucidate the changes in bone turnover in relation to fracture, we have utilized a clinical fracture model, the corrective proximal tibial osteotomy, a procedure to treat degenerative changes of the medial knee compartment. The procedure mimics a fracture of a major bone, but has the advantage of allowing for assessment both prior to the fracture and longitudinally.

Material and methods: We studied 14 patients (mean age 57 (35–73) years), who underwent proximal tibial osteotomy. Postoperative treatment included 6–8 weeks in an ankle-high plaster allowing for immediate full weight bearing, thereafter, unrestricted mobilization.

Blood and urine samples were collected at five time points. Bone marker analysis for bone formation (BF) and bone resorption (BR) were performed, including the use of newly developed antibodies for total (tot) and carboxylated (cxy) osteocalcin (Oc) in serum and urine.

Results: BF: S-Oc_{tot} increased to peak at 4–7 mo after fracture ($p < 0.0001$) and a similar increase was seen for Oc_{cxy} ($p < 0.04$) (Figure). Total alkaline phosphatase followed the same pattern ($p < 0.01$) and BF was normalized after about a year.

BR: increased significantly with a doubling of urinary deoxy-pyridinoline excretion at 6 weeks and a S-ICTP (c-telopeptide) increase of 70%. Values returned to baseline after a year. U-Oc increased to a maximum at 6 weeks ($p < 0.05$) (Figure).

The initial percentage increase in BR was greater than that of BF, suggesting a net loss of bone at least in the early phase.

Conclusions: 1) Bone turnover is immediately altered after a fracture. 2) The major changes occur between 6 weeks and 6 months. 3) The alterations persist up to 12–18 months after fracture. These findings suggest long-term post-fracture effects on bone turnover, where increased BR may lead to enhanced bone loss also in those already osteoporotic. Importantly, fracture related bone turnover changes may significantly contribute, but be underestimated in studies of osteoporotic populations. 4) The new serum Oc assays readily detects alterations of BF, while 5) it remains unclear if the changes in U-Oc are related to resorption or formation.

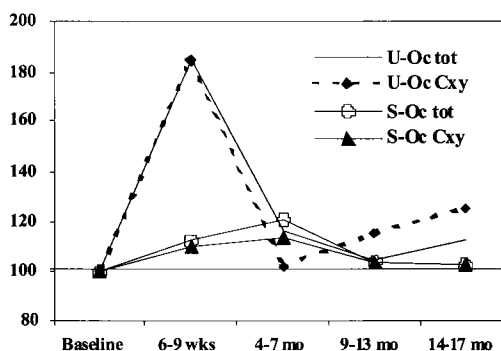


Figure. Paper 34

35. Assessment of upper level bone resorption and formation markers in healthy female

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To evaluate clinical usefulness of representative markers of bone turnover the attempt to assess the upper level of normal values in a group of 179 healthy women at the age of 25–69 years has been taken. We measured activity of bone formation markers: serum bone alkaline phosphates (FAP), serum osteocalcin (OC), and bone resorption markers: urine deoxypyridinoline (DP/Cr) and C-terminal telopeptides of Type-I collagen in urine (CrossLaps/Cr) and calciuria (Ca/Cr

Table. Paper 35

Age	Serum FA (IU/L)			Serum OC (ng/ml)			Urine Cross Laps (ug/mmolCr)			Urine D-pir (nmol/mmol Cr)		
	n/mean	90 per.	95 per.	n/mean	90 per.	95 per.	n/mean	90 per.	95 per.	n/mean	90 per.	95 per.
< 30	17/19.32	21.40	23.90	17/19.32	25.40	27.20	15/235.2	399.90	480.73	18/8.66	13.97	14.00
31–40	51/14.08	19.20	22.40	50/17.82	22.20	24.70	47/204.2	370.00	490.92	54/9.70	13.91	14.52
41–50	34/13.9	21.60	23.20	30/16.68	21.05	25.10	26/180.4	328.33	362.85	35/9.87	12.24	16.30
> 50	64/20.69	31.50	39.60	62/20.36	25.90	26.90	54/249.7	490.44	605.90	64/10.9	16.05	18.34

ratio). All these markers we assessed in 4 groups of age: before 30, 31–40, 41–50 and over 50 years. Empirical distributions characterised distribution of concentration or activities of markers tested have been drawing and value of 90 and 95 percentyl created hypothetical upper limit. Values above that limit may indicate bone pathology. Results are listed in Table.

Value of 90 and 95 percentyl may indicate the possibility of existence higher upper limit of bone markers levels in healthy woman population than traditional values definite by 2 standard deviations.

Bone mineral density

36. Late height growth is related to low bone density in 19-year-old men

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Development of bone in adolescence is considered to be related to general growth.

The purpose of this study was to relate annual measurements of BMD, between 16–19 years of age to anthropometric factors, birth height and height growth after the age of 16, peak height velocity and to hormonal factors.

250 16-year-olds of both sexes were randomly sampled and invited to participate in a longitudinal study with annual examination of bone mineral density, body composition and blood samples. 238 subjects responded. Bone mineral density and body composition were measured with a pencil beam DXA, Hologic 2000 plus. Weight, height, pubertal state, testicular volume were measured annually and blood samples collected.

At the age of 19 body height in women correlated to BMD LI-L4 ($r = 0.26$), area ($r = 0.74$), BMC ($r = 0.60$) and in hip total, BMD ($r = 0.28$), area ($r = 0.67$), BMC ($r = 0.57$) and HAL ($r = 0.58$). Height growth in women between 16–19 years of age did not correlate to BMD or BMC but only to HAL ($r = 0.34$).

In men at the age of 19 height correlated to BMD LI-L4 ($r = 0.24$), area ($r = 0.58$), BMC ($r = 0.43$) and in Hip total, BMD ($r = 0.11$, ns), area ($r = 0.57$) HAL ($r = 0.56$).

Body weight at the age of 19 showed strong correlations to BMD, BMC and area in both sexes. Height growth between 16–19 years of age in young men showed strong negative correlations in LI-L4 BMD ($r = -0.48$), area ($r = -0.29$) and in hip total ($r = -0.40$), area ($r = -0.10$, ns), BMC ($r = -0.34$). Birth height was related to HAL in women ($r = 0.29$) and in men ($r = 0.20$, ns).

Height growth in men between 16–19 years was subdivided in to quartiles. Cut of levels were 1.5, 2.6, and 4.5 cm. The mean height at the age of 16 was about 178 cm in quartile 1–3 and 171 cm in quartile 4. HAL was similar in all quartiles. BMD, BMC and area in total Hip and Lumbar spine was much lower in men in quartile 4 at the age of 16 and at the age 19. Testicular volume was correlated to BMD, BMC, area and body weight but not to height, birth height or HAL. Testicular volume was negatively correlated to height growth ($r = -0.35$) at the age of 16.

Conclusion: Young men at the age 19 with late height growth have lower BMD, BMC and area in lumbar spine and hip total.

37. Increased risk for secondary hyperparathyroidism in hip fracture patients

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Hip fracture is an increasing clinical and economic problem worldwide as populations age. Increased bone resorption with ageing may in part be caused by impaired calcium and vitamin D homeostasis with resultant secondary hyperparathyroidism. Signs of secondary hyperparathyroidism are usually the first indication of vitamin D deficiency and PTH mediated bone loss is an important consequence of vitamin D deficiency which may lead to osteoporotic fractures. The bone lost in hyperparathyroid states is mainly cortical bone, which means an increased risk of fractures of tubular bone eg. hip fracture. The aim of the present study was to determine intact PTH in frozen specimen from patients with hip fracture and in subjects from two hundred and nine patients (147 women, 62 men, mean age 82.1) presenting to Sahlgrenska University Hospital, Göteborg with a of hip fracture

during a 8-month follow up were included. A longitudinal population study from age 76 (n = 625) to age 86 (n = 183) was a control. Venous blood sample were obtained at the emergency ward preoperatively, and were then frozen and stored in sealed glasampoules below -20 °C until analysis were performed. Parathyroid hormone was increased (> 65 ng/L, range 9.4–312) in 50% of the patients with hip fracture as a sign of impaired calcium and vitamin D, homeostasis.

Proportion (%) of subjects with PTH > 65 ng/L

Age	Hip (fx)	P	Controls
76	33	0.02	15
86	59	0.003	36

The relative risk of increased PTH in hip fracture patients compared to controls was 2.5 (1.9–3.2). We conclude that hip fracture patients have increased risk for impaired calcium and vitamin D homeostasis.

38. Association between body morphology, physical activity, and bone mineral density in Polish postmenopausal women

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Osteoporosis is most common metabolic disease among postmenopausal women. Body morphology and physical inactivity are considered as risk factors of osteoporosis.

Materials and methods: The participants (n = 101) included in this analysis were Polish healthy postmenopausal women age from 50 to 68 years, who was divided into 3 groups BMD-dependent (I – osteoporosis [n = 43]; II – osteopenia [n = 43]; III – normal bone density–control group [n = 15]). Measurements: BMD lumbar spine measured by dual energy X-ray absorptiometry (DEXA), body weight, high, body mass index (BMI), body circumferences (waist, hip) and their ratio (WHR), 4 skin-fat folds by Harpenter's foldmeter, which was use to estimate fat body mass (FBM) and lean body mass (LBM), physical activity and physical work during all life.

Results: The mean value of BMD was: I: 0.762 ± 0.102 g/cm²; II: 0.950 ± 0.079 g/cm²; III: 1.124 ± 0.075 g/cm². The mean value of BMI and WHR were: I: 24.1 ± 3.5 and 0.77 ± 0.05 ; II: 27.4 ± 4.6 and 0.79 ± 0.05 ; III: 28.8 ± 3.9 and 0.79 ± 0.05 . The differences of BMI and WHR between this 3 groups were statistically significant ($p < 0.01$ and $p < 0.05$), and BMI correlated with BMD ($r = 0.3$; $p < 0.05$). Obesity % (BMI > 30) were I: 4.6%; II: 23.3%; III: 40.0%. The value of FBM and LBM were I: 26.7% and 73.3%, II: 29.9% and 70.1%, III: 32.9% and 67.1% (differences between groups $p < 0.01$). We observed significant correlation between: LBM

and T-score ($r = -0.5$; $p < 0.01$); FBM and T-score ($r = 0.5$; $p < 0.01$); FBM and BMI ($r = 0.8$; $p < 0.01$). Physical activity before age 30 was related with BMD ($r = 0.2$; $p < 0.05$). Physical activity level in this 3 groups, during all life, differed significantly ($p < 0.05$).

Conclusions: Polish osteoporotic postmenopausal women have both lower BMI and FBM then ones with osteopenia and normal BMD. BMI, FBM and LBM are related to BMD. Physical activity may be considered as a protective factor for postmenopausal osteoporosis.

39. Biological age, bone mass and balance in 75-year-old women

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Biological age may be an underestimated factor for fracture prediction. However, biological age lacks definition. The study was done to evaluate if biological age, assessed by a subjective fragility score, can predict bone mineral density (BMD) and balance.

Patients and methods: 500 women, 75 years old, randomly selected from the city files of Malmö participated. One investigator gave each participant a subjective score from 1–100 within 15 seconds from first sight (1: fragility and a high biological age; 100: no fragility and a low biological age). BMD of the hip (neck and trochanter region) and lumbar spine was measured with a Lunar DPX-L scan. A modified Romberg balance test was performed.

Results: There was no correlation between the subjective fragility score and the BMD of the hip region (neck: $r = -0.09$, $p = 0.05$, $n = 452$; trochanter: $r = -0.04$, $p = 0.39$, $n = 452$). Between the fragility index and the BMD of the lumbar spine there was an inverse correlation ($r = -0.18$, $p < 0.0001$, $n = 473$). A marked correlation existed between the clinical score and the balance test ($r = 0.54$, $p < 0.0001$, $n = 500$).

Conclusion: Biological age can quite well predict balance, an important risk factor for fracture, but not the BMD of the hip. An inverse correlation between fragility and the BMD of the spine could be explained by vertebral fractures and degenerative changes which are common at this age and may be associated with a higher biological age.

40. The relation of some dietary minerals intake to bone mineral density in Polish postmenopausal women

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Nutritional factors have significant influence on the cause of osteoporosis. The aim of this study was evaluation relation between calcium (Ca), magnesium (Mg), zinc (Zn), phosphorus (P) and sodium (Na) dietary intake and bone mineral density (BMD).

Materials and methods: BMD spine was measured using dual energy X-ray absorptiometry (DEXA). The participants (n = 101) included in this analysis were Polish healthy postmenopausal women age from 50 to 68 years. They did not use pharmacological macro- and microelements supplementation during last 3 months. We evaluated daily Ca, P, Na, Mg, Zn intake by 24 hours nutritional history. We assessed daily intake of this macro- and microelements using computer programme FOOD. We estimated achievement of Polish Recommended Daily Allowances (RDA) on safety level.

Results: The mean value of BMD was 0.896 ± 0.156 g/cm² (T-score: -2.26 ± 1.26). The mean value of Ca intake was 579.7 ± 213.1 mg/24h; ($65.1 \pm 24.1\%$ of RDA). The mean value of P intake was 1192.0 ± 427.2 mg/24h; ($174.8 \pm 64.8\%$ of RDA). Ca:P ratio was low 0.50 ± 0.15 , whereas the recommended Ca:P ratio is 1.0. The mean value of Na intake was 289.3 ± 155.4 mg/24h; ($331.8 \pm 111.0\%$ of RDA). No relation between Ca, P, Na and BMD was observed. The mean value of Mg intake was 289.3 ± 155.4 mg/24h; ($103.3 \pm 55.5\%$ of RDA). The mean value of Zn intake was 10.4 ± 3.3 mg/24h; ($103.9 \pm 33.0\%$ of RDA). There was statistically significant relation between Mg intake and BMD ($r = 0.2$; $p < 0.05$); and Zn intake and BMD ($r = 0.3$; $p < 0.01$).

Conclusion: Zinc and magnesium intake is positive associate with BMD in postmenopausal Polish women. They intakes in their diet not enough calcium, and too much phosphorus and sodium.

41. Predicting regional and total BMD in perimenopausal women—very limited value of anthropometric measurements apart from body weight

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Bone mineral density (BMD) is strongly influenced by body weight (BW), probably through several mechanisms. Evaluating the separate and combined effects of body weight, frame size, and tissue composition variables may allow a better prediction of total and regional BMD and a better understanding of the mechanisms underlying the association.

Materials and methods: Baseline values recorded in one centre of the Danish Osteoporosis Prevention Study (DOPS) including 595 healthy perimenopausal women (mean age 50.5 years). The physical examination included height, BW, hip and waist circumference, skinfolds at the biceps, triceps, subscapular, and suprailiac sites and biohumoral breath as a

measure of frame size. BMD of the radius (proximal and ultradistal), femoral neck, lumbar spine, and total body were measured using the Hologic 1000W and 2000 equipment.

Results: BW correlated to all bone mineral measurements ($R^2 = 0.05-0.28$, $p < 0.001$). BMI was a slightly weaker predictor for BMD than pure BW. None of the anthropometric measurements added clinical significant additional information on BMD (R^2_{change} values 0.0–1.3%). The relation between BW adjusted BMD and clinical measures of fat mass (skinfolds and waist circumference) were negative, indicating that in these women lean body mass is more determinant for BMD than fat mass.

Conclusion: Anthropometric measurements are not superior or additive to BW measured on a scale weight when predicting BMD in perimenopausal women.

42. The osteoporosis in women-students of the University of Third Age in Poznan

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Lower physical activity and undernutrition are important factors of osteoporosis development. Encouraging to daily exercises, organizing gymnastic groups are the best ways of osteoporosis prophylaxis and one of the main forms of activity of the University of Third Age in Poznan (UTA). The authors decided to observe the appearance of dependences between physical activity and bone mass density and between the nutritional state of women after 60, participants of UTA, who complain of bone pains. We examined 38 women estimating: daily physical activity (AP) (except living activities), Body Mass Index (BMI), Bone Mass Density (BMD), selected markers of nutritional components important for the metabolism of the bone as: proteins, Ca, P, Mg, vitamin D. The results were statistically elaborated and authors observed correlations between examined parameters. Average AP per 24 h in examined women exceeded 1 h per day (2.51 ± 0.98 points; 2 points = 0.5–1.0 h/day, 3 points = 1–2 h/day). Correlation between average AP per 24 h and BMI (25.44 ± 3.78) was positive (0.229). It is explained by the fact that all of the women with higher BMI were participating in gymnastic groups in order to lower their body mass. The lack of the positive correlation between BMD ($89.26 \pm 18.19\%$) and the components of diet important for the structure of the bone tissue in examined women (correlation with proteins: -0.074 , with Ca: -0.045 , with P: -0.077 , with Mg: -0.026 , with vitamin D: -0.074) seems to results from the fact that women having higher BMI according to recommendations of education of UTA followed the diet reducing their body mass. The fact is likely to cause the negative influence on their diet's composition. Negative correlation between BMD and AP (-0.022) resulted from the fact, that women with higher BMD led physically active life because of family's duties, not because of taking part in physical ex-

ercise in UTA. There was a positive correlation between BMD and BMI (0.266), between BMD and the concentration of the blood albumin (0.086) and between BMD and the blood cholesterol level (0.030).

43. Femoral neck is a sensitive indicator of bone loss in mouse

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Mechanical stimuli are essential for the skeleton, and immobilization produces rapid bone loss in the weight-bearing bones, which is comparable in extent to the osteopenia induced by sex hormone deprivation. It is probable that a reduction of physical activity may also affect the involutional osteopenia seen in elderly people. Immobilization of a limb provides an experimental way to study mechanical influences on bone tissue without interfering with hormonal homeostasis. The present study was carried out to evaluate a unilateral hind limb immobilization model in the mouse.

Materials and methods: The right legs of male NMRI mice (age 10–12 weeks) were immobilized for three weeks against the abdomen by an elastic bandage with the hip joint in flexion and the knee and ankle joints in extension. The bones were scanned with a peripheral quantitative computed tomographic pQCT system Stratec XCT 960A. The three-point bending strength of the tibial and femoral shaft and the strength of the femoral neck were measured in two mechanical loading configurations.

Results: Body weight decreased significantly during the immobilization. pQCT analysis showed that the cross-sectional cortical area (CSA) and the cortical bone mineral density (CtBMD) of the tibial diaphysis were lower in both legs of the immobilized animals than in age-matched controls. At the tibial metaphysis, total cross-sectional area and total bone mineral density were also reduced in both legs of the immobilized animals. At the femoral neck, CSA, CtBMD, and bone mineral content were significantly lower in both legs of the immobilized animals, and the difference between the hind legs of the immobilized animals was also highly significant. The findings of the pQCT study were in good agreement with the changes in mechanical strength. The bending breaking force was reduced in both legs of the immobilized animals. The tibia was a more sensitive indicator of bone loss in bending strength than the femur. The femoral neck also showed decreased strength, and the difference between the immobilized leg and the contralateral leg was most clearly seen in lateral loading.

Conclusion: We conclude that three weeks of hind limb immobilization weakened the tibia and femur significantly compared to their contralateral counterparts. The reduction was more significantly seen in the mechanical bending strength than in the pQCT evaluation, and the femoral neck was the most sensitive indicator of bone weakening.

44. Bone density and physical ability in women with a previous hip fracture

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Associations between bone mass and parameters of physical ability were examined in 47 elderly women (mean age 80 years) who had suffered from a hip fracture 3 to 36 months (mean 17 months) previously. Bone mineral density (BMD) of the spine and hip was assessed by DXA. Measures of physical ability included isokinetic quadriceps strength of both the nonfractured and fractured leg, and walking and stair climbing speed. An estimate of current physical activity was made using the Northwick Park activity index questionnaire specifically designed for hip fracture patients. Statistics: multiple regression analyses taking into account the confounding effects of age, height, weight and months since fracture.

Quadriceps strength of the fractured leg was on average 18% lower than that of the contralateral leg ($p < 0.001$). Quadriceps strength of the fractured leg independently predicted walking speed ($R_{\text{partial}} = 0.69$, $p < 0.0001$), stair climbing speed ($R_{\text{partial}} = 0.46$, $p < 0.001$) and the activity index ($R_{\text{partial}} = 0.56$, $p < 0.0001$).

BMD was predicted by body weight ($p < 0.001$), not by any of the parameters of physical ability or by the Northwick Park activity index.

Conclusion: The main benefit of muscle strengthening exercises in women with hip fractures may be to promote mobility, not to reduce further bone loss.

45. Bone mineral density and calcium consumption from milk and dairy products in women from Warsaw region

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An adequate calcium intake is a known factor maintaining bone mass or reducing bone loss. Milk and dairy products are basic nutrition source of calcium.

Assessment of bone mineral density of women in the age of peak bone mass and premenopausal age and its dependence on dietary calcium intake was the aim of this study.

Subjects and methods: Bone mineral density in lumbar spine (anterior-posterior projection; BMD-AP) and femur neck (BMD-FN) and calcium intake were evaluated in 97 women from Warsaw region aged from 20 to 49 years. BMD was measured by dual-energy X-ray absorptiometry (Lunar

DPX-L). Calcium intake from milk (CaML) was assessed by food-frequency questionnaire. Association between BMD, age and calcium intake was evaluated using the linear correlation coefficient.

Results: There was no significant correlation between BMD-AP and age ($r = -0.180$; NS) but it was a significant negative correlation between BMD-FN and age ($r = -0.241$; $p < 0.05$). No significant correlation between CaML and BMD-AP or BMD-FN was found neither was a correlation between age and CaML.

Conclusion: Bone mineral density of femur of women significantly correlated with age. Bone mass diminution starts sooner in femur neck than in lumbar spine.

46. Diagnostic value of a single densitometry

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The use of bone densitometry in clinical practice is wide, since it is very useful to confirm osteoporosis, predict a fracture or monitor the treatment. Nowadays the availability of the examination is high and its consequences are many confusing results. Moreover, the description of the result without personal contact with patient is not uncommon. In some cases the result of a single sometimes by chance densitometry can provide a false conclusion and therapeutic decision when interpreted without sufficient knowledge of an individual clinical picture and methodological conditions.

Material and methods: In healthy male, the following densitometric analyses were carried out: Forearm (SPA, SXA, pDEXA, pQCT), lumbar spine (DEXA, QCT), hip (DEXA), total body (DEXA), tibia (QUS), calcaneus (QUS), and phalanx (QUS). The results were compared according to age, race and sex matched normal population values.

Results: A considerable dispersion in the results of densitometry was shown. Especially methods used in screening studies (SPA, SXA, QUS) provided results lower in contrast to results obtained by standard methods (DEXA, QCT). It is suggested to be very careful when interpreting or describing the result of a single densitometry without personal contact with the patient and his history, or without sufficient knowledge of densitometric methods.

Conclusion: The diagnosis of osteoporosis could be false when based on single measurement.

47. Lumbar spine density in healthy children and adolescents—usefulness of the percentile method for bone mass diagnostics

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Normative values for quantitative evaluation of bone mass are most commonly expressed by mean reference and standard deviations, percentage scale and T-scores in adult patients. In paediatric subjects, the interpretation of the densitometric measurement is often difficult because of lack of an objective reference standard. The aim of this study was to establish a useful reference system for dual-energy x-ray absorptiometry of the lumbar region in children and adolescents.

Material and methods: A total of 473 healthy Caucasian subjects aged 2–18 years were examined by means of anthropometric measurements and bone densitometry. All children, living in the North-East Poland, born with gestational age > 37 weeks and birth weight above 2500 g, ranged between 3 and 97 percentile for body weight and height at the moment of examination, were applied normal diet with customary daily consumption of dairy products.

Dual energy x-ray absorptiometry (DXA) with DPX-L Densitometer (LUNAR Radiation Corp., version 1.3z) was used to assess lumbar Bone Mineral Density (AP SPINE BMD).

Results: The values of BMD increased with age with distinct acceleration in the first 3 yrs of life and during puberty ($r = 0.91$, $p < 0.00001$) and correlated strongly with height, weight, BMI and midarm circumference. Data analyzed by STATISTICA pl 5.0 program considered the accordance of the normal and empiric distribution (Kolmogorov-Smirnov test) of the parameters. Statistical series for each one-year class of chronologic age and sex were created and system of percentiles was ranked /5, 25, 50, 75, 90/ and expressed as growth charts of BMD.

Conclusions: The construction of the percentile standard charts gives the possibility of diagnosis and monitoring bone mass in individuals as well as involving risk groups of osteopenia. The range between 5th and 25th percentile should play a role of the 'alarm zone' for identifying children with low lumbar spine density. There would be necessity of following up and longitudinal densitometric evaluation in this group up to peak bone mass achievement.

The presented percentile method might be a proposal of a Polish reference system for lumbar spine investigation by DXA in children and it might contribute to the prognosis of peak bone mass in this population.

48. Peak bone mass of Icelandic women and association with physical activity and nutrition—a longitudinal study

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The aim of this study was to evaluate at which age peak bone mass is reached and assess nutritional and physical factors associated with peak bone mass.

Study group and methods: A 2 years longitudinal study on a random sample of 16–22 years old women (144) in Reykjavik. Bone mineral density (BMD), lean mass and fat mass were measured by DEXA (Hologic QDR-2000). Physical activity (PA), calcium and vitamin-D intake were assessed by a questionnaire.

Results: Total skeletal BMD increased in each age group (Table). Calcium and vitamin-D intake were not significantly related to BMD. Physical activity was a significant factor in a multivariate analysis. Peak height was gained at the 18th year and PA 1996 explained 13% of the increment in total skeletal bone mass for the age group 18–20 years.

Conclusions: Peak bone mass seems to be reached around the age of twenty. Physical activity at the age of 16–20 seems to increase peak bone mass.

Table. The difference between measurements 1996 and 1998

	16–18 years (n=48)	18–20 years (n=32)	20–22 years (n=63)
Total skeleton	2.8%	2.0%	1.2%
Spine(LII-LIV)	3.2%	2.1%	0.1% n.s.
Total hip	1.1%	0.8% n.s.	-0.8% ^a
Total forearm	6.6%	1.9% n.s.	1.3%
Lean mass	1.6%	1.1% n.s.	-0.7% n.s.
Fat mass	26.2%	16.7%	4.7% n.s.
Height	0.85 cm	0.16 cm n.s.	0.013 cm n.s.
Weight	3.80 kg	3.13 kg	0.15 kg n.s.

p < 0.01 except: ^ap < 0.05 and n.s. = nonsignificant.

Bone resorption

49. The ruffled border membrane of resorbing osteoclast consists of two subdomains performing endocytic and exocytic functions respectively

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Osteoclasts are multinucleated cells derived from the hematopoietic bone marrow. The function of these cells is to resorb bone during the growth and remodeling of bone in vertebrates. They destroy mineralized bone matrix by acidifying and secreting the proteolytic enzymes into the resorption lacuna, a specific compartment in resorbing osteoclast.

Endocytic membrane traffic from basal membrane to the ruffled border and transcytic route from the ruffled border to the functional secretory domain have recently been showed to play vital role in the maintenance of the ruffled border and osteoclastic bone resorption activity. In this study we used

indirect immunofluorescence and confocal microscopy to locate several markers of membrane docking /fusion and endocytic budding machineries at the ruffled border. The bulk of V-H+-ATPase and rab7 were found to colocalize in the periphery of the ruffled border, while clathrin, adaptin AP-2 and AP-2 parter Eps15 were clustered into patches and concentrated on the central area of the ruffled border and membrane patch with unknown function adjoined to the sealing zone. The location of another late endosomal marker, rab9, showed the same pattern as clathrin.

To conclude, our data demonstrates the formation of microdomains in the ruffled border during bone resorption. The peripheral part of its membrane is the targeting /docking area of membrane traffic to the ruffled border and associates with secreting activities while the membrane in the middle is the site of endocytosis from the resorption lacuna. Our finding also suggested that the newly identified transcytic pathway for the removal of degraded bone matrix may be mediated by clathrin dependent mechanism.

50. Bone resorbing osteoclasts contain gap junctional protein connexin-43

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Intercellular gap junctions have been described in contact sites between surface osteoblasts, between osteoblasts and underlying osteocytes and between osteocyte cell processes in the canaliculi. The subunits of gap junction channels are assembled from a family of proteins called connexins. The purpose of this study was to investigate the role of gap junctional communication in bone resorption.

Materials and methods: Rat bone cells were cultured on bovine bone slices and stained with connexin-43 (Cx-43) antibody. Immunostaining of bone cells was localized using confocal microscopy. Bone cells were cultured in the presence of heptanol, a known specific gap junction inhibitor, and percentage of active osteoclasts i.e. osteoclasts with actin ring were counted and the resorbed area was measured.

Results: The Cx-43 immunostaining of osteoclasts revealed punctate distribution of Cx43 immunoreactivity. The staining could be seen in cell-cell contacts at the interface of adjoining cells, but numerous immunoreactive sites were also apparent within the cytoplasm. Treatment of the bone cell cultures with heptanol decreased the amount of active osteoclasts as well as the resorbed area.

Conclusion: Our results show that osteoclasts express gap junctional connexin-43. Heptanol decreases both the number of active osteoclasts and the total resorbed area. This suggests either a direct communication through gap junctions between multinucleated osteoclasts and mononuclear cells, or an indirect effect through gap junctions between osteoblasts.

51. Prevention of bone loss following gastrectomy or ovariectomy in the rat

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The aim of the study was to determine whether alendronate (A), estrogen (E), or parathyroid hormone (PTH) are able to prevent gastrectomy (Gx) or ovariectomy (Ovx) induced bone loss in the rat.

Materials and methods: 96 female Sprague Dawley rats were randomized into twelve groups: 1) sham (Sh) operated + E (10 µg/kg-day, s.c. inj.); 2) Sh + A (0.01 mg P/kg-day, s.c. inj.); 3) Sh + PTH (75 µg/kg-day, s.c. inj.); 4) Sh + vehicle (V; sesame oil, s.c. inj.); 5) Ovx + E; 6) Ovx + A; 7) Ovx + PTH; 8) Ovx + V; 9) Gx + E; 10) Gx + A; 11) Gx + PTH; and, finally, 12) Gx + V. Drug treatment was initiated immediately after surgery and continued for 8 weeks. Changes in bone mass were assessed on the left femur using peripheral computed tomography *ex vivo*.

Results: Both surgical procedures markedly reduced trabecular bone density in the metaphyseal area of the distal femur. A was able to prevent both Gx- and Ovx-induced bone loss, while E and PTH prevented bone loss induced by Ovx but not Gx.

Conclusion: Since the drugs tested (A, E, and PTH) differed in their ability to counteract Gx- and Ovx-evoked osteopenia, it indicates that the mechanism behind Gx-evoked bone loss differs from that which causes Ovx-evoked osteopenia.

52. Use of a novel TRAP immunoassay to determine osteoclast differentiation and bone resorption

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Osteoclasts secrete tartrate-resistant acid phosphatase (TRAP) into the circulation during bone resorption. We have developed a novel TRAP immunoassay, and studied if medium TRAP amount could be used as an index of the number of osteoclasts and the amount of bone resorption in *in vitro* bone cell culture models.

Materials and methods: Polyclonal antibody was produced in rabbits using purified human TRAP as antigen. The antibody was used to develop an immunoassay.

Results: The antibody stained specifically osteoclasts in bone cell culture, and it detected specifically TRAP from culture medium in Western analysis. The amount of TRAP

secreted to the culture medium showed significant correlation with the amount of osteoclasts formed in osteoclast differentiation assay, and with the amount of resorbed area in resorption assay.

Conclusion: The TRAP immunoassay detects specifically TRAP released from osteoclasts. It is a useful method to determine osteoclast differentiation and bone resorption in bone cell culture models, saving a lot of time and making it unnecessary to count cells and resorbed area.

53. Effect of gastrectomy on calcium homeostasis in rats

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The stomach is thought to play a role in calcium homeostasis since surgical removal of the stomach causes bone loss. The present study was performed to evaluate the role of stomach on blood-calcium homeostasis.

Materials and methods: Rats were gastrectomised, Gx, or sham-operated and subjected to calcium loading experiments 1–2 weeks or 2–4 months later. Before the experiments they were allowed free access to food or deprived of food (48h) and then given calcium chloride (CaCl₂) by the oral route or by intravenous infusion. Blood [Ca²⁺] and pH were monitored by repeated sampling from the tail for 2 h.

Results: Oral calcium raised the blood [Ca²⁺] more in Gx rats than in sham-operated rats, more so after 2–4 months than after 1–2 weeks. The rise was greater in food-deprived (48h) rats than in fed rats regardless of whether the rats were Gx or sham-operated. The blood pH dropped in response to peroral calcium more in food-deprived rats than in fed rats and more in Gx rats than in sham-operated rats. In Gx rats the high blood [Ca²⁺] and low blood pH values following oral calcium were associated with high mortality. Sham-operated fed rats survived also large oral calcium loads while fasted rats had high mortality. Fasted rats that received calcium by intravenous infusion showed a greater and more rapid rise in blood [Ca²⁺] than similarly treated fed rats; this was the case in both sham-operated and Gx rats.

Conclusion: The stomach plays a role in calcium metabolism. It remains to be shown whether gastrectomy enhances absorption of calcium from the gut or impairs clearance from blood.

54. Effects of calcium deficiency and calcium supplementation on gastrectomy-induced osteopenia in the rat

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Gastrectomy induces osteopenia in the rat. In this study we examined the effect of calcium deficiency and calcium supplementation on gastrectomy-evoked osteopenia.

Materials and methods: Rats were subjected to gastrectomy (surgical removal of the glandular stomach) and sham operation. They were divided into groups receiving calcium supplementation or calcium free diet. Calvariae and tibiae were examined various times after operation and treatment. They were sectioned and analysed by histomorphometric techniques.

Results: Gastrectomy resulted in osteopenia. Calcium free diet alone and gastrectomy combined with calcium free diet caused a greater loss of bone volume than only gastrectomy. Calcium supplementation had no effect on the gastrectomy-evoked osteopenia. In tibia, loss of trabeculae could be seen with reduction in bone volume in both tibia and calvaria.

Conclusion: This study shows that calcium deficiency alone induces rapid and marked osteopenia similar to that observed after gastrectomy and the gastrectomy-evoked osteopenia is accelerated by calcium deficiency but unaffected by calcium supplementation.

55. Effects of two selective estrogens, raloxifene and FC1271a, on osteoclast differentiation

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Postmenopausal osteoporosis is mainly caused by estrogen deficiency and estrogen replacement therapy is known to be efficient both in preventing and treating postmenopausal osteoporosis. In the recent years, there have been several efforts to create estrogen-like compounds without estrogen-like effects on breast and uterus. In this study we have examined the effect of raloxifene and a new triphenylethylene derivative, FC1271a, on osteoclast differentiation.

Eight weeks old NMRI mice were used to study osteoclast differentiation in vitro. Mouse bone marrow cells were cultured for 6 days in the presence of 1,25(OH)₂D₃ to induce osteoclast differentiation on multi-well plates.

Raloxifene did not have any effect on osteoclast differentiation at concentration range from 10 pM to 100 nM. 10 µM Raloxifene induced osteoclast apoptosis in rat osteoclast culture and was found to be toxic to the cells of bone marrow culture. FC1271a did not affect on osteoclast apoptosis at any concentration between 10 pM and 10 µM. However, this new selective estrogen was dose-dependently seen to inhibit osteoclast differentiation. Both results are comparable to our previous studies with estrogen and in future FC1271a could be potent compound to treat postmenopausal osteoporosis.

56. Cadmium-induced calcium release and prostaglandin E₂ production in neonatal mouse calvaria are dependent on cox-2 induction and protein kinase C activation

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The mechanisms by which cadmium (Cd) causes skeletal impairment have not been fully clarified. Prostaglandin E₂ (PGE₂) dependent stimulation of osteoclastic bone resorption has been suggested as a tentative mechanism. Our aim was to determine whether Cd-induced Ca release and PGE₂ production in neonatal mouse calvaria involve induction of cyclooxygenase-2 (cox-2) and, if so, to ascertain whether that effect is mediated by activation of protein kinase C (PKC).

Materials and methods: ⁴⁵Calcium labelled calvaria from new-born mice of the BALBc strain were cultured for 48 hours in the presence of Cd and different drugs, and the ⁴⁵Ca release was determined.

Results: Cd dose-dependently stimulated Ca release with maximal effect at 0.4–0.8 µM. Dexamethasone inhibited Ca release, an effect which was not overcome by addition of arachidonic acid, suggesting inhibition of cox-2 expression. Cox-2 selective inhibitors (NS-398, meloxicam, DFU) and dexamethasone potentially impeded Cd-induced Ca release and PGE₂ production. The PKC activator phorbol 12-myristate 13-acetate (PMA; 20 nM) stimulated Ca release from the calvaria. PMA- and Cd-induced Ca release was inhibited by calphostin C (0.5µM) and NS-398. The effects of Cd and PMA were not additive.

Conclusions: We suggest that Cd-induced Ca release from neonatal mouse calvaria in culture depends on induction of cox-2 that occurs via the PKC signaling pathway.

57. Osteoblasts remove collagen from resorption lacunae and form new bone in vitro

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Bone remodelling is a highly regulated cycle in which old bone is resorbed by osteoclasts (OCs) and subsequently new bone is formed by osteoblasts (OBs). However, the precise cellular mechanisms behind this have remained unclear. We have established a consecutive cell culture system, in which the resorption lacunae are first created by OCs and new bone subsequently created by OBs. OCs were isolated from 2-day-old rats' bone marrow and cultured on bovine bone slices for 48 hours to create resorption lacunae. OBs were induced from rat bone marrow cells. After cell confluency primary cultures were trypsinized and the cells replated for two

weeks on the resorbed bone slices, from which OCs had been removed beforehand. The cultures were then examined by confocal microscopy, FESEM and TEM. OBs appeared to accumulate around the resorption lacunae, remove remaining organic matrix from the lacunae and replace it by novel cross-linked collagen fibrils. As a control, we used RAW-264 macrophage cell line, which—surprisingly—showed no signs of collagen degradation. Calcification of the matrix was found specifically in the resorption lacunae as visualised by tetracycline labelling and TEM. Interestingly, an electron dense layer representing most probably the cement line emerged before mineralization to separate the old and newly formed bone matrix. This culture system may provide a useful in vitro model to understand the mechanism of osteoclast-osteoblast interaction during the bone remodeling.

Cartilage and osteoarthritis

58. Weight-bearing radiographs and histologic changes in a rabbit meniscectomy model of early knee osteoarthritis

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Analysis of weight-bearing radiographs is still the standard procedure for clinical evaluation of knee joint osteoarthritis. Only in few instances the degree of osteoarthritis as interpreted from weight-bearing radiographs has been compared to the morphologic changes of articular cartilage. The purpose of this study was to compare weight-bearing radiography to cartilage histology in a rabbit meniscectomy model of the early stage of osteoarthritis.

Material and methods: 15 rabbits were operated with medial meniscectomy in one knee and sham-operation in the other knee. Five rabbits each were killed 13, 25 and 40 weeks after surgery, and the knees evaluated by weight-bearing radiography and histology. Five non-operated animals were used as controls.

Results: The joint space width of the peripheral part of the medial knee compartment was narrower in meniscectomized knees than in sham-operated knees. Meniscectomized knees had more cartilage changes at the joint surface area of contact during the radiographic examination than sham-operated knees. However, there was no correlation between the degree of histologic cartilage change and the corresponding joint space width measurements.

Conclusions: Joint space width as measured on weight-bearing radiographs is reduced after meniscectomy, but does not reflect the degree of cartilage damage of the loaded joint surface at early stages of osteoarthritis.

59. Transverse MR relaxation times T_2 as a measure of the water content in human articular cartilage

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Early stages of osteoarthritis are associated with a changed water content in articular cartilage. In the present study we present correlations between water content and transverse MR relaxation times in human articular cartilage and discuss the influence of the orientation of the cartilage to the magnetic field on the relaxation times.

Materials and methods: T_2 values (collagen fibrils of the radial zone oriented parallel (0°) and perpendicular (90°) to the magnetic field) and water contents of human cartilage samples of 5 patients who underwent total knee-replacement surgery were determined.

Results: The water content in human articular cartilage can be determined from the relaxation times with a root mean square error of 2 wt.% and a mean of 71.1 wt.% for the 90° orientation (Fig. 1). The relaxation times in the 0° orientation are smaller than in the 90° orientation by a factor of approximately 1.5 and 1.2 for cartilage of the tibia plateau and the femoral condyles, respectively (Fig. 2).

Conclusion: The water content in human articular cartilage can be determined from the transverse relaxation times T_2 . However, the angular dependence of T_2 has to be taken into account.

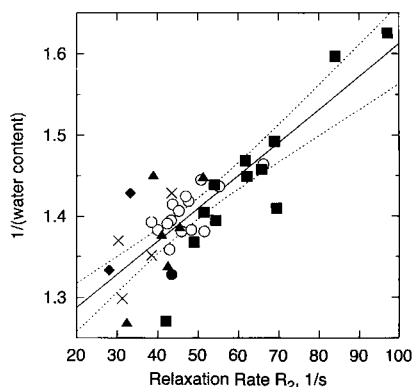


Figure 1. Correlation between inverse water content and transverse relaxation rates R_2 of cartilage water.

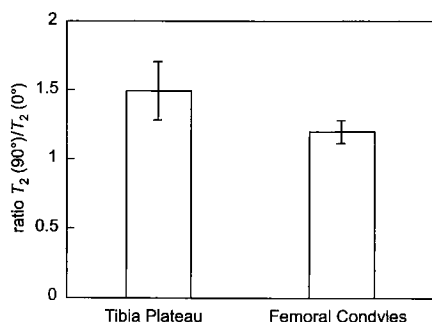


Figure 2. Ratios of relaxation times between the 90° and 0° orientation for cartilage of the tibia plateau and femoral condyles.

60. Upregulation of cartilage oligomeric matrix protein (COMP) at the onset of articular cartilage degeneration in a transgenic mouse model for osteoarthritis

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In the present study we have tested the suitability of COMP as a marker for articular cartilage degeneration in a transgenic model for osteoarthritis, where the disease results from structural weakening of cartilage due to a mutation in type II collagen gene.

Materials and methods: We first constructed cDNA clones for mouse COMP for hybridization probes. The expression and distribution of COMP mRNA and protein were then studied in normal and transgenic mouse cartilages during development, growth and ageing of the skeleton.

Results: Northern analysis of epiphyseal cartilages revealed differences in the expression profiles of COMP mRNA between transgenic Del1 and control mice both during early development and at the age of 3 months, i.e. at the onset of osteoarthritic lesions in Del1 mice. The most intensive immunostaining of transgenic articular cartilage for COMP was seen in the deep articular cartilage, and in some areas a pericellular deposition of the protein was seen. In nontransgenic mice, the staining for COMP was weaker and evenly distributed, except for articular cartilages of 15 month old mice where the distribution of COMP closely resembled that seen in their transgenic littermates from the age of 3 months onwards.

Conclusion: The results demonstrate upregulation of COMP mRNA and altered distribution of COMP in articular cartilage upon the appearance of osteoarthritic lesions.

61. Small proteoglycans biglycan, decorin and fibromodulin in the knee joints of transgenic mice with early onset osteoarthritis

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Transgenic mice of Del1-line carrying a 15 amino acid deletion mutation in the triple helical domain of pro α 1 (II) collagen gene develop early onset osteoarthritis in their knee joints. Here we describe a followup-study of the expression and distribution of small collagen binding proteoglycans biglycan, decorin and fibromodulin in the knee joint structures during development, growth and ageing in these mice and in their nontransgenic littermates.

Materials and methods: Epiphyseal samples from knee joints were processed for immunohistochemistry, *in situ* hybridization and RNA isolation at different ages between the birth and the age of 15 months. Samples for RNA isolation contained knee joint structures delineated by joint capsule and growth plates of proximal tibial and distal femoral heads.

Results: Northern hybridization studies indicated a 9-fold increase in mRNA for biglycan of newborn and a 12-fold increase in mRNA for fibromodulin of 10-day old knee joints of Del1 mice, as compared to nontransgenic littermates. Decorin mRNA levels remained unaltered or slightly reduced in the developing Del1 knee joints, whereas in 9 and 15 month old mice the decorin mRNA level progressively reduced to about one half of the level observed in nontransgenic littermates, thereby opposing the else increasing trend of decorin mRNA in ageing nontransgenic littermates. In transgenic mice, immunohistochemical and *in situ* hybridization studies also indicated altered and distinct distribution patterns for small proteoglycans.

Conclusion: The results indicate that a mutation in a single structural gene of cartilage extracellular matrix, type II collagen, can cause alterations in the expression of several other extracellular matrix components. In this mouse model for osteoarthritis one of the cellular responses towards altered extracellular environment is to express elevated levels of biglycan and fibromodulin mRNAs during the early post-natal development. Decorin mRNA level decreased in the late adulthood, perhaps reflecting the end-stage processes of osteoarthritis and increased subchondral bone sclerosis observed in Del1 mice.

62. Simultaneous changes in bone mineral density and articular cartilage in a rabbit meniscectomy model of knee osteoarthritis

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Already after 3 month, beginning cartilage changes were found after complete removal of the medial meniscus in the rabbit. The hypothesis of the study was that a successive increase in subchondral bone density, preferentially in the medial tibial plateau, would precede or coincide with the development of more severe cartilage changes after meniscectomy.

Materials and methods: 15 adolescent rabbits were operated with meniscectomy in one knee and a sham-operation in the other knee. Changes in cartilage morphology and subchondral bone density were quantified after 13, 25 and 40 weeks. Five non-operated animals were used as controls.

Results: Meniscectomy clearly induced cartilage changes typical for osteoarthritis, which progressed over time on the posterior aspect of the medial tibial plateau, which is physiologically covered by meniscus. After both operations the mineral density in the medial tibial subchondral bone was found decreased with no change with time, an effect that was most pronounced in the meniscectomized group. Only in the latter group, there was a significant lower bone density in the medial tibial plateau than the corresponding lateral one.

Conclusion: Cartilage changes typically for osteoarthritis will occur after medial meniscectomy. In contrary to the hypothesis, bone mineral density decreased indicating that increased bone mineral density has no role in the progression of early osteoarthritis.

63. Quantitative maps of transverse MR relaxation times T_2 of human articular cartilage

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The transverse MR relaxation time T_2 shows a close relation to the water content in cartilage and hence is a potential measure of the water content *in vivo*. In this study we present first quantitative T_2 maps of human articular cartilage measured *in vitro* and *in vivo* in a clinical whole-body MR system at a field strength of 1.5 Tesla.

Materials and methods: MR images of human articular cartilage (tibia plateau cartilage *in vitro*, patellar and femoral condyle cartilage *in vivo*) were measured in a Siemens MAGNETOM Vision scanner by means of a multi-spin-echo sequence. T_2 maps were calculated from these images by using a monoexponential fitting procedure.

Results: The relaxation times T_2 in human articular cartilage increase from approximately 20 ms near the bone to approximately 80 ms near the articular surface (Fig. 1) supporting data obtained in MR systems of higher magnetic fields and gradients.

Conclusion: Our data show that quantitative T_2 maps of

human knee cartilage can be measured in clinical MR scanners. The rising T_2 values with increasing distance from the subchondral bone correlate very well with the changing orientation of the collagen fibrils within the cartilage layer and support data obtained at higher field strengths.

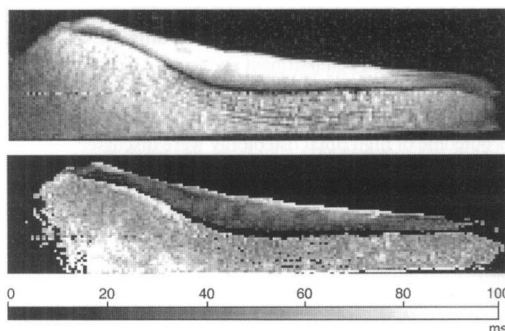


Figure 1. Proton-density weighted image (TE = 13 ms, TR = 3000 ms) of the tibial plateau of a 44-year-old man (a) and corresponding calculated T_2 map (b).

64. Assessment of bone mineral density of proximal tibia in lower extremity axis deviation

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Bone densitometry is a currently widely used method for estimation of bone mineral density in many various bone metabolic diseases, particularly in osteoporosis. Nowadays, a whole body device is disposable to evaluate measurements of bone mineral density in any point of the skeleton. That allows to make analyses of different local bone disorders, for example diagnosis and monitoring of Sudeck atrophy as well as evaluation of total hip arthroplasty in general. This paper is devoted to present diagnostic possibilities in estimation of bone mineral density in proximal tibia in lower extremity axis deviations.

A group of 30 women and men, age 15–72 (average 46) were admitted to the Orthopedic Department because of osteoarthritis due to lower extremity axis deviations on the knee level with both valgus and varus deformity. All patients were qualified for high tibial osteotomy. For preoperative planning, bone density was measured in the lumbar spine, femoral neck and proximal tibia on ROI (region of interest). We analysed 3 ROI: the lateral, the middle and the medial side. The results were expressed in g/cm². Anthropometric measurements of low extremity axis deviation were performed by using Metrecom (Faro). Before operation, long standing radiographs (goniometry) was also measured. The results were compared to the control group of 20 patients with normal limb axis. Increased bone mineral density was found on the side of overweighted compartment in comparison to the opposite side in all patients. These differences

were not observed in the control group. The coefficient (ratio of BMD in overweighted compartment to BMD in opposite side) ranged from 1.2 to 24.5 (SD 5.7), while in the control group the ratio was from 0.95 to 1.4 (SD 0.15). It seems that increased pressure for the compartment is bound with increased bone mineral density of the side of the proximal tibia. We found strong correlation between differences of bone mineral density in compartment and angle of lower extremity axis deviation. The possibility of applying the bone mineral density method in prognosis of osteoarthritis as well as outcome of high tibial osteotomy were discussed.

65. Ilizarov joint distraction in treatment of knee osteoarthritis

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The authors evaluated early results of the application of corticotomy in the epiphysis of tibia and arthrodiastasis of knee joint with the use of ring distractor in case of single-compartment knee arthrosis with significant deformation of limb axis and severe pain in the knee joint.

Material: In 3 women aged 64–69 after several years of ineffective pharmacological treatment of severe pain of both knee joints in the course of arthrosis with notable valgus deformation, percutaneous devarised corticotomy was performed of the epiphysis of tibia with a simultaneous arthrodiastasis of the knee joint with the use of a ring distractor. Two days after the surgery the patients could walk with full loading of the limb and on the third day they could leave the hospital. After 8 weeks the distractor was removed and intensive rehabilitation was started.

Results: During follow-up 6–14 months after operation the patients did not report any disorder and the radiographic examination did not show any pre-operative degenerative-deformation changes in the treated joint.

66. Analysis of the factors which may influence degree of disability in patients with coxarthrosis (COA)—part 1

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In the presence of discrepancy between clinical symptoms and particular features of radiographs of the hip in the case of COA, we compared demographic and anamnestic data patients with COA and functional disability index.

Materials and methods: We analysed 109 patients, males and females, with COA taking into consideration disease duration, profession and their residence (village or town). In

addition we evaluated height, weight, BMI, type of obesity (WHR) and presence of Heberden's nodules (HN). The degree of disability was assessed using Lequesne Index (LI) for hip joints.

Results: Statistically significant correlation between LI and age of patients, disease duration, working years was found. We not observed essential dependence between patient's weight, BMI and WHR. Significant serious disability occurred in farmers, villagers and women. There is no link between LI and localisation of changes in COA (unilateral or bilateral) and between LI and coexistence of HN or occurrence of degenerative changes in lumbar spine.

Conclusions: The degree of disability in patients with COA may depend on age of patient's, disease duration, profession (farmers!) and working years.

67. The comparison of radiological features of coxarthrosis (COA) and Lequesne Index (LI)—part 2

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In the presence of discrepancy between clinical symptoms and radiological picture of COA and because of mostly pain is used as clinical comparative with radiographic changes factor, we simultaneously analysed particular radiographic features and disability index in patients with COA.

Materials and methods: We qualified 109 persons with osteoarthritis of the hip, excluding patients with diseases influencing function of the lower limbs. The degree of disability we assessed using pain and functional Lequesne Index (LI). The individual radiological features were estimated by the use of three-degrees scale according to Altman Atlas.

Results: The comparison data showed the significant correlation between degree of disability and all analysed radiological features except buttressing and osteophytes of acetabulum of hip joint, particularly between hip joint space narrowing and the presence of subchondral cysts in femoral head.

Conclusions: There is a correlation between clinical symptoms and radiologic features highly significant in the case of joint space narrowing and presence of cysts in femoral head with exception of buttressing and osteophytes in acetabulum.

68. The growth of osteophytes in the osteoarthritic femoral head—a radiographic and histologic study and a hypothesis

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Osteoarthritis is characterized by many signs which are proliferative rather than destructive. Proliferative are the increased vascularity, the high intraosseous pressure, the increased calcification of the cartilage and reactivation of bone formation for example in the osteophytes. The medial flat osteophyte are among the biggest in coxarthrosis. These osteophytes grow by endochondral bone formation in the joint cartilage. A reawakening of bone forming cartilaginous cells in the joint cartilage, which existed before adulthood, is conditional.

The new start of the cartilage growth often happens in the middle part of the cartilage and not the basal part. The osteophytes therefore can get double cartilages, one at the basis and the other at the top of the osteophyte, which forms the bone in the osteophyte.

It is not sure that the osteophytes are secondary to the degenerative changes, which has been a very common view. For growth of the greater osteophytes, the cartilage with its added growth potential must be relatively undamaged and in a phase before degeneration. In late stage of osteoarthritis, when being operated, the medial flat osteophytes have no longer any active bone formation, but the marginal osteophytes at the rim between the femoral head and neck, have many osteoblasts.

The amount of growing of the cartilage in general and subchondral bone are difficult to measure, the osteophytes easy. The degree of calcification of the cartilage is highly increased, the tidemark moves outwards and capillaries grow into the calcified cartilage. The calcification, the increased vascularity, the occurrence of unusual collagens (e.g. collagen X), and apoptotic bodies are typical for osteoarthritis as also for fetal growth. Nobody knows whether these signs of growth result in any increase of the size of the femoral head or other arthrotic epiphyses.

The calcification of large parts of the joint cartilage combined with an outgrowth of small vessels in the calcified cartilage brings about a more fragile cartilage, which easily is broken down by weight bearing, enzymes and cytokines. The degenerative changes can be secondary to a, from the beginning, proliferative disease.

69. Concentration of strontium in bone and joint cartilage of rats after its per os administration

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Strontium salts stimulate osteoblasts and chondrocytes but inhibits osteoclasts. Because distribution of strontium after its per os administration in trabecular and cortical bone as well as in joint cartilage is unknown, we have tested it in rats.

Material and methods: Four groups of male rats 6 week of age received for 6 months 0.001% (1.75 µM/day), 0.05%

(87.5 µM/day) and 0.1% (175 µM/Day) water solutions of strontium chloride vs water as a control. Cartilages of knee and hip joints as well as cortical and trabecular tissue of femur bone were prepared than dried and strontium were measured by AAS-ETA method by Perkin-Elmer 4100ZL machine with THGA graphite cuvette.

Results:

Concentrations of strontium, mg per kg of dry tissue

	Controls	0.001%	0.05%	0.1%
Knee cartilage	85	1917	3681	4800
Hip cartilage	83	2011	4604	5719
Cortical bone	151	2316	3962	5681
Trabecular bone	131	1947	3561	4826

Conclusion: In three examined solutions strontium concentrations in bone and cartilage are comparable, bigger in hip than in knee cartilage, higher in cortical than in trabecular bone.

70. Differential expression patterns of matrix metalloproteinases and their inhibitors during development of osteoarthritis in a transgenic mouse model

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Metabolic disturbances in osteoarthritic cartilage degeneration involve imbalances in the dynamic equilibrium of proteolytic enzymes i.e. matrix metalloproteinases (MMPs) and their natural inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). This study is based on the characterization of transgenic Del1 mice harboring a 15 amino acid deletion in the triple helical domain of the $\alpha 1(\text{II})$ collagen chain. Mice heterozygous for the Del1 transgene locus develop degenerative changes in the articular cartilages of knee joints from the age of 4 months.

Materials and methods: In order to study the expression of MMPs and TIMPs we cloned cDNAs for TIMP-1, -2 and -3 and MMP-13 and -14 from mouse calvaria using RT-PCR and primers based on previously published sequences. Total RNA was extracted from knee joints of >300 male Del1 mice and their nontransgenic littermates at different time points between birth and the age of 15 months analyzed individually by Northern hybridization.

Results: Several MMPs and TIMP-1, -2 and -3 mRNAs were present in cartilage with characteristic expression patterns during growth, development and aging. The mRNA for MMP-13 demonstrated a striking increase at the onset of degenerative lesions. The mRNAs for the three TIMPs were lower in Del1 mice than in the nontransgenic control mice. In addition, immunohistochemical analyzes of MMPs and TIMPs revealed age-dependent differences between trans-

genic and control mice.

Conclusion: Differential expression patterns for MMPs and TIMPs during the progression of osteoarthritis suggests a role for them in cartilage breakdown and provides a basis for designing new therapies for this disease.

Implant – bone interface

71. Synovial fluid from loose total hip replacements inhibits proliferation of normal human osteoblast-like cells

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Aseptic loosening of the prosthetic components in patients who have undergone total hip replacement is a major clinical problem. Earlier studies on this topic have mainly focused on different aspects of bone resorption.

Materials and methods: We have investigated the influence of synovial fluid (SF) from patients who underwent revision surgery due to aseptic loosening, and SF from patients with osteoarthritis (OA), on [³H]thymidine incorporation into DNA in normal human osteoblast-like cells (hOB cells).

Results: Incubation of cells with 10% SF from revision patients had an inhibitory effect on [³H]thymidine incorporation in hOB cells ($-69.8 \pm 6.9\%$, mean $\pm$ SEM, $n = 12$, $p < 0.001$) compared to control conditions, whereas 10% SF from patients with OA had a stimulatory effect ($+125 \pm 29.3\%$, $n = 12$, $p < 0.01$).

Conclusions: These findings correlate with the clinical picture seen in patients with aseptic loosening or OA, i. e. increased net bone resorption around the prosthesis in patients with loosening, and increased periarticular bone formation in patients with OA.

72. Changes in bone mineral density around cementless hip prostheses with proximal hydroxyapatite coating

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Within 7–10 years following the operation the stems of hip prostheses fixed with cement become loose in 20% of pa-

tients. The purpose of the study was to determine, by means of dual energy X-ray absorptiometry, whether application of cementless, hydroxyapatite coated ABG prostheses prevents bone mass loss next to their stems.

Patients and methods: 56 patients (24 women, 32 men) aged 22–71 years, have been examined prospectively for at least 12 months. 38 of them completed 2-year, and 22 a 3-year observation period. DXA scans were performed within 3 weeks after the operation and then after 3, 6, 12, 24, 36 months following the procedure. BMD was determined in both standard and Gruen zones. BMD of the lumbar spine and of the opposite proximal femur were measured every year and biochemical markers of bone turnover were determined every 6 months.

Results: It was found that within the first 3 months following the operation patients after total hip arthroplasty showed decrease in BMD by 2–14%. During the next months BMD was raising gradually and after 2 years approached the baseline values with exception of upper medial part of the femur where progressive reduction in BMD was observed.

The decrease in BMD was significantly more pronounced in women than in men, in patients with higher bone turnover, and was independent of the changes in BMD in other parts of the skeleton.

73. The effect of soaking versus pipetting transforming growth factor β 1 to a porous coated implant

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The method of applying transforming growth factor β 1 (TGF β 1) to an implant surface was investigated in a canine model of impaired bone ingrowth. A porous-coated rod, designed to leave a 3-mm gap adjacent to the implant and treated with hydroxyapatite and tricalcium phosphate was implanted bilaterally in ten dogs. The implant in the left humerus was always treated with 120 μ g of TGF β and the implant in the contralateral humerus served as a control. Two groups of five animals each were compared: one where the growth factor was applied by soaking implants in a solution of TGF β 1, and the other where the TGF β 1 was pipetted on to the surface of the implants. All implants treated with TGF β 1 had more bone ingrowth than their paired controls. Although the pipetted group had a greater degree of variability, the mean extent of bone apposition did not differ between the groups. There was a statistically significant higher volume fraction of bone ingrowth within the porous coating in the soaked group compared to the pipetted group ($28.7\% \pm 3.3$ versus $17.3\% \pm 3.3$, $p = 0.002$). We conclude that application of TGF β 1 by soaking results in a more consistent distribution of bone ingrowth and an increased volume fraction of bone ingrowth as compared to a technique where the growth factor is pipetted to the surface of the implant.

Osteoporosis – epidemiology

74. Risk factors for hip fracture in a middle aged population

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Hip fractures have always been a considerable health care problem, and lately we have seen an increasing number of fractures that cannot be explained by longer life expectancy only. The economical and social consequences are great, and increasing.

Earlier published studies on this subject have mainly been done in women around 70 or older, which leaves little room for preventive measures. In our study we were interested in trying to identify risk factors already detectable in the middle aged individual, to make early prevention possible.

The participants in our study were 22,000 men and 11,000 women, all living in Malmö. They were collected through a cardiovascular prevention study performed by the Department of Internal Medicine, Malmö.

The mean age at screening was 44 years and 49 years for men and women, respectively. The patients were followed prospectively, the men 17 years and the women 13 years. The data collected were those concerning the participants' general health as well as social situation. These were analysed with age adjusted logistical regression and multivariate analysis.

Several risk factors were significant in both men and women. A selection of clinically important risk factors is as follows: low body weight, low BMI, elevated resting pulse, low FEV 0.5 s, diabetes, > 20 cigarettes a day.

With these findings we hope to be able to construct a risk score for hip fracture that can be used for screening of 50-year-old patients. The score will hopefully help us to identify high risk patients, and with early prevention maybe we'll be able to turn the fracture trend.

75. The prevalence and incidence of vertebral deformation in an urban population of Southern Sweden

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Vertebral deformation–fracture is an important part of the clinical entity of osteoporosis. A subject with one or more deformed vertebrae due to osteoporosis has an increased morbidity and mortality risk as well as an increased risk of other osteoporosis fractures such as hip fracture. The epidemiology of vertebral deformation shows geographical as well as age and sex variation (EVOS). The objective of this study was to analyze the epidemiology of vertebral deformation in an urban population of Southern Sweden.

Subjects and methods: Lateral radiograms of the thoracic and lumbar spine were obtained from altogether 797 subjects, age 50 and over, participating in two population based studies. The prevalence of vertebral deformation was calculated using a quantitative morphometry method. After three years in one study and seven years in the other those subjects still alive were asked back for a new spine radiograph. 443 subjects responded. The incidence of new deformation was calculated comparing the baseline and follow-up radiographs.

Result: At baseline altogether 43% of the women and 30% of the men had vertebral deformation using a 3 SD reduction of any of the vertebral height ratios as deformation criterion. Adjusted for age women had a significantly higher prevalence as compared with men. Both the prevalence and incidence increased with age in both sexes. The vertebrae most commonly deformed were L1, Th12 and Th11.

Conclusion: The prevalence of vertebral deformation is high and increases with age in both sexes.

76. The incidence of hip fractures in Vilnius, Lithuania

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Hip fractures, as a consequence of osteoporosis is an important public health problem. There is no information about hip fractures in Lithuania available.

Patients and methods: Hip fracture cases were recorded retrospectively in Vilnius over 1 year period with the catchment population of 574,446.

Results: During 1995-year period 175 low energy trauma hip fractures for men and women over the age of 50 were recorded. The crude incidence was 30.6 per 100,000 population per year (40.6 for women and 19.4 for men). The mean age of patients with hip fracture was 75.5 years for women and 67.7 years for men. The age-standardized incidence rates to the 70 year were higher for men. Under the 70 years we observed exponential increase of women fracture rates with the peak at age group 85+. The ratio of cervical to trochanteric fracture was 1.2 in men and 1.65 in women. Mortality rate was 4% during the stay in the orthopaedic ward.

The reasons for the lower hip fracture rates as compared to other European countries are under investigation.

77. Nutritional risk factors in Lithuanian women with postmenopausal osteoporosis

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Many behavioral factors are believed to be determinants of bone mass and bone mineral density. One of them is calcium intake from milk and dairy products.

Patients and methods: A total of 73 women with postmenopausal osteoporosis and 80 controls (random sample) were studied retrospectively as to determine the risk factors. The dietary calcium intake was assessed by the special life-style questionnaire.

Results: The mean age of women with osteoporosis was 61.9 ± 1.2 years, controls aged 60.7 ± 0.8 years. The difference between groups in their nutrition was disclosed by the questionnaire. In osteoporotic group 52.2% women were not consuming enough milk and dairy products. In control group only in 28.4% cases adequate intakes of calcium-rich milk products were low.

Conclusion: These results suggest that low milk and dairy products consumption may be important in the genesis of osteoporosis.

78. Age-adjusted incidence of hip fractures has not changed in ten years in Central Finland

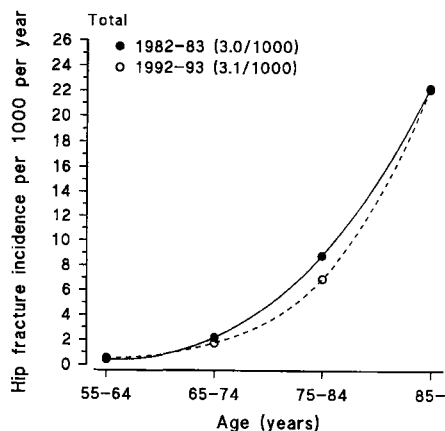
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The purpose of this study was to find out if the age-adjusted incidence of hip fractures has changed in ten years in Central Finland. Earlier Finnish studies report that the incidence of hip fractures in Finland is increasing more than expected due to the aging of the population.

Patients and methods: Patients with acute hip fracture admitted to Jyväskylä Central Hospital in 1981–1983 ($n = 317$) and in 1992–1993 ($n = 351$) were selected from the hospital discharge register. Medical records of all patients were studied and errors in the data were corrected.

Results: There was no change in the age and sex stratified incidence of hip fractures during the last ten years (Figure).



The mean age of the patients increased from 75.4 to 78.4. With the aging of the population the proportion of patients 85 years or older increased from 18.0% to 30.2%.

79. Incidence of hip fractures in Oslo

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The incidence of hip fractures in Oslo has shown a continuous increase during the past decades (Falch et al., *Bone* 1993). The aim of this study was to estimate the current incidence of hip fractures in Oslo.

Materials and methods: Using the electronic diagnosis registers and the lists of the operating theatre for the hospitals in Oslo with somatic care, all patients with the ICD 9-code 820.X (hip fracture) from May 1, 1996 to April 30, 1997 were identified. Medical records for all the identified patients were obtained and the diagnosis was verified. The number of fractures recorded was compared with expected number of fractures, calculated by projecting the sex specific incidence rates from 1988/1989 in 5-year age groups on the present population. Chi squared test was applied.

Results: A total number of 1316 hip fractures were recorded. 77.8% of the fractures occurred in women. Annual incidence per 10,000 in the age group 50 years and older was 118 in women and 44 in men compared with 119 and 45 in 1988/1989, respectively. The number of fractures recorded in the population 50 years and older was 1015 for women and 278 for men, whereas the expected number of fractures was 1069 (n.s.) and 283 (n.s.), respectively.

Conclusion: The present study shows that the incidence of hip fractures in Oslo has been similar during the last decade.

Osteoporosis – treatment

80. Effect of nasal calcitonin on bone mineral density (BMD) in postmenopausal osteoporosis—a dose response study

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Previous results of treatment of postmenopausal osteoporosis with nasal calcitonin have been inconsistent and the

dose-response relationship remains unclear.

Patients and treatment: Our study comprised 85 postmenopausal women, aged 51–78 years, with previous forearm fracture and a BMD_{z-score} <0. Participants were randomly allocated to treatment for 3 years with: 1) calcitonin (Miacalcin®) 400 IU b.i.d., 2) calcitonin 200 IU b.i.d., 3) placebo in the morning + calcitonin 200 IU in the evening, or 4) placebo b.i.d. All participants received Calcium Sandoz® 500 mg daily. BMD was measured using a Hologic QDR-1000 densitometer. Moreover, biochemical bone markers were measured.

Results: Data were analysed according to the intention-to-treat principle using ANOVA. 55 patients completed the study. The change in BMD following treatment for 3 years in relation to calcitonin-dosage is shown in the table.

Conclusion: No significant positive effect of salmon calcitonin nasal spray on BMD at the spine, proximal femur, or distal forearm could be demonstrated in the dosages tested. At the spine and forearm sites, however, the possibility of type-II errors should be considered.

	800 IU	400 IU	200 IU	Placebo	P
N completing the study	18	14	11	12	-
D-BMD (%)					
spine	0.5±1.0	-0.8±1.7	1.1±1.4	0.3±1.2	n.s.
femora					
neck	-3.7±0.9	-5.0±1.5	-4.7±1.7	0.6±0.8	<0.01
ultra-distal forearm	-3.2±1.5	-6.9±2.1	-5.2±1.8	-1.7±2.5	n.s.

Data are shown as mean ± SEM

81. Effects of thiazide and loop diuretics, alone or in combination, on calcium and bone metabolism

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Thiazide and loop diuretics exert different effects on calcium homeostasis. We compared loop and thiazide diuretics in a randomised placebo controlled design.

Material and methods: 45 postmenopausal women were treated for 7 days with either bendroflumethiazide 10 mg/day (n = 13), bumetanide 2 mg/day (n = 12), bendroflumethiazide 10 mg/day plus bumetanide 2 mg/day (n = 8), or placebo (n = 12). Serum and urine (24h) levels of electrolytes and bone markers were measured together with calcitropic hormones.

Statistical inferences are made in relation to the concomitant changes in the placebo group.

Results: In the bendroflumethiazide-group the tubular reabsorption of calcium (TRCa) increased (mean ± SEM) 0.46 ± 0.11% (p = 0.009) while the urinary calcium to creatinine

ratio (U-Ca/Cr) decreased 30.3 ± 5.5% (p < 0.001). In the bumetanide-group TRCa decreased 0.54 ± 0.1% (p = 0.013) while U-Ca/Cr increased 51.5 ± 17.7% (p = 0.08). No changes occurred in S-calcium (S-Ca) or in tubular max. reabsorption of phosphate (TmP/GFR). In the group treated with both diuretics TmP/GFR decreased 13.1 ± 5.5% (p = 0.013), S-Ca increased 2.7 ± 1.0% (p = 0.007), although TRCa and U-Ca/Cr remained unchanged. Later S-PTH, 1,25(OH)₂D₃, S-osteocalcin, S-bone isoenzyme alkaline phosphatase, and urinary N-telopeptide levels will be reported.

Conclusion: It makes a great difference on the urinary calcium excretion whether a loop or thiazide diuretic is chosen. Adding a thiazide to treatment with a loop diuretic may reduce the calcium loss.

82. The use of prednisolone and concurrent pharmacological prophylaxis against osteoporosis—a population based study using a drug prescription database

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Long-term use of systemic glucocorticoids leads to bone loss but it is unknown whether prophylactic treatment with bisphosphonates, HRT, and D-vitamin are used adequately.

Methods: Odense University Pharmacology Epidemiological Database (OPED) contains detailed data on all prescription refunds from Funen County, Denmark (471,000 inhabitants). We searched OPED for patients prescribed more than 1350 mg of prednisolone and concurrent bisphosphonates or HRT during 1997. Data concerning vitamin-D and calcium supplementation were omitted since these drugs are available over-the-counter.

Results: 1581 men and 2176 women (0.7% and 0.9% of the population) used prednisolone. 17% of the women using prednisolone also used HRT (33%, 23%, 15%, 10%, and 8% at age 50, 60, 70, 80, and 90, respectively). 2 and 4% of the women and men using prednisolone also used bisphosphonates. Data concerning the period 1993–1998 will be presented.

Conclusion: Use of systemic glucocorticoids is highly prevalent in the county of Funen while only a minor fraction of these patients receive adequate pharmacological prophylaxis against osteoporosis.

83. Effect of hormone replacement therapy on muscle strength and physical activity in healthy postmenopausal women

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This study was designed to evaluate the effect of six-months of hormone replacement therapy (HRT) on muscle strength and physical activity in postmenopausal women.

Forty healthy postmenopausal women (aged 60–78, mean 67.6) were included in the study. They were divided in two groups with 20 women in each group. One group received HRT (Menorest® 50 µg/24 hours + T. Gestapuran 2.5 mg daily) and the other placebo for 6 months. The study was conducted as a double blinded, prospective and placebo controlled trial. Physical activity, handgrip strength, isokinetic knee flexion, and extension strength was measured before receiving HRT, after three months and after six months.

Handgrip strength increased significantly in both groups during the study (right hand : placebo 27.5 ± 6.3 vs. 29.5 ± 7.7 , $p = 0.008$; HRT 26.1 ± 4.7 vs. 27.6 ± 4.1 , $p = 0.0003$; left hand : placebo 26.5 ± 7.1 vs. 27.9 ± 6.0 , $p = 0.0709$; HRT 23.4 ± 4.6 vs. 26.4 ± 3.7 , $p = 0.0065$). Knee flexion and extension improved slightly in the HRT group and in the right leg in the placebo group. Physical activity level raised in the placebo group. There were no significant differences in muscle strength or physical activity between the two groups.

Conclusion: Hormone replacement therapy for 6 months did not increase muscle strength in handgrip or knee flexion and extension or change the level of physical activity, as compared to placebo treatment.

84. Treatment of postmenopausal osteoporosis with estrogen, calcitonin, bisphosphonate, 1 α -OH vitamin D₃, calcium and fluoride

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The aim of the study was to quantify and compare the effects of different treatment regiments on bone mineral density and vertebral fracture rate in women with postmenopausal osteoporosis.

180 women suffering from postmenopausal osteoporosis (T-score below -2.5), aged 55–85 years, on an average 11 years after the menopause were enrolled in a 2-year prospective study. The patients were divided into 8 comparable groups regarding age, BMD and years after the menopause, and treated as follows: 1. (n = 25) CT 100 IU daily for 10 consecutive days every month and 2g CaCO₃ daily; 2. (n = 30) estradiol 2 mg daily and CaCO₃ 2 g/day; 3. (n = 20) CaCO₃ 2 g daily; 4. (n = 20) 1 α -OH vitamin D₃ (1 α -OHD₃) 0.5 µg daily; 5. (n = 20) 1 α -OHD₃ 0.5 µg/day and CaCO₃ 2 g/day; 6. (n = 25) clodronate 400 mg, 1 α -OHD₃ 0.25 µg and CaCO₃ 2 g daily; 7. (n = 20) NaF 40 mg/day, 1 α -OHD₃ 0.5 µg/day and CaCO₃ 2 g/daily; and 8. (n = 20) control group /untreated/.

Biochemical parameters of Ca-P homeostasis, bone turnover markers, BMD of the spine and proximal femur were determined every 6 months and radiographs of the thoracic and lumbar spine every 12 months.

It was found that 2-year therapies with estradiol, CT, clodronate and 1 α -OH vitamin D₃ with calcium supplement resulted in a significant increase of BMD in both lumbar spine and proximal femur and a decrease in a number of new vertebral fractures. Treatment with fluoride increased BMD in the spine while decreased in femoral neck. The therapy with calcium alone did not influence bone mass.

Conclusion: Treatment with estradiol, CT, clodronate and 1 α -OH vitamin D₃ with calcium supplement can effectively prevent loss of both spongy and cortical bone in patients with postmenopausal osteoporosis but careful clinical examination of the patients and search for contraindications are necessary at baseline to determine the appropriate treatment.

85. The effect of tamoxifen on growth, development and mineralization of broiler chicken limb bones

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The aim of the experiments was to determine the effect of tamoxifen on developmental changes of femora and humera in broiler chickens.

Materials and methods: The experiments were carried out on 120 broiler chickens divided into control (untreated) and experimental groups (tamoxifen administered in the dose of 10mg/kg b.w./day) additionally divided into females and males. On the 28th, 42nd and 56th day of life the chickens were sacrificed and femora and humera were isolated. The bones were submitted to a three-point bending test using INSTRON 4302 apparatus for determination of mechanical parameters such as the maximal force, the force of resilience limit and the value of resistance. Geometric parameters such as the second moment of inertia [I_x] and the mean relative wall thickness [MRWT], and also bone mineral density [BMD] of the shaft of the column were examined.

Results and Conclusion: Tamoxifen increased the values of mechanical parameters of both examined bones in females and femora in males during the first 42 days of life but decreased them on the 56th day. The values of the second moment of inertia increased after tamoxifen treatment on the 28th, 42nd and 56th days of life in comparison to the control group. BMD was higher in humera and femora in females on the 28th and 42nd day of life, whereas in males the increase of BMD was observed only on the 42nd day of life.

86. A meta-analysis on the effectiveness of bisphosphonates in preventing vertebral fractures

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Osteoporosis is characterised by low bone mass, enhanced bone fragility and a consequent increased fracture risk. Many studies have demonstrated the ability of bisphosphonates to reduce bone loss or even increase bone mineral density (BMD), but only few studies demonstrate a statistical significant clinical effect in preventing osteoporotic fractures. The aim of this meta analysis was to obtain data from clinical studies on bisphosphonates in postmenopausal osteoporosis and hence to calculate the over all effect on the incidence of vertebral fractures.

Material: Data were obtained by search sessions in Medline, Excerpta Medica, Index Medicus and data-on-file and included only randomised prospective studies. Ten clinical studies with published data on the incidence of vertebral fractures were included in the analysis: 4 on etidronate, 4 on alendronate, 1 on pamidronate and 1 on risedronate. In all studies but the risedronate trial, the BMD in the lumbar spine was increased in the treated patients when compared to controls.

Results: The meta-analysis demonstrated a significant over-all effect of bisphosphonates in preventing vertebral fractures. Two large alendronate trial could themselves claim a statistical significant result evaluated by 95% confidence intervals for the calculated relative reduction in the incidence of vertebral fractures. One of these studies, comprising more than 2000 individuals, had a relative statistical weight exceeding 50%. We made a sub-analysis recalculating data with the exclusion of the two large alendronate studies and could still demonstrate a significant effect in favour of treatment with bisphosphonates although none of the studies in the sub-analysis could themselves demonstrate a statistical significant result evaluated by 95% confidence intervals for the calculated relative reduction in the incidence of vertebral fractures. The over-all effect of the treatment with bisphosphonates reduced the relative risk of vertebral fracture to 40%. The absolute reduction in risk of vertebral fracture was calculated to 6% (95% confidence interval: 4–8%) and the number needed to treat (NNT) to 16.7 (95% confidence interval: 12–25).

Discussion: Bisphosphonates are very effective drugs in the treatment of postmenopausal osteoporosis not only by increasing bone mass but also in preventing vertebral fractures. When compared to other major health issues, i.e. reducing the risk of stroke in hypertension or heart disease in dyslipidemia, the effectiveness of bisphosphonates in preventing vertebral fractures are very high.

87. Cost-effectiveness of the treatment of osteoporosis in the prevention of fractures—an overview

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Osteoporosis interventions reduce the great burden on patients and society of fractures, but incurs additional costs and call for economic evaluation.

Methods: Medline was searched using the terms osteoporosis and cost-effectiveness. The studies were classified according to type of evaluation (cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and the type of intervention.

Results: Of 12 publications (6 CEA, 6 CUA), there were 8 studies of HRT, 2 of bisphosphonates, 1 of calcitonin, 1 of calcium supplementation. All studies were based on life tables or Markov models, but varied widely with respect to inclusion criteria, age at onset of intervention, duration of intervention, risk reductions (effectiveness), quality of life assessments, and hip fracture mortality. The cost per life year or quality adjusted life year gained varied from zero (cost savings) to \$ 6.000.000.

Conclusion: The cost-effectiveness of osteoporosis interventions mainly depends on selection of patients and effectiveness of the interventions. Osteoporosis treatment appears to compete favourably with commonly accepted interventions such as anti-hypertensive or anti-hyperlipidemic treatment when reserved for high risk groups.

Secondary osteoporosis

88. Structural and kinetic characterization of hypophosphatasia mutations

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Hypophosphatasia is a rare heritable disease caused by mutations that affect the activity of the tissue non-specific alkaline phosphatase (TNAP) isozyme. The clinical severity varies widely from complete absence of bone mineralization and stillbirth in the perinatal/infantile form to spontaneous fractures and loss of deciduous teeth in adult and odontohypophosphatasia. While hypophosphatasia is usually inherited

as an autosomal recessive trait, variable expressivity, incomplete penetrance and autosomal dominant inheritance have been reported. Several missense mutations in the TNAP gene have been reported in hypophosphatasia and compound heterozygosity appears frequently. The present studies aims at testing the hypothesis that the TNAP molecule possesses more than one functional domain and that the different modes of inheritance of hypophosphatasia are the result of mutations affecting one or another domain.

Materials and methods: A 2.4 kb HindIII/BglII fragment from the human TNAP cDNA was used as the source of template to generate all the hypophosphatasia mutations. Site-directed mutagenesis was performed as described by Tomic (1990). The recombinant plasmids were expressed in COS-1 cells and the mutants enzymes purified and tested for their kinetic and stability properties as previously described (Bossi et al. 1993; Hoylaerts et al. 1997).

Results: We generated and tested 17 mutations known to cause perinatal/infantile as well as adult/odontohypophosphatasia. Nine of these 17 mutations were active while 8 showed no remaining activity. The kms of the active mutants were comparable to those of the wild-type enzyme except for mutations at position 277 and 361, which showed a two-fold and a 100-fold increase, respectively. While most mutations appeared destabilizing in terms of thermal stability, mutations at positions 174 and 281 increased the stability of the mutant enzymes. Positions 174, 281 and 162 were also shown to maintain Kcat values very similar to the wild-type enzyme.

Conclusions: Six of the nine active mutations are associated with the adult/odontohypophosphatasia phenotypes. Since the kinetic properties of these mutations appear sufficient to perform an enzymatic role in bone tissue, these data strengthen the hypothesis that a dominant negative mechanism must exist in order to explain their involvement in the pathogenesis of hypophosphatasia.

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89. Fracture risk is increased in Crohn's disease, but not in ulcerative colitis

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Our aim was to study fracture rates and risk factors for frac-

tures in patients with Crohn's disease (CD) and ulcerative colitis (UC).

Material and methods: Historical follow-up. A total of 998 self-administered questionnaires were issued to members of the Danish Colitis/Crohn association and 1000 questionnaires were issued to randomly selected control subjects. Among the patients 845 (84.5%) and among the controls 645 (65.4%) returned the questionnaire ($p < 0.01$). Among the respondents 817 patients and 635 controls were analysable.

Results: The material consisted of 383 CD patients (median age 39 [8-82] years, median age at diagnosis 26 [1-75] years), 434 patients UC patients (median age 39 [11-86] years, median age at diagnosis 29 [10-78] years), and 654 controls (median age 43 [19-93] years, $p < 0.01$). The fracture-risk was increased in female CD patients (RR = 2.5, 95% CI: 1.7-3.6), but not in male CD patients (RR = 0.6, 95% CI: 0.3-1.3) or in UC patients (RR = 1.1, 95% CI: 0.8-1.6). An increased proportion of low-energy fractures was observed among CD patients (15.7% vs. 1.4% in controls, $2p < 0.01$), but not in UC (5.4%, $2p = 0.30$). The increased fracture frequency in CD was present for fractures of the spine, feet and toes and fractures of the ribs and pelvis. Fracture risk increased with increasing duration of corticosteroid use in CD ($2p = 0.03$), but not in UC ($2p = 0.50$).

Conclusions: An increased risk of low-energy fractures was observed in female CD patients, but neither in male CD patients nor in UC.

90. Bone mineral density in premenopausal and menopausal women with hyperthyroidism

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The increased secretion of thyroid hormones leads to the increased bone metabolism and decreased bone mineral density, especially in postmenopausal women. The main objective of the research was to assess bone mineral density in premenopausal and menopausal women depending on the duration and severity of hyperthyroidism. There have been examined 26 women aged 30-60 years (mean 47.7 ± 7.8) with hyperthyroidism. We analyzed bone mineral density using DEXA (LUNAR, EXPERT XL).

The data are presented in Table 1.

The obtained results showed that BMD was markedly decreased in postmenopausal women, than in premenopausal women. In premenopausal women with hyperthyroidism BMD was not dependent on the duration and severity of hyperthyroidism. In menopausal women the decreased BMD correlated with free serum T4 level and the duration of hyperthyroidism.

Table 1. Paper 90.

BMD g/cm ²	Duration of hyperthyroidism			
	0.2–12 years Premenopause	3.0–15 years	0.6–3.0 years Postmenopause	3.0–15 years
Lumbar spine L2–L4	1.361±0.125	1.301±0.104	0.832±0.124	0.745±0.350
Femoral neck	1.083±0.201	1.015±0.099	0.733±0.765	0.638±0.710
Wards	0.908±0.156	0.902±0.012	0.401±0.651	0.453±0.210
Trochanter	0.901±0.110	0.843±0.100	0.536±0.249	0.475±0.780
Total femur	1.125±0.089	1.052±0.703	0.664±0.654	0.632±0.250

91. Parathyroid disorders in patients with chronic renal failure

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Here we describe our findings concerning two patients with renal diseases. The first patient is female, aged 28, in the age of 13.5 years underwent severe hemorrhagic vasculitis, leading to the acute and then chronic glomerulonephritis with the rapid progression of chronic renal failure, the course of the disease was extremely severe, two times unsuccessful renal transplantation, during the last 13 years on chronic haemodialysis, we assessed this patient in 1998, ultrasonography showed enlargement of right lower parathyroid gland enlargement: 3.1 x 1.5 x 1.1 cm with calcified capsule. The thyroid gland was not enlarged, V = 7.6 ml. Patient had severe osteomalacia, multiple bone deformities, calcifications in the skin, calcium level was increased, PTH level was 1250 pg/ml (normal 8.0–76.0). DEXA (LUNAR, EXPERT XL, USA) showed bone mineral density L2–L4 830 ± 10 mg/cm², T-score varied from –2.1SD to –3.6 SD. That case was considered as tertiary hyperparathyroidism. Second case is female, aged 41 years, with the chronic glomerulonephritis and renal failure, along with impaired glucose tolerance. Ultrasonography of that patient showed the presence of two enlarged right upper parathyroid glands: 0.6 x 0.5 x 0.3 cm. and 0.8 x 0.4 x 0.3 cm, along with the multinodular goiter, V = 17 ml. Calcium level was decreased, PTH level was 954 pg/ml, TSH 2.01 mIU/ml. DEXA (LUNAR, EXPERT XL, USA) showed bone mineral density L2–L4 1.016 mg/cm², T-score varied from –1.4 SD to –1.8 SD; Z-score varied from –2.1 to –2.6 SD. That case was considered as secondary hyperparathyroidism.

is inherited in an autosomal recessive way. It occurs very seldom with frequency of 1/150,000. Because of marfanoid habitus and lens subluxation it is often diagnosed as the Marfan syndrome, however, it's characteristic additional symptoms like joint stiffness, thrombotic events, often mental retardation and generalized osteoporosis allow for an immediate establishment of diagnosis. Increase of homocystine and methionine levels in blood serum and urine confirm the diagnosis.

The aim of our paper was to present one case of homocystinuria with especially advanced symptoms observed in a newborn child, as well as generalized osteoporosis in the age of 12. The propositus was a 12.5-year-old girl of non-related parents. In the newborn period arachnodactyly with limited joint movement was observed. At the age of 5, bilateral lens subluxation was stated, the sign usually noticed not earlier than at the beginning of the 2nd decade of life. At the age of 10, because of minimal trauma there was a fracture of the left femur with dislocation, with embolism which accompanied it leading to pulmonary infarction of the 10th lung segment.

At present, the 12.5-year-old girl suffers from generalized osteoporosis stated by densitometric measurements of the spine, forearm and calcaneal bone. In L2–L4 vertebral bodies, BMD was 0.585 g/cm² (T-score –3.57). BMD in the distal fragment of the forearm bones was 0.208 g/cm² (T-score –4.9). SOS in calcaneal bone was 1526.504 m/s (T-score –3.08) and BUA was 37.668 db/MHz (T-score –2.23).

In the performed examination of homocystine level in blood serum, it's level was 23 times higher than the acceptable value.

The above presented case is very interesting considering clinical picture as well as because of early onset of the first symptoms and generalized osteoporosis in such a young age.

92. Osteoporosis in genetic disorders: homocystinuria—a case report

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Genetic factors play an important role in the pathogenesis of osteoporosis. It is related to both chromosomal aberrations and monogenic or multifactorial syndromes. Homocystinuria

93. The dynamics of bone mass changes in type 1 diabetes—a 3-year follow-up

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Available evidence indicate a relationship between reduced bone density and type 1 diabetes, its duration and complications, especially neuropathy. Bone density and its relation to

metabolic nonnormalization and chronic complications had been observed for 3 years. A group of 30 patients with diabetes type 1, disease duration of 5 years or more, aged 21–68 (mean age 38 years) and receiving intensive insulin therapy was examined at baseline and after 3 years. Metabolic normalization was evaluated from mean daily glycemia and percent of glycosylated hemoglobin. Chronic complications of diabetes: retinopathy (ophthalmoscopy), cardiovascular neuropathy (ProSciCard) were analyzed. Bone density was measured using an ultrasound densitometer Achilles, Lunar. Bone density was expressed according to the Stiffness index. Analysis revealed a relationship between diabetes duration and the Stiffness index. The index decreased markedly in patients with lower initial glycosylated hemoglobin level (negative correlation $r = -0.50901$, $p < 0.05$). The present findings indicate that worse control of diabetes precipitates bone mass loss. T-score was more frequently decreased in patients with chronic complications, thus confirming the contribution of nervous system disorders in the development of osteopenia.

94. Fracture risk is increased in epilepsy

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Our aim was to study fracture rates and risk factors for fractures in non-institutionalised patients with epilepsy.

Material and methods: Historical follow-up. Self-administered questionnaires were issued to 755 patients with epilepsy (ICD 10: G40.0 to G40.9) and 1000 randomly selected controls from the background population.

Results: A total of 345 patients (median age: 45, range 17–80 years) and 654 control subjects (median age: 43, range 19–93 years) returned the questionnaire. Before epilepsy was diagnosed there was no difference in overall fracture rate between patients and controls (RR = 1.0, 95% CI: 0.8–1.3). After the diagnosis the overall fracture rate was significantly higher in the patients (RR = 2.0, 95% CI: 1.6–2.5). Fractures of the spine, forearms, femurs, lower legs, and feet & toes were significantly increased. Fractures related to seizures accounted for 33.9% (95% CI: 25.3–43.5%) of all fractures. After elimination of seizure related fractures the increase in fracture frequency was only borderline significant: RR = 1.3 (95% CI: 1.0–1.7, $p = 0.042$). No difference in fracture energy between patients and controls was observed (low energy fractures: 1.7/1.4%, medium energy fractures: 59.8/52.0%, and high energy fractures: 38.3/46.6%). Use of Phenytoin (OR = 2.4, 95% CI: 1.1–5.4) and a family fracture history (OR = 2.4, 95% CI: 1.3–4.6) was associated with an increased fracture risk.

Conclusions: Fractures were more common in epileptics than in controls especially among users of phenytoin. Most of the increase in fracture frequency was related to seizures and not to low bone biomechanical competence.

95. Correlation between radiographic, MRI and CT findings in detection osteoporotic spinal fractures in men with ankylosing spondylitis

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Recognition of fracture in ankylosing spondylitis (AS) patients is often delayed. The purpose of the paper is to examine the relationship between radiography, MRI and CT examination in recognition of vertebral fractures due to osteoporosis in patients with AS.

Materials and methods: 46 male patients with confirmed AS, mean age 49 years old, were examined. Radiography of cervical, thoracic and lumbar spine (lateral projections) were performed in all patients. From patients with fractures in radiographic examination, 11 had MRI examination and 6 of these patients had CT. To detect vertebral body fractures with radiographs, the anterior, posterior and central heights of each vertebral body were measured with callipers. The ratios of each height to that of the two adjacent vertebrae, the ratio of the anterior height to the posterior height and of the central height to the posterior height were calculated. According to this ratio the subjects were considered to have mild, moderate or severe fracture.

Results: Radiographic examination found fractures in 16 (35%) of 46 patients. In further study we examined 12 patients. Radiography of these 12 patients showed total 26 vertebral fractures. MRI examination found 26 fractures in 11 patients. In MRI examination we confirmed 7 from 21 (33%) fractures found on radiographs. In CT examination we confirmed 3 from 12 (25%) fractures found on radiographs. None fracture found in MRI was confirmed in CT.

Conclusion: Detection of osteoporotic spinal fractures in AS patients is difficult. It is important to find the best method for detection of vertebral body fractures.

96. Pre-transplant bone densitometric and biochemical findings in patients with end-stage kidney and liver diseases

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Table. Basic biochemical findings, paper 96

Pts prior to	N	Markers	Findings	p	Control	N	Markers	Findings	p	Control
KTX	56	bALP	0.48	*	8.5–	46	PTH	211.7	***	10.0–
LTX	32	µg/L	2.37		18.0	32	pg/L	26.7		65.0
KTX	45	ACP	105.0	**	< 220.0	30	ICTP	15.2	ns	1.8–
LTX	32	nkat/L	153.0			20	µg/L	12.1		5.0
KTX	41	U-D-Pyr	17.2	ns	< 13.0	45	S-Alb	42.3	***	35.0–
LTX	31	nmol/mmol Cr	18.5			33	g/L	34.6		45.0

* $p < 0.05$

Chronic nephropathy and hepatopathy belong to the risk factors of secondary osteoporosis. We focused our attention on differences in the severity of skeletal damage in the above identified population of patients.

Patients and methods: A total of 85 pts of both sex were examined: 48 prior to kidney transplantation (KTX), 37 prior to liver transplantation (LTX) with a mean age of 48.9 yrs, with n.s. differences in groups. The patients were examined using a DXA Hologic 2000 system (mean BMD g/cm² of 4 sites of the femoral neck (FN) and the lumbar spine (LS) related to SD ranges: up to -1.0, -2.5, -3.5 and below -3.5). Using biochemical analyses, we evaluated: in serum – Ca, P, Mg, Al, bone isoenzyme of alkaline phosphatase (bALP), total acid phosphatase (ACP), osteocalcin (OC), type I cross-linked C-telopeptide (ICTP), intact PTH (PTH), albumin (Alb), hydroxyvitamines D3 (25OHD₃, 1,25(OH)₂D₃); in urine-deoxypyridinoline (U-D-Pyr).

Results: FN demineralization of up to -2.5SD of BMD affected about 30% of pts with n.s. differences in groups: below -2.5SD there were 48.6% of pts prior to LTX, 14.6% of pts prior to KTX ($p < 0.001$). At LS, a value of up to -2.5 was found mostly in pts prior to KTX ($p < 0.05$). BMD deficit below -2.5SD was present in 78.4% of pts prior to LTX, and in 37.5% of pts prior to KTX ($p < 0.01$ –0.001). Basic biochemical findings are listed in the Table.

Other parameters were found to be within normal ranges and they are not shown. The relationships between some investigated parameters were also studied.

Conclusions: Bone mass loss in pts prior to the above transplant procedures is significant. Pts prior to LTX formed more impaired group. Unlike the situation in pts prior to LTX, osteoporosis develops in pts prior to KTX under conditions of higher levels of PTH.

ing to a stable loss of work ability and invalidisation. Secondary osteoporosis and consequent fracture play a major part in determining the long-term morbidity and mortality of rheumatoid arthritis (RA) patients. With an aim to study the structural-functional bone tissue state in women with the RA 22 patients aging 20–44 years were examined as well as 24 patients aging 45–59 years and 21 patients aging 60–74 years. 35 women were taking steroids (RA+S) – among them 10 in group of 20–44 years old; 12 in group of 45–59 years old; 10 in group of 60–74 years old. 36 healthy age-, height- and weight-matched women served as controls (CG). The bone tissue was examined using an ultrasound densitometer “Achilles+” (Lunar Corp., Madison, WI). The speed of the sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and an estimated stiffness index (SI, %) were measured. In the age group of 20–44 years women taking corticosteroids had the worst results and ultrasounds parameters: CG (SOS – 1568±7.3; BUA – 115 ± 3.9; SI – 94 ± 4.1); RA (SOS – 1558 ± 11.5; BUA – 109 ± 5.0; SI – 89 ± 6.1); RA+S (SOS – 1534 ± 10.0; BUA – 99 ± 2.2; SI – 75 ± 4.0). In the age groups of 45–59 years – CG (SOS – 1553 ± 9.7; BUA – 109 ± 2.6; SI – 87 ± 3.3); RA (SOS – 1528 ± 9.5; BUA – 102 ± 4.6; SI – 76 ± 5.3); RA+S (SOS – 1530 ± 8.7; BUA – 101 ± 3.7; SI – 75 ± 4.7) and of 60–74 years – CG (SOS – 1525 ± 7.3; BUA – 101 ± 2.5; SI – 74 ± 3.6); RA (SOS – 1505 ± 6.1; BUA – 92 ± 3.7; SI – 63 ± 3.2); RA+S (SOS – 1504 ± 6.2; BUA – 89 ± 3.3; SI – 62 ± 4.0) indexes of the structural-functional state were veritably lower among the patients with the RA as well as with the RA+S. In summary, according to the ultrasound densitometry data the structural-functional state of the bone tissue in women of medium (45–59 years) and old (60–74 years) age with the RA veritably worsens disregarding the corticosteroids, meanwhile in the group of young women with the RA the veritable decrease of ultrasound parameters was revealed only in women taking corticosteroids.

97. Bone loss in women of different age with rheumatoid arthritis

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Rheumatoid arthritis is a widespread disease causing the development of a severe functional joint deficiency and lead-

Tumors

98. Inhibition of neoplasm progression and bone mass loss with 1α -OH vitamin D₃ and clodronate in patients with advanced prostatic carcinoma

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A complete androgenic blockade used in the treatment of advanced prostatic carcinoma may result in bone mass loss and increased number of bone fractures. Active metabolites of vitamin D inhibit the proliferation of neoplastic cells, increase their differentiation and restrain angiogenesis. Bisphosphonates, inhibiting bone resorption and reducing a release of growth factors from bone tissue, can retard development of bone metastases.

The purpose of the study is to assess whether 1α -OH vitamin D₃ and clodronate are able to retard the progression of prostatic carcinoma and bone changes induced by complete androgenic blockade.

42 patients with advanced prostatic carcinoma, with skeletal metastases, treated with orchidectomy and flutamide were examined for at least 12 months. 12 patients were additionally given 1α -OHD₃ in a dose of 0.5 µg/d and CaCO₃ in a dose of 1 g daily, while 15 patients were treated with the same drugs and clodronate in a dose of 1600 mg daily. Carcinoma extension was determined with USG, biochemical analyses (PSA, acid phosphatase, PAP) and with scintigraphy of the skeleton, while BMD by means of DXA and bone turnover with biochemical markers of bone resorption and formation processes.

It was found that treatment with 1α -OHD₃, CaCO₃ and clodronate decreased bone mass loss in the lumbar spine and proximal femur, without significant changes in serum Ca and P concentrations. Serum alkaline phosphatase activity decreased promptly in all groups of patients, while urine calcium that increased in patients with complete androgenic blockade was reduced by clodronate therapy. Serum acid phosphatase, PAP and PSA decreased promptly in all groups of patients indicating inhibition of neoplasm progression with the treatment used.

99. Matrix metalloproteinase 13 in human chondrosarcomas

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Chondrosarcomas are malignant cartilage-forming tumors of bone. The exact origin of chondrosarcomas remains unclear, but the basic proliferating tissue is cartilaginous. Chondrosarcomas have the ability to arise de novo in skeletal tissues and to invade normal bone tissue. A typical feature of the invasive process is degradation of bone matrix.

As collagenase 3 (MMP-13) seems to be the predominant collagenase in skeletal tissues and because it is capable of degrading native fibrillar collagens, we decided to investigate the level and cellular localization of MMP-13 parallel with other MMPs and TIMPs in human chondrosarcomas.

Materials and methods: Chondrosarcoma samples were obtained from seven patients who underwent surgical removal of the tumor. The resected tumor samples were cleaved into two symmetrical parts. One was used for routine histopathologic analysis, the other piece was cut serially into 5 mm slices which were used alternatively for Northern hybridization and immunohistochemistry.

Results: Northern analyses of these samples revealed considerable different expression patterns of MMPs and TIMPs. The present analyses clearly demonstrate activation of MMP-13 gene in some but not all chondrosarcomas analyzed. MMP-2, MMP-7 and MMP-14 mRNAs were also elevated and peaked in the same tumors, while MMP-3 mRNAs were elevated in only one tumor. TIMP-2 mRNA levels were high in all tumor samples studied.

Conclusions: This study demonstrates the importance of analysing the expression of several MMPs and their inhibitors together to get accurate results. Northern analyses also confirmed the heterogeneity of the tumors and emphasize the importance of thorough analysis of chondrosarcomas to detect this heterogeneity. The high expression of MMP-2, TIMP-2 and MMP-14 correlated with poor prognosis and perhaps they could be useful prognostic indicators in chondrosarcomas. Further studies including immunohistochemistry and in situ hybridization are needed in order to characterize the roles of MMPs in tumor growth and invasion.

100. Alkaline phosphatase isoenzymes in differentiation of bone cysts and osteoblastoclastoma

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Aim of the study was to investigate alkaline phosphatase isoenzymes (ALP-i) in patients with osteoblastoclastoma and bone cysts.

Patients and methods: 8 patients with bone cysts and osteoblastoclastoma, four in both group. Similar clinical and x-ray picture of both groups. Final diagnosis was confirmed histologically. Serum samples were obtained before and after operation. ALP-i serum composition was evaluated by agarose gel electrophoresis with neuraminidase pretreatment samples before electrophoresis.

Results: ALP activity was normal, but differences in electrophoretic patterns between liver and bone isoenzymes were found. We obtained difference in sensitivity to neuraminidase digestion of liver and bone ALP-i of osteoblastoclastoma patients before and after operation, but no difference comparing to normal in patients with bone cysts. Usually, after neuraminidase digestion liver and bone ALP-i moved less anodal than before. The rate of migration depends on sialic acid content of ALP-i. In our investigation, both fractions showed changed sensitivity to neuraminidase digestion. Before osteoblastoclastoma operation position of electrophoretic patterns was more anodal after neuraminidase treatment. Neuraminidase behavior of liver and bone fractions were normalized in all cases of osteoblastoclastoma patients after operations.

Conclusion: Abnormal neuraminidase behavior of ALP-i before operation may be helpful in confirmation of diagnosis of osteoblastoclastoma.

101. Induction of bone resorption in vitro by multiple myeloma cells, lack of evidence for involvement of interleukin-1, tumor necrosis factor- β , and parathyroid hormone-related protein

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During multiple myeloma (MM) osteolysis, caused by increased osteoclastic activity, is a common complication. MM cells are believed to secrete factors capable of inducing this bone resorption. Among these factors TNF β , IL-1 and PTHrP have attracted most attention. Seven MM cell lines (EJM, Karpas 707, LP-1, U266-1970, U266-1984, HL407E, HL407L) were used in this study. To investigate if these MM cell lines could initiate resorption in vitro we cocultured EJMs, Karpas 707 and LP-1, respectively, with calvarial bones and all cell lines tested could. By using RT-PCR mRNA for TNF β and PTHrP were detected in all seven cell lines, whereas mRNA for IL-1 was not detected. The amount of PTHrP transcribed were very low. Quantitative PCR calculated amounts comparable to those found in e.g. osteoblasts and much lower than in e.g. breast cancer cells. Finally, TNF β neutralizing antibodies were not capable of inhibiting bone resorption induced by MM cells in vitro.

Conclusion: The MM cell lines cause bone resorption in vitro. Due to the low amounts PTHrP expressed and the inability to block the MM induced resorption by TNF β antibodies it is unlikely that any one of these factors are the major factor responsible for osteolysis associated with MM.

Ultrasound – bone quality

102. Mechanical tissue quality in cancellous bone from ultrasound and μ FEA

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Stiffness of cancellous bone (highly correlated with strength) depends on bone quantity, and qualities of trabecular architecture and the mineralized tissue. Ultrasound speed-of-sound (SOS) measures stiffness directly. Micro-mechanical Finite Element Analysis (μ FEA) from μ CT reconstructions determines the contributions of quantity and architectural quality to stiffness. We tested whether combined application of both can be used to diagnose the mechanical quality of the mineralized tissue.

Methods: Fifteen bovine femoral bone cubes were used. SOS was measured in three directions and a Young's modulus was calculated for each. The same specimens were μ CT reconstructed and the moduli were calculated with μ FEA, using an arbitrary tissue modulus of 1 MPa. The two data sets combined, for each specimen, determined the true tissue modulus, representing tissue quality.

Results: SOS correlated well with μ FEA predicted Young's moduli ($R^2 = 84-92\%$). Realistic values of a mean 3733 MPa (SD 604) were found for the tissue moduli. When adjusting the μ FEA-determined Young's moduli with their calculated tissue moduli, an overall correlation of $R^2 = 95\%$ with SOS-predicted values was obtained.

Conclusion: Ultrasound SOS predicted stiffness characteristics agree closely with those from μ FEA. Both methods in combination enable diagnosis of mineralized tissue quality. This method will be clinically applicable in the future, and can already be used for biopsies.

103. Visualisation of bone micro structure and measurement of 3D parameters describing bone structure quality by in vivo high resolution magnetic resonance imaging

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The three dimensional trabecular bone structure in the human phalanges was visualised in vivo by high resolution magnetic resonance imaging (HRMRI). We determined different 3D structure quality parameters like the 3D connectivity or the relative plate volume.

Methods: We investigated 27 subjects (age 25 to 78) with a Siemens Magnetom Vision (Siemens Medical Systems, Erlangen, Germany). A 4cm surface coil was positioned on the phalanx and a 3-D spin echo sequence with $T_E = 15$ ms,

$T_R = 65\text{ms}$ and an acquisition time of 17min was applied. The spatial resolution was $150 \times 150 \times 280(\mu\text{m}^3)$. The raw 3-D HRMR images were processed to define a volume of interest (VOI), to segment the data set into bone and marrow in this VOI, and to filter out noise and artefacts. The resulting binary 3D was visualised and the 3D connectivity density and the relative plate volume (rPV) were determined for the whole network and particular regions.

Results: Figure 1 shows visualisations of bone micro structures of different quality from two subjects with 68 and 73 years of age. The respective values for the connectivity density and the relative plate volume are 0.82 conn./mm^3 , $rPV = 0.40$ and 1.79 conn./mm^3 , $rPV = 0.24$.

Conclusion: HRMR imaging allows for non-invasive visualisation of the micro structure in the phalanges and its quantification in vivo and may be a method for differentiation between structures of different quality.

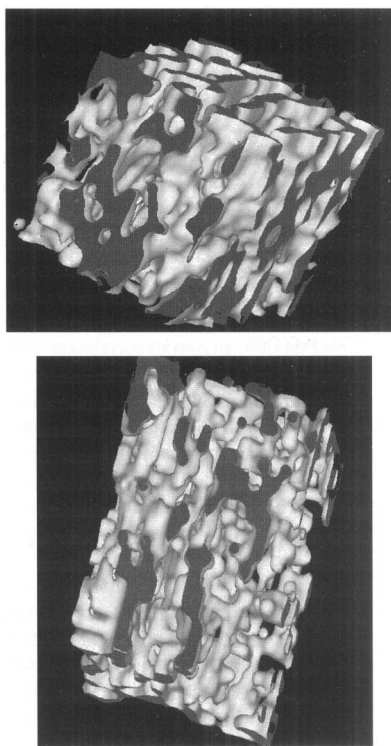


Figure 1. 3D visualisations of a part of the trabecular network in the phalanx of a 68-year-old subject (left) and a 73-year-old subject (right).

104. Ultrasound densitometry indices among women with Colles' fracture in postmenopausal period

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This research was aimed at studying the bone tissue state among women with Colles' fracture with aid of the ultrasound densitometry method. The total of 41 healthy postmenopausal women 4–74 years old (62.1 ± 7.5) having Colles' fracture in their anamnesis (CF) were examined by ultrasound bone densitometer "Achilles+" (Lunar Corp., Madison, WI). The control group included postmenopausal women without any osteoporotic fractures in their anamnesis (WF), being standardized by age, BMI, etc. The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated "Stiffness" index (SI, %) were measured. The main risk factors for the osteoporotic Colles' fracture turned out to be a menarche after 15 years, an early and late menopause. 29,3% of patients with Colles' fractures had a bone tissue stiffness index coinciding with the limit of fracture risk or under it. There was no revealed relation between the age and the ultrasound densitometry indices among women of postmenopausal age without fractures. Only 12,5% of patients with Colles' fractures were noticed to have a normal bone tissue. The ultrasound parameters were veritably lower among postmenopausal women with CF than among WF (SOS: CF – 1524 ± 28.4 ; WF – 1543 ± 24.3 , $p < 0.05$; BUA: CF – 102 ± 17.8 ; WF – 109 ± 12.0 , $p < 0.05$; SI: CF – 76 ± 14.9 ; WF – 85 ± 13.5 , $p < 0.05$; all values are the mean $\pm$ SD). It is caused by the decrease of bone tissue mineral density, it's accelerated aging, and the development of osteopenia and osteoporosis. The most tangible differences in these indices were noticed among the elderly patients. Colles' fracture indicates osteopenia and osteoporosis in postmenopausal period. In summary, ultrasound densitometry is an effective screening method to reveal the women of risk group having future osteoporotic Colles' fracture in postmenopausal period.

105. Ultrasound densitometry of the calcaneus in children and adolescents of Ukraine

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The bone tissue state in children and adolescents of Ukraine, subjects of both sexes, was studied. The purpose of this study is to determine normal values in Ukrainian children and adolescents. The total of 577 healthy children and adolescents (205 males and 372 females; 7–18 years old) were examined by ultrasound bone densitometer "Achilles+" (Lunar Corp., Madison, WI). The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated "Stiffness" index (SI, %) were measured. Ultrasound parameters increased with age in both sex (Figure 1). It was found out that the ultrasound parameters characterizing the state of spongy bone tissue, its density increase dur-

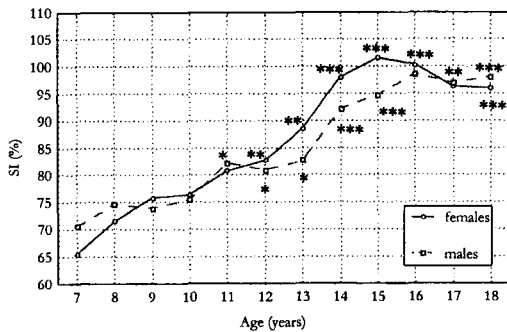


Figure 1. SI values in children and adolescents in an association with age and sex. Note: * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$ in comparison with the 10-year-old males and females.

ing the age of 10–14 years. Results of liner regression analyses revealed a significant correlation between ultrasound parameters and height ($SOS = 1413 + 0.99 \times \text{Height}$; $r = 0.45$; $R^2 = 20.2$; $p < 0.001$; $BUA = 7.0 + 0.62 \times \text{Height}$; $r = 0.60$; $R^2 = 36.1$; $p < 0.001$; $SI = 0.69 \times \text{Height} - 19.6$; $r = 0.60$; $R^2 = 36.1$; $p < 0.001$). With use of the method of stepwise multiple regression mathematical models for determination of the structural-functional age of the bone system (SFA BS) in children and adolescents are worked out:

SFA BS (males) = $9.01 \times H + 0.06 \times W + 0.04 \times BUA - 7.7$
($r = 0.88$; $R^2 = 78\%$; $p < 0.0001$);

SFA BS (females) = $8.02 \times H + 0.05 \times W - 0.008 \times SOS - 13.9$
($r = 0.78$; $R^2 = 61\%$; $p < 0.0001$),

where: H – height (m), W – weight.

In summary, basic preventive measures against the development of “future” osteoporosis in children need to be carried out during the period from 10 to 15 years.

106. Influence of natural physical factors of the sanatorium treatment on children and adolescents with disturbances of structural-functional status of the bone tissue, residing in radiation contaminated zones

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With purpose to study influence of the natural physical factors of sanatorium treatment on children and adolescents with disturbances of structural-functional bone tissue residing in radiation contaminated zones we examined 148 children and adolescents (gr. 1), which were on sanatorium treatment in an International children's medical center “Evpatoria”. Patients' mean age $\pm$ SD was 12.5 ± 3.2 years (range 7–16 years). The control group included children, being standardized by age, sex, etc., who resided on the non-con-

taminated lands. The heel bone examinations were performed by means of an ultrasound bone densitometer “Achilles+” (Lunar Corp., Madison, WI). The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated “Stiffness” index (SI, %) were measured. In comparison with control group the most expressed modifications in a structural-functional state of bone tissue (decrease of elasticity and the stiffness) are detected in 8–9 and 12–13 year-old girls, 12 year-old boys. Knee arthralgias, identified in 21.6%, were the complaints most commonly present in children and adolescents of the 1 group. Arthralgias in other joints comprised 18.2% of present complaints, back pain was reported in 12.2%. In 4 patients we found Osgood-Schlatter syndrome, 32 – osteochondrosis of the spine, 3 – juvenile rheumatoid arthritis. After sanatorium treatment we found increase of ultrasound densitometry parameters: in girls (SOS – by 2.8 ± 1.2 m/s; BUA – 0.7 ± 0.81 dB/MHz; SI – $1.0 \pm 0.62\%$) and boys (SOS – by 5.7 ± 2.5 m/s, $p < 0.05$; BUA – 1.2 ± 1.01 dB/MHz; SI – $2.5 \pm 0.86\%$, $p < 0.05$). Knee arthralgias after treatment we identified only in 3.4%, arthralgias in other joints in 4.1%, and back pain in 1.4%.

In summary, natural physical factors of the sanatorium treatment improved structural-functional state of musculoskeletal system in children and adolescents with disturbances of structural-functional state of the bone tissue residing in radiation contaminated zones.

107. Comparison of BMD and QUS in postmenopausal women

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The aim of our study was the assessment of BMD of the forearm and BUA and SOS of the calcaneus in postmenopausal women.

Materials and methods: 77 healthy women, average age 60.70 ± 8.3 years (range 47–78 years) were involved in the study. The average age of menopause was 49.0 ± 3.6 years (range 37–56 years). BMD was measured by DXA using DTX-200 and QUS parameters by DTU-ONE (all systems produced by Osteometer Medi-Tech A/S Denmark).

Results: Average BMC and BMD values were: 2.647 ± 0.482 g and 0.387 ± 0.061 g/cm². Average BUA and SOS values were: 45.5 ± 8.5 db/MHz and 1540 ± 17 m/s. T-score values < -2.5 SD for BMD were indicated in 19 (24.7%) women, and for BUA and SOS in 18 and 7 women (23.4% and 9.1%, respectively). We have not found correlation between BUA, SOS and BMC ($r = 0.2642$, $r = 0.2861$, respectively) and between BMD and SOS ($r = 0.3114$). The low correlation between BMD and BUA was observed ($r = 0.3572$).

Conclusion: The relationships between QUS and DXA are too weak and this indicates that these methods present information about different aspects of bone.

108. Quantitative ultrasound (QUS) discriminates osteopenia from osteoporosis with no fractures in senile female population

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Our previous analyses (ref) showed low 30–40% determination coefficient (r^2) between QUS of heel and BMD by DEXA of spine and hip in the group of 188 healthy female at the mean age of 44.1.

Patients and methods: In this elaboration we compare QUS values (Sahara-Hologic) in two groups of 310 women classified according to WHO criteria with osteopenia (T-score -1.0 to -2.5) and that with osteoporosis (≤ -2.5) (DEXA, by QDR4500SL-Hologic) with no fracture at mean age of 67.4 (45–82).

Results: All the QUS parameters QUI, BUA, SOS significantly ($p < 0.0001$) distinguished osteopenia from osteoporosis. BMD of heel were 0.456 and 0.369 corresponding to T-score -1.12 and -1.89 , BUA were 62.5 and 48.6 and SOS 1534 and 1516, respectively.

Conclusion: QUS is able to discriminate osteopenia from osteoporosis in senile women. Threshold between them is on the level of -1.5 .

Reference: Daniluk S et al. Post Osteoartrol 1998, 10, 15.

109. Osteoporosis by young women—a serious health problem

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Most studies on osteoporosis deal with women of postmenopausal age. But little attention has been given to osteoporosis by young women of the reproductive age.

Materials and methods: The subjects of this study were young Estonian women, aged 20–25 ($n = 32$). The subjects answered a questionnaire on their eating habits, life-style, family history and menstrual cycle. Bone density screening was conducted using the Achilles + ultrasound method.

Results: Bone metabolism disorders was detected in 5 of the 32 subjects. The rank of risk factors was the following: 1) long-term calcium-deficient diet, complemented with protein deficiency, vitamin D deficiency and low caloric content; 2) family history supporting osteoporosis risk; and 3) menstrual disorders. All the subjects with high osteoporosis risk were of leptosomic body build. When the diagnosis had been determined, the diet was adjusted to meet the requirements by adding complex calcium food supplements. As shown by our previous studies, this corrected diet for young women will give positive results as early as in six months of treatment.

Conclusions: The calcium intake deficiency below the two thirds of norm constitutes a serious osteoporosis risk for young women. To promote osteoporosis prevention, it is essential to define the limits of the adaptive responses to different calcium intakes in our era of modern restricted diets.

110. Quantitative ultrasound is able to detect differences between estrogen-treated and untreated groups of women

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Early diagnosis of bone loss is important in order to start treatment and prevent further bone loss. Absorptiometry techniques are still considered the golden standard for determining the quality of bone, but the use of quantitative ultrasound (QUS) measurement for diagnosis of osteoporosis is emerging as an alternative to absorptiometry techniques. In our study, we have compared the two techniques.

Materials and methods: 263 healthy, postmenopausal women from the Danish Osteoporosis Prevention Study (DOPS) were studied. 98 women, (age 50–61 years, mean 54.1, SD 2.7) were estrogen treated for five years, and 165 (age 50–63 years, mean 55.9, SD 2.9) were untreated as controls. Whole body, lumbar spine (L2–L4), femoral (trochanter, neck, total), and radius-ulna total (UD-radius) densitometry was performed at baseline and after 5 years, using a Hologic 2000 DEXA scanner. QUS was determined as broadband ultrasound attenuation (BUA), velocity (SOS), and stiffness of the right calcaneus using a Lunar Achilles, at the five year visit.

Results: Estrogen-treated women increased bone mass, assessed with DEXA of spine and total hip during the five year period. The untreated group lost 5–8% of their bone mass during the same period. After five years, the differences between treated and untreated were comparable in respect to DEXA and QUS, with the most pronounced differences between the groups in spine (15.4%) and in stiffness (10.8%). Correlation coefficients between QUS and DEXA were calculated, with the best correlations for stiffness and SOS (0.5–0.6 for all DEXA regions). Using a ROC curve, the optimal cut-off T-score was found to be app. -2.0 . The specificity for stiffness to DEXA of either the femoral neck or the spine was 0.67, and the sensitivity 0.59/0.63 respectively. The positive predictive values were 0.80 (neck) and 0.82 (spine), whereas the negative predictive values were 0.49 and 0.41, respectively.

Conclusion: QUS can detect the differences between treated and untreated groups. Due to the lack of QUS measurements at baseline, it is impossible to determine whether the treated group increased the calcaneal bone mass or had a less pronounced loss than the untreated group. The predictive value of QUS in the single patient cannot be evaluated from the present data, but hopefully later in the ongoing study.

111. Age-related bone loss in normal population of Ukraine—data of ultrasound bone densitometry

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The bone tissue state in the residents of Ukraine, subjects of both sexes, was studied. The total of 1866 persons (1364 women and 502 men; 20–89 years old) were included. Patients with the diseases influencing their bone tissue metabolism were excluded from the study. The heel bone examinations were performed by means of an ultrasound bone densitometer "Achilles+" (Lunar Corp., Madison, WI). The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated "Stiffness" index (SI, %) were measured. It was found out that the ultrasound parameters characterizing the state of spongy bone tissue, and its density decrease after 45 years old in women and after 70 years old in men (Figure 1).

SI lower than the fracture threshold was found in: 2.4% – men; 13.4% – women in age group of 50–59 years; 9.6% – men; 24.6% – women in age group of 60–69; 22.6% – men; 50.0% – women in age group of 70–79 years, 20.1% – men; 53.3% – women in age group of 80–89 years.

Thus, while aging the ultrasound parameters characterizing the bone tissue state decrease significantly and the number of the examined with indices lower than the fracture threshold increases.

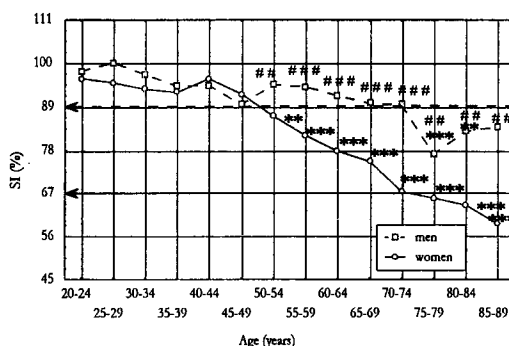


Figure 1. SI values in population of Ukraine in association with age and sex. Note: * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$ in comparison with age group 35–39 years old; # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$ in comparison with women.

Varia

112. Bone density in Baltic grey seal

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Different organochlorine pollutants are known to accumulate in both animals and man and to effect bone tissue in rodents, both in vivo and in vitro. The Baltic has been seriously contaminated by organochlorines in the past. Monitoring has been conducted in Sweden since the late 1960s by annual collection and chemical analysis of selected biological matrices making it possible to evaluate temporal trends in the pollution impact of the Baltic. A decrease in concentrations of DDT compounds started during the beginning of the 1970s, whereas concentrations of PCB compounds did not decrease until late 1970s. The annual decrease since the 1970s has been about 11% for DDT compounds and about 8% for PCB. Concentrations of dioxins have also decreased in the Baltic during the last three decades although slightly less than that of PCBs.

Materials and methods: In this study, bone mineral density of mandibular and radius bones from male Baltic grey seals (4–15 years of age) was examined by peripheral quantitative computed tomography (pQCT). The bone material from the Swedish Museum of Natural History was divided according to year of collection, into three groups: A) 1850–1955, representing the period before the introduction of organochlorines; B) 1965–1985, representing the period of maximum contamination; and C) 1986–1997, representing a period of fairly low contamination levels. The material from 1850–1955 did not contain any radius bones.

Results: When mandibular trabecular bone density was related to year of collection, a U-shaped curve was found ($p < 0.05$). The highest density was obtained in bones collected between 1850–1955; 151.9 ± 30.5 (mean $\pm$ SD), $n = 9$ and the lowest in bones collected between 1965–1985; 119.2 ± 48.6 , $n = 22$. The trabecular bone density of the radius was significantly higher in bones collected between 1986–1997 (196.9 ± 48.2 , $n = 11$) compared with those collected between 1965–1985 (129.6 ± 37.7 , $n = 5$). The mandibular cortical density showed a continuous decline over time ($p < 0.05$).

Conclusion: These results show different responses over time in trabecular and cortical bone of Baltic grey seal. During the period of maximal contamination, the trabecular bone density was lowest, whereas the cortical bone density showed a continuous decline. The mechanisms behind these effects are not known, but organochlorines are most likely involved.

113. Mechanisms of calcium signaling in osteoblast-like cells

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Bone cells respond in vitro to mechanical stimulation by increases in intracellular calcium concentration, that spread from cell to cell in monolayers, a phenomenon referred to as intercellular calcium waves (ICW). The two rat osteoblastic cell lines ROS17/2.8 (ROS) and UMR106-01 (UMR) possess two different mechanisms for propagation of these calcium transients. UMR cells propagate ICW by autocrine action of ATP on the nucleotide receptor P2Y₂, while ROS waves depend on intact gap junctional communication.

Methods: Measurement of calcium concentrations was performed using video imaging/fluorescence microscopy and the Ca²⁺ indicator fura-2. UMR or ROS cells in monolayer were mechanically stimulated to show ICW propagation.

Results: ROS cells, like UMR cells, propagated calcium waves in response to mechanical stimulation. The gap junction channel blocker heptanol, inhibited ICW in ROS. Intracellular calcium stores were not required for the propagation of ICW, as emptying of the stores with thapsigargin failed to block the wave. The role of extracellular Ca²⁺ was assessed by removal of extracellular calcium after which no waves was observed. Adding extracellular ATP or UTP, in order to desensitize P2Y receptors, did not affect wave propagation. Adding the L-type voltage-gated calcium channel antagonist nifedipine to the cell medium, inhibited ICW propagation, as well as depolarizing the membrane with potassium resulted in a rise in intracellular calcium and a resulting inhibition of the wave propagation.

Conclusion: ROS cells propagate intercellular calcium signals in response to mechanical stimuli. These waves are dependent upon gap junctional communication, membrane depolarization of the neighboring cell and subsequent influx of extracellular calcium, but not by autocrine action of ATP. The exact nature of the messenger traversing gap junction channels resulting in the depolarization has not yet been identified, but it is not IP₃, as intracellular calcium stores are not required for the propagation.

114. The spongy bone tissue state in children and adolescents with orthodontic pathology

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With purpose to determine a structural-functional state of

spongy bone tissue in children and adolescents with orthodontic pathology we examined 118 children and adolescents aged 8–17 years, which were on sanatorium treatment in an International children's medical center "Evpatoria". According to the results of orthodontic researches all patients were divided into 5 groups: 1 gr. – without orthodontic pathology; 2 gr. – with anomaly of separate teeth; 3 gr. – with anomaly of tooth series, 4 gr. – with anomaly of jaws, 5 gr. – with malocclusion. Measurements of bone tissue were done with an ultrasound bone densitometer "Achilles+" (Lunar Corp., Madison, WI) with heel bone application. The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated "stiffness" index (SI, %) were measured. In children and adolescents with malocclusion we found significantly decreased SI values compared with patients without orthodontic pathology:

- 1 group (Age – 13.3 ± 0.5; SOS – 1558 ± 6.3;
BUA – 110 ± 2.1; SI – 90 ± 2.1);
- 2 group (Age – 12.6 ± 0.8; SOS – 1566 ± 8.4;
BUA – 104 ± 3.9; SI – 87 ± 4.0);
- 3 group (Age – 13.1 ± 0.4; SOS – 1570 ± 12.0;
BUA – 112 ± 5.7; SI – 94 ± 6.6);
- 4 group (Age – 13.2 ± 0.7; SOS – 1558 ± 2.8;
BUA – 108 ± 2.7; SI – 88 ± 1.9);
- 5 group (Age – 13.8 ± 0.6; SOS – 1541 ± 6.3;
BUA – 106 ± 2.9; SI – 82 ± 2.8).

Conclusion: Decreased ultrasound bone tissue parameters in children and adolescents with pathology of bite testifies to structural-functional disturbances of bone system at the given quota.

115. Prevention and reduction of osteoporotic rarefaction in mandibular segments

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Literature data indicate that osteoporotic changes could exist in different bones. In this study the changes of segments of mandibles of 11 partially edentated postmenopausal osteoporotic women, having lighten hues of skins were investigated in two periods of 3 months. The 1st 3-month period of observation for every woman lasted from late winter to middle spring time and the 2nd 3-month periods of observations lasted from late spring to the end of summer. Three standardized orthopantomograms were committed for every woman at the baseline, after 3 months and after 6 months. At the baselines, BMD scan analyses of L_{2,3,4} were performed for every woman too. Mean value of L₂₋₄ T results amounted -2.78 cm² and the mean value of BMIs index was 20.1. During the 2nd observations' period women have been intaking 0.025 grams of alphacalcidol tablets and AD capsules every

morning and 500 mg effervescent every late evening. For indirect assessments of segments of mandibular bones, the light beam from DT II 05 densitometer was transmitted through segments of regions of previously existed roots of premolars, PRRs and PRLs, determined on the right and the left sides of orthopantomographs. For the numerical values of measurements, expressed in $U/2\text{ mm}^2$ trends of bone's rarefactions $G_{0,3}$ for the 1st 3-month period of observations and $G_{3,6}$ for the 2nd 3-month period of observations were calculated. For PRRs $G_{0,3} \approx 1.023$ (2.3%) and for PRLs $G_{0,3} \approx 1.022$ (2.2%). For PRRs, $G_{3,6} \approx 1.017$ (1.7%) and for PRLs $G_{3,6} \approx 1.016$ (1.6%). Those results indicated that increased calcium intake, as well as stimulation of vitamin D receptors, under favorable circumstances could decrease osteoporotic changes in certain mandibular segments.

116. Local hormone therapy increased density in mandibular segments—a case report

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In a postmenopausal female patient (65 years of age), systemic osteopenia was diagnosed according to: analyses of optical densities of certain predominantly cancellous structures, mandibular segments, performed on dental-retroalveolar radiographs with grid incorporated, analyses of 2nd metacarpals on two radiographs and osteodensitometries of $L_{2,3,4}$. DT II 05 densitometer was used for assessments of optical densities of radiographs. Mean values of optical densities of right 2nd metacarpal amounted - $1.59\text{ U}/2\text{ mm}^2$ at the baseline and - $1.71\text{ U}/2\text{ mm}^2$ after 3 months, indicating osteopenic changes. Mean values of optical densities of cancellous segments CSright and CSleft of woman's mandible amounted for CSright - $1.57\text{ U}/2\text{ mm}^2$ at the baseline and - $1.64\text{ U}/2\text{ mm}^2$ after 3 months, and - $1.59\text{ U}/2\text{ mm}^2$ at the baseline and - $1.67\text{ U}/2\text{ mm}^2$. During that 3 month period woman was advised to consume a solution of Ca efferrlet after evenings. After 3 month observations' period, $L_{2,3,4}$ T result amounted - 1.52 cm^2 , and BMI was 28.5. After that, the mixed liquid, consisted of 1 ml calcitonini (Calcitonin Hubber, ICN Galenika) and 1 ml calcii glubionasi (Calcium Sandoz 10%, Sandoz) was submucously applied - an injection areas were about 4 mm on the right and about 4 mm on the left side of labial frenum, as a depot expected to be dispersed and than gradually incorporated into a segments of bone. The liquid was injected in 3 intervals - 7 days of duration each. After 21 day mean values of optical densities amounted for CSright - $1.51\text{ U}/2\text{ mm}^2$ and for CSleft - $1.52\text{ U}/2\text{ mm}^2$. The results of the study indicate positive influence of locally applied calcitonin on bone mineral composition, as well as on quality of cancellous mandibular bone.

117. Histologic and structural changes in the proximal epiphysis of femur during development and aging in spine mice (*Acomys cahirinus*)

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The aim of these investigations was to analyse the histological structure of the proximal epiphysis of the femur during the entire life-span of spine mouse (*Acomys cahirinus*), a rodent species living in the Middle East.

Material and methods: The age of mice ranged from the second day of postnatal life up to the 1350th day. The epiphyseal sections were stained with erythroline and analyzed microscopically using light and fluorescent microscope (Nikon, Eclipse 800).

Results: Directly after birth, the epiphyseal center of ossification appeared with the first trabeculae in the 7th day of postnatal life. In the second month of life the tiny structure of trabeculae enlarged progressively and were accompanied by large spaces filled with marrow. The epiphyseal and joint cartilage were thinner at the second month of life when sexual maturity occurred while the epiphysis were characterized by typical lamellar forms. In the second year of spine mouse life the disappearing process of trabeculae advanced more rapidly. In the fourth year of life the number of trabeculae decreased further and this was accompanied by enlargement of their diameters. At the age of 3-4 years the epiphyseal cartilage did not contain chondrocytes.

Conclusion: The spine mouse (*Acomys cahirinus*) is characterized by rapid growth and development of the epiphysis and more advanced processes of aging in comparison with other rodent species. This animal species may be considered as an alternative experimental animal for research of bone growth and aging under various nutritional, pharmacological and toxicological investigations.

118. Prenatal growth and development of histological, mechanical and geometric properties of femur and humerus in the pig

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The aim of these investigations was to determine the time of prenatal ossification of epiphysis of pig femora and humera and their mechanical, geometric and histological properties.

Material and methods: Investigations were carried out on 25 pigs foetuses at the age from 12-15 weeks of prenatal

life. The femora and humera were isolated and histologically assessed for fluorescent and light microscopic analysis of ossification processes. Additionally three point bending test using Instron 4302 apparatus was used for measurements of mechanical parameters such as maximum strength, maximum elastic force, Young's modulus of elasticity and stiffness. The following geometric parameters were measured as well: the second moment of inertia, the cross sectional area and mean relative wall thickness.

Results: The epiphyses of femora and humera of the foetuses at 12 weeks of life were composed exclusively of cartilaginous tissue. The first symptoms of ossification occurred in the epiphysis of the humerus in foetuses in the 14th week of prenatal life. Between the 12th and 15th weeks of foetal life the increase in maximum strength rose in the humerus from 47.4 N to 391.2 N and stiffness rose from 9.5 to 54.0 N/mm while that of the femur from 82.1 N to 306.2 N and 14.8 to 46.7 N/mm, respectively. Geometric parameters of both bones were increased more similarly than did mechanical parameters during the period of foetal development.

Conclusion: The results indicate the beginning of ossification during the prenatal development of foetuses in the pig and prove existence of differences between the humerus and femur.

119. Developmental changes in the mechanical properties and mineral content of tibiae and humera of the Pharaoh quail

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The purpose of these investigations was to determine the development of the physical properties of limb bones in relation to growth and mineralization of the skeletal system during the first year of life in the quail (*Coturnix coturnix Pharaoh*).

Materials and methods: Tibiae and humera were isolated and dynamically loaded at a constant strain of 10 N/min using INSTRON 4302 apparatus. Ultimate strength and maximum elastic strength were determined. The length and weight of bones, ash weight and their mineral content were measured as well. Blood plasma, calcium, phosphorus and alkaline phosphatase activity were estimated.

Results: There was a progressive increase in measured mechanical properties of bones with the highest rate during the first week of life, which was accompanied by the highest number of osteoblasts and osteoclasts in the bone marrow. The ash content of bones increased from 31.8% in 1-day-old males and 30.3% in 1-day-old females to 55.2% and 62.9% in 1-year-old males and females respectively. The increase of alkaline phosphatase activity was extended to the first two weeks of life and the most expressed increase in plasma cal-

cium occurred at 8 weeks of life, when the laying period begins. Significant differences were observed in the ash content of Ca, P, Mg and Zn related to the age and sex groups.

Conclusion: Obtained results indicate age related changes different in male and female quails correlated with maturation, laying time and aging.

120. Reindeer antler matrix as bone inducing material

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Ectopic ossification is a phenomenon where bone is induced in extra skeletal sites. This phenomenon can be seen in surgery where growth factors liberated in the operation activate bone formation in the wound. Urist et al. 1965 first demonstrated that extracts from demineralized bone induce new bone formation when implanted into muscle fascia.

Reindeer antler is one of the fastest growing tissues. Growth of antler resembles endochondral ossification. Young antler, also called velvet antler, is fast growing and contains cartilage instead of bone, but when growth proceeds, cartilage is replaced by bone. Hard antler contains mainly calcified bone, reverse mesenchyme and perichondrium are crunched and epidermal tissue is peeled off before rut.

Materials and methods: Male rats of 3 months age were used for ectopic bone assay. Decalcified matrix was produced from 1 month old antler (none or very little calcification), 4 month old antler (rapid calcification process going on) and casted, totally calcified antler. Decalcified bone matrix produced from rat femur was used as positive control. Different matrix were implanted in gelatin capsules under the fascia of latissimus dorsi muscle for 3 weeks (all 4 matrix preparations) or 2 months (allogenic or casted antler matrix). Mineral density of the formed ectopic ossicles were measured with peripheral quantitative computer tomography. Histological hard tissue sections were stained with von Kossa staining. Proportional mineralisation area was measured with digital image analysator.

Results: During the 3 weeks induction period the mineral density was 115 mg/cm³ in decalcified allogenic matrix, 48 mg/cm³ in casted antler matrix and 8 mg/cm³ in 4 months old antler matrix. One months old antler matrix failed to induce ectopic ossification. Results from the histological staining of the accumulated mineral was in agreement with the density measurements. There is a clear difference between allogenic rat bone matrix and antler matrix bone inducing capacity: allogenic bone matrix induces normal endochondral ossification but antler matrix induced formation of few ossicles surrounded by fibrous tissue without cartilage.

Conclusion: Ectopic bone assay revealed that the decalcified reindeer antler matrix induces ectopic bone formation. However, it is less potent for inducing ectopic ossification

than allogenic rat bone matrix. There is a clear correlation between antler age and mineralization activity. The more calcified antler, the more calcificated ossicles.

121. Estimation of mechanical properties of hare (*Lepus europaeus Pallas*) and rabbit (*Oryctolagus cuniculus*) femora and humera

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The aim of these investigations was to determine and compare the mechanical properties of limb bones (femora, humeri) of two species: the household rabbit and free-range wild European hare.

Materials and methods: Investigations were carried out on hares living in 5 different hunting districts of Poland. The rabbits were kept in conditions typical for household and experimental animals. Body weight of hares and rabbits was approximately 4.1–4.5 kg. The three-point bending test using Instron 4302 was used for measurements of physical parameters of humera and femora such as bone maximum strength, maximum elastic force, Young's modulus of elasticity and stiffness. The following geometrical parameters were measured as well: the second moment of inertia, the cross section area and mean relative wall thickness.

Results: The mean lowest and highest values in 5 different groups of hares indicate that mass and length of femora and humera were highest in the hares (mass of femur 23.8–25.2 g, humerus 11.5–13.2 g) in comparison with rabbits (mass of femur 19.6 g, humerus 9.5 g). The bones of hares were characterized by significantly higher values of physical parameters (max. strength of femur in hares 162–206 N/kg b.w.; max. strength of femur in rabbits 130 N/kg b.w.; and of humerus in hares – 128–166 N/kg b.w., and rabbits 90 N/kg b.w.).

Conclusion: Obtained results prove that hares were characterized by considerably greater values of mechanical parameters of limb bones in comparison with household rabbits of nearly the same body mass.

122. More refractures with the Gamma-nail than with a sliding screw plate in pertrochanteric fractures

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Despite several studies showing a higher incidence of new periimplant femoral fractures with the Gamma-nail compared to a sliding screw plate (SSP) in pertrochanteric fractures, the Gamma-nail has been continued as the standard implant in some hospitals in Oslo.

Material and methods: We registered all pertrochanteric fractures in Oslo during 2 years, and compared the reoperation frequency in the patients treated by the Gamma-nail compared to a SSP.

Results: 921 patients were treated with a SSP or the Gamma-nail. 67 of the 921 patients with SSP or Gamma-nail needed reoperation. 17 of the 379 patients treated with the Gamma-nail had a new femoral fracture postoperative, compared to 3 of the 542 with SSP. The relative risk factor for a postoperative new femoral fracture was 11.9 (95% CI: 2.7–51.7) if the surgical device was the Gamma-nail, compared to a SSP.

Discussion: In Oslo 2 hospitals have continued using the Gamma-nail, one abandoned it after a randomized study several years ago. Despite changes in the Gamma-nail the refracture frequency is unchanged around 5% compared to less than 0.5% for a SSP. The Gamma-nail can therefore not be recommended, as shown several times previously.

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HIP ARTHROPLASTY

1. Fixation and bone remodelling of a low modulus stem

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This study aimed to measure fixation and bone remodelling of a new design of a composite stem using radiostereometric analysis (RSA) and dual energy x-ray absorptiometry (DEXA). Cemented and uncemented metallic stems were used as controls.

Patients and methods: 60 patients (61 hips, 37 male, 23 female, median age 60 [32–69]) with non-inflammatory arthrosis of the hip with a wide femur (stem size ≥ 14) were studied. They were randomly allocated to receive a cemented Anatomic-Option stem (O), an uncemented Anatomic (A) stem (proximal third with porous + hydroxyapatite/tricalcium phosphate coating [HA/TCP], middle third has pure HA coating, distal third polished) or an uncemented EPOCH (E) stem. This design has a central core made of cobalt-chromium-molybdenum alloy covered with a layer of polyaryletherketone. A porous titanium fibre mesh (pore size: 300 [50–600] microns) is attached to the plastic. The proximal 2/3 of this mesh is coated with HA/TCP ($75 \pm 20\%$ HA). This stem was only available from stem size 14. The patients were followed with radiostereometric analysis postoperatively, after 3, 6 months, 1 and 2 years. 30 patients operated in one of the 2 hospitals were studied with DEXA examinations postoperatively and after 1 and 2 years. Harris Hip Score was used for clinical evaluation.

Results: The Epoch and the Anatomic stems showed no or minimum subsidence (median -0.01 and -0.06 mm), whereas the majority of the cemented stems migrated distally and especially between 1 and 2 years (median at 2 years: -0.17 ; $p < 0.0005$, *Kruskal-Wallis test*). Small stem rotations (median values: 0.005 – 0.3°) were recorded without any difference between the groups. DEXA measurements revealed more loss of bone at 2 years around the Anatomic compared with the EPOCH stem in Gruen region 2 (A: -29 / E: -13) and

region 7 (A: -43 / E: -18 ; $p < 0.05$; *Mann-Whitney test*). The Option stems had more bone loss than the EPOCH stems in region 6 (O: -15 / E: -5 ; $p < 0.05$), but less bone loss than the Anatomic stems in region 1 (O: -8 / A: -39), 2 (O: -14 / A: -30) and 7 (O: -22 / A: -42 ; $p < 0.05$). A regression analysis using the mean value of bone density change in the proximal four regions as result parameter, displayed significantly more bone loss around the Anatomic stems ($p < 0.002$) *adjusted* $r^2 = 0.32$. The Harris Hip and pain scores at 2 years did not differ between the 3 stem designs.

Conclusions: Previous designs of elastic stems have showed high failure rate because of poor fixation^{1,2}. In our study the EPOCH stem displayed minimum migration and less bone loss than the 2 control groups up to 2 years. Further studies to evaluate the long-term efficacy of this prosthetic design are motivated.

2. All Exeter femoral components showed early migration—a stereophotogrammetric analysis

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The objective was to determine the migration pattern of the Exeter femoral component during the first postoperative year.

Methods: A primary Exeter hip arthroplasty was performed in 21 patients with non-inflammatory arthritis of the hip. Radiostereometric analysis (RSA) was done before mobilization and at 4 and 12 months. The migration of the stem relative to the femoral bone (all cases) and the stem relative to the cement mantle (12 cases) was analyzed.

Results: All the femoral components migrated distally during the first 4 months, mean 1.0 (0.4 – 1.7) mm. 13 continued migrating and the mean distal migration at one year was 1.2 (0.5 – 2.2) mm. At 1 year lateral displacement of mean 0.6 (0.5 – 1.0) mm was seen in 6 cases. Posterior displacement of mean 1.1 (0.7 – 2.4) mm was seen in 11 cases and one moved 0.3 mm anteriorly. In 10 of the 12 cases in which it was pos-

sible to analyze the migration between the stem and cement the distal migration was found to occur within the cement mantle only, in one case between the cement and the femoral bone and in one case at both interfaces.

Conclusions: The magnitude and incidence of early migration of the femoral component in this study is much higher than in previous RSA studies on femoral components of other designs. The distal migration occurs mainly within the cement mantle. This might be due to the design of the Exeter stem which seems to facilitate migration within the cement without disrupting the cement.

3. Histology of impacted graft incorporation

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To study the metabolic events taking place in a graft bed after impaction grafting, core biopsies were taken from proximal femur 1–11 months after revision total hip arthroplasty combined with graft impaction and cementing a Lubinus SP-II or a Charnley prosthesis in 18 patients. Core biopsies from distal femur and proximal tibia were taken 14 and 23 months after revision total knee arthroplasty combined with impaction grafting and cementing a Link Rotation Knee. One retrieved proximal femur in one of the patients earlier investigated with core biopsy after 1 month, was investigated again post mortem 48 months after surgery.

The core biopsies of 4 mm diameter from proximal femur were percutaneously taken under general anesthesia from the proximal lateral aspect of the femur under radiology and using an image intensifier to control for the location. The specimens were stained according to Goldner. 13 of the patients received one dose of fluorochrome.

1 month postoperatively based on samples from 2 patients showed necrotic bone chips surrounded by a fibrin clot invaded by granulocytes. In one area a loose fibrous stroma and an area of woven bone with filled osteocyte lacunae were seen.

4 months postoperatively based on samples from 5 patients showed many of the dead trabeculae had layers of living bone and osteoid embedded in a fibrous stroma.

6 months postoperatively based on samples from 5 patients showed a picture similar to that found after four months.

9 months post-operatively based on samples from 6 patients showed less dead and more living trabeculae and more normal fat marrow. The fibrous stroma had mostly reached the cement layer but the layer of new formed bone had not, though it had advanced compared to four and six months. Fluorochrome confirmed the presence of osteoid in 12 of 14 evaluated patients.

Samples from proximal tibia and distal femur from 2 patients 14 and 23 months after surgery: A fibrous stroma surrounding dead allograft chips and osteoid laid upon those chips were frequently seen. Closer to the cement, areas with-

out living bone or osteoid were seen. Fluorochrome confirmed the presence of osteoid

48 months postoperatively based on 1 retrieved femur a mixture of living new formed bone embedding remnants of dead allograft bone was found. Closer to the cement layer, bigger pieces of dead allograft bone were seen mostly embedded in a fibrous stroma, together with living bone.

This study suggest a rapid ingrowth of a loose fibrous tissue followed by a border of osteoid and living new bone laid upon dead trabeculae, to take place after graft impaction in the proximal femur but also to some degree in the proximal tibia and the distal femur. The healing was not complete, areas of "fibrous bone" containing dead allograft trabeculae surrounded by a fibrous stroma seem to persist throughout time, but may be a reliable tissue for supporting endoprostheses. Completely dead areas containing only dead impacted allograft trabeculae were occasionally seen and are likely to persist in this form.

4. Ultrastructural characterization of the interface between Cr/Co implants and bone in humans

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Uncemented joint prostheses are usually made of either titanium- or chrome/cobalt-alloy. Limited information is available concerning the interface between Cr/Co implants and bone in humans. The purpose of this study was thus to characterize the fine structure of the bone adjacent to Cr/Co implants retrieved after clinical use.

Material and methods: We retrieved 3 uncemented PCA hip components, 1 femoral stem and 2 acetabular cups. There was no radiographic or clinical suspicion of loosening. The stem was removed at 14 months for unexplained thigh pain. One cup was revised at 92 months for fracture of the plastic liner. The other cup was removed at 128 months for acute hematogenous infection.

The entire specimens were embedded in PMMA. 2–3 mm-thick sections were made on an Exakt cutting machine. Under polarized light, areas with bony ingrowth were identified and small sectors were broken off from the beaded surface of the implants and reembedded in Epon B (1). Each embedment contained on its surface the imprints of Cr/Co beads. One micron-thick sections were prepared to select areas with osseointegration. Ultrathin sections were then cut on an Ultracut E (Leica) microtome and counterstained with uranyl acetate and lead citrate.

Results: In the 3 patients, the sections revealed areas with an undisputed direct contact between normal-appearing bone and the beaded surface. In 2 of the 3 patients, bone resorption was noted adjacent to the area of osseointegration. The fractured plastic liner induced a macrophage-rich granuloma, whereas the infected case showed inflammatory cells close to the osseointegrated bone.

At the ultrastructural level, the area of osseointegration showed normal aspects of bone tissue, marrow cells and organic matrix (typical type I collagen). Within 10 microns of the interface, there was always normal mineralisation. Closer to the implant, there was either fully mineralized lamellar bone right up to the implant surface, or osteoid with a thickness of 3–10 microns. In neighboring areas, a thin layer of fibrous tissue could appear between bone and implant. Within observed macrophages there was sometimes foreign material, probably plastic and/or metal. However, some macrophages did not show foreign material at all, notably in the infected case.

Discussion: The ultrastructure of the interface between bone and Cr/Co implants has never been described. In all 3 patients there was definite bony ingrowth. The bone remodelling did not appear disturbed, revealing that the implants were well tolerated by bone. These results are in full agreement with results obtained when using pure titanium implants in rabbit bone (1) and in humans (2). In fact, if only the interface showing osseointegration is considered, it would not be possible to detect a difference between pure titanium and chrome/cobalt implants.

References:

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5. Migration of cemented and cementless revision stems using impacted allograft—6-year follow-up with radiostereometry

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The experience with cemented collared and uncemented matte stems in hip revisions combined with impaction of allograft is sparse. In this study we used radiostereometry to measure the fixation of alternative stem designs used with this revision technique.

Patients and methods: 31 hip revisions were done (30 patients, 66 [range 30–83] years). Ten had type I, 20 type II and 1 type III bone loss (Gustilo-Pasternak). Allograft bone was impacted into the femur with trial stems. In the first 19 hips an uncemented (UC) titanium stem with proximal porous and HA/TCP coating. (Anatomic, Zimmer) was used. In the last 12 hips a cemented (C) SP2 (Waldemar Link) was inserted. Radiostereometric examinations were done after 1 week, 6 months and 1, 2 and 5–8 years. Conventional radiographs and Harris hip score were evaluated at two and six years.

Results: The uncemented stems migrated distally –0.76 mm (median) the first 6 months and then seemed to stabilise (Fig. 1). The cemented stems subsided less (median value: –0.15 [–1.3 to 0.5] mm,) during the first 6 months. During the following 5 years the median subsidence increased to –0.33 [–1.8 to 0.7] mm (n.s., *Wilcoxon signed rank test*). A tendency to medial migration of the femoral head was noted in the

cemented group (0.23 [–1.1 to 1.2] mm), whereas the uncemented migrated mainly laterally (–0.19 [–4.2 to 1.3] mm). In both groups the femoral head migrated posteriorly (C: –1.3 [–4.3 to 1.5]; UC: –1.4 [–9.6 to 0.5]). One stem (UC) with a peroperative fracture was re-revised 2.2 years after the index operation due to clinical loosening (Fig. 1). The uncemented hips showed proximal bone ingrowth and graft remodelling with resorption distally and marked cortical thickening. The cemented stems had less cortical thickening, more uniform graft remodelling (except in Gruen zone 1) and almost no lucent zones. Hip scores increased from 50 / 40 to 83 / 77. (UC/C). 4 patients (3 UC, 1 C) did not attend the follow up at 6 years, but claimed that they were satisfied with the operation.

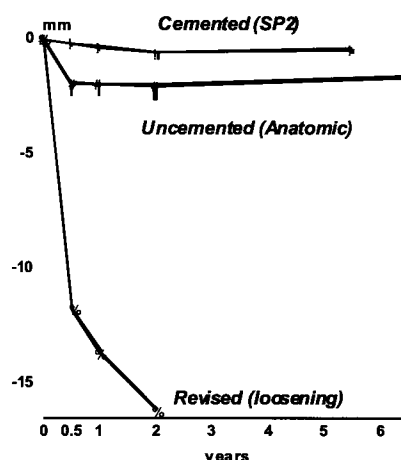


Fig. 1. Subsidence of the femoral head center

Discussion: Early subsidence followed by stability and a minimum of radiolucent lines suggest good long-term result in the cementless group. We believe, however, that a still more reproducible fixation can be achieved by the use of a more extensive coating. The use of a slightly matte and collared stem resulted in small micromovements, uniform graft remodelling and no revisions up to 5 years after operation suggesting that this concept might become a viable alternative.

6. Fixation of hip prostheses with a low temperature curing bone cement

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Aseptic loosening of cemented implants is a complex process where the interfaces play a crucial role. These should preferably be well sealed and stable to avoid particle penetration and abrasion wear. Since loosening is a very complex

and partly unpredictable mechanism a well controlled clinical trial of a new cement is mandatory. This study aimed to compare a new low temperature curing bone cement with a standard one, regarding implant migration, wear and adverse effects on bone.

Patients and methods: 50 hips in 45 patients between 50 and 80 years of age, with a noninflammatory osteoarthritis and planned for a cemented THA were randomly allocated to implant fixation with Cemex (Tecres®) or Palacos (Shering-Plough®) cement. Palacos cement was prechilled and vacuum mixed and Cemex handmixed in room temperature according to manufacturers recommendations. The cements are chemically similar but Cemex has a larger and more uniform powder size, 30% less monomer and barium instead of zirconia as contrast medium. Laboratory tests have shown about 10 °C lower curing temperature and less monomer leakage for Cemex, but equal strength.

Lubinus SP 2 (Waldemar Link) stems of titanium, standard UHMWP cups and a 28 mm alumina heads were used in all cases. Both cements were applied in a similar doughy state with third generation cementing technique. Tantalum markers for RSA measurements were inserted in implants bone and cement. Migration, bone remodelling in the Gruen zones, conventional radiography and Harris hip score were followed for 5 years.

Results: At 5 years the mean medial-lateral, proximal-distal and anterior-posterior migration of the cups reached 0.24/0.13, 0.28/0.27, 0.24/0.15 mm (Palcos / Cemex) (ns; Mann Whitney U-test). Most cups moved laterally and proximally. The inclination changed, mostly increased, at a mean of 0.69°/0.34° (ns)

The stems subsided 0.22/0.17 mm, (Palacos / Cemex), the first 5 years (ns). In 26 of the stems were subsidence inside the cement mantle could be measured it was 0.26/0.16 mm ($p=0.05$). Stems fixed with Palacos tilted slightly more forward-backward, 0.43°/0.19° ($p=0.02$). The rotations into ante-retroversion reached 0.84°/0.71° and in varus-valgus direction 0.29°/0.21° (ns).

Mean proximal wear at 5 years was 0.23 mm for both groups. Conventional radiographs or hip scores revealed no differences between the two types of bone cement.

Discussion: Both the tested cements fixed the implants well, but Cemex slightly better. The differences might be attributed to a lower curing temperature and less toxic monomer, but also other factors as mixing technique and physical properties as less shrinkage for Cemex could have interacted.

The lack of more favorable bone response in the Cemex group as measured on radiographs might indicate that there is no such effect or the tools for measurements are to blunt.

The cement mantles were well fixed to the bone and the stem subsidence took place between stem and cement. When a stem loosens from cement there is a risk for abrasion wear, especially so if the hard and abrasive ZrO is used as a contrast medium, as in Palacos. Loosened particles could enter the joint as third bodies and increase cup wear. However, with this combination of a "scratch resistant" alumina head and excellent UHMWP we found a similar and very low wear in both groups.

7. Patient satisfaction in revision total hip arthroplasty

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Also irrational factors affect the clinical result in revision total hip arthroplasty. The aim of this study was to determine whether patient satisfaction is a relevant outcome measure.

Patients and methods: 83 patients (53 women, median age 70) revised for the first time, answered a mailed questionnaire 3.6 (1.5–6.3) years postoperatively, concerning different aspects of the clinical result as well as patient satisfaction. A Harris hip-score was calculated; range of motion was assessed by the patients ability to enter a bath or to perform foot care. With satisfaction as dichotomised endpoint (77% satisfied) a logistic regression analysis was performed.

Results: If surgery had decreased pain, turned out to be the best predictor of high patient satisfaction, odds ratio 12.0 (95% confidence interval 3–42). The model was not confounded by either gender, Charnley class, preoperative waiting-time or postoperative walking ability, limp and range of motion. An excellent/good Harris hip score was not associated with a high patient satisfaction.

Discussion: Considering pain as one of the main indications for revision surgery and the found association, we believe patient satisfaction to be a relevant outcome measure in revision total hip arthroplasty.

8. Survival analysis of total hip replacements—a comparison of a prospective, randomized study with the results obtained from the Swedish National Hip Registry

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At Sahlgrenska Hospital 410 primary total hip replacements were performed on 372 patients between September 1, 1985 and May 31, 1989. All hips were assigned randomly to receive a Charnley prosthesis with an ogee-flanged cup or a Spectron prosthesis with a metal backed cup. 11-year survivor analysis, using revision as the end point definition of failure, revealed a survival rate of 93.2% $\pm$ 5.8% for the Charnley replacement and 95.9% $\pm$ 3.0% for the Spectron. If each component of the systems was analyzed (concerning aseptic loosening) the ogee cup and the Spectron stem had 100% survival. The survivorship for all 410 hips was 94.5% $\pm$ 3.4%. If the end point definition of failure was expanded to include patient dissatisfaction the survival rate decreased to 86.3% $\pm$ 4.9%. These survival rates were compared with the rates obtained by the Swedish National Hip Registry. The national cohort included all patients in Sweden surgically treated with a Charnley (14,053) or Spectron (metal backed cup) prosthesis (726) between September 1, 1985 and May

31, 1989. 11-year survivor analysis revealed a national survival rate of $92.1\% \pm 0.7\%$ for the Charnley replacement and $88.6\% \pm 6.1\%$ for the Spectron.

The analyses from the Swedish Registry are based on more than 160,000 primary operations and 11,500 revisions. Despite these enormous amounts of data there are drawbacks and registries can never replace the prospective, randomized trial. One reason is that the Swedish National Registry is unable to discriminate between the individual cup and stem components when analyzing the cause of revision, and no clinical or radiographic information are collected. A potential drawback for the randomized trial is, however, performance bias as centers of excellence might perform better than the general orthopaedic surgeon.

9. Revision total hip arthroplasty in Jehovah's Witnesses—a technical note and preliminary report

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The purpose was to develop strategies to perform revision THA in patients who for religious reasons do not accept allogeneic blood transfusions.

Method: 3 Jehovah's Witnesses were revised because of aseptic loosening with pronounced bone loss. The surgical strategy was preoperative treatment with r-EPO when Hb < 140 g/L, preoperative plasmasequestration, intraoperative blood salvage with cell saver, transfemoral approach according to Wagner, a correct timing of steps in the surgical procedure, the use of an autologous platelet glue derived from the sequestration procedure and no postoperative drainage.

Results: Total blood loss was 1,700, 1,300 and 1,800 ml respectively. The Hb concentration was at lowest level 78, 103, 99 g/L. There were no peri- or postoperative complications. The rehabilitation was uneventful.

Conclusion: With a well planned surgical strategy we have been able to successfully perform revision THA in patients who for religious reasons do not accept blood transfusions.

10. Fixation failure of cemented Option anatomic stems

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Excellent mid-term results have been reported using stems with hydroxyapatite coating suggesting that this type of fixation might become a viable alternative to cemented fixation.

These observations were mainly based on the use of straight stems. In this prospective and randomized study we compared anatomically shaped cemented with a cementless stems. The cemented stem had grit blasted surface (Ra=80µm, Option, Zimmer, USA). The uncemented had porous and ceramic coatings (HA/TCP and pure HA, Anatomic, Zimmer, USA).

Patients and methods: 101 hips have entered the study. 79 patients (32 male, 47 female, 81 the remaining Option stems) with non-inflammatory arthrosis and with complete 2 years follow up are reported. 42 patients received an Option 39 an Anatomic stem. The migration of the stems was studied with radiostereometric analysis (RSA) postoperatively, 3, 6 months, 1 and 2 years after the operation. Clinical evaluation was done using Harris hip score.

Results: Up to 1 year after the operation the median value of subsidence and rotations of the stems were close to zero in both groups (less than -0.05 mm and 0.15°). Between the 1 and 2 years follow up the cemented stems showed increasing subsidence (2 years: $p=0.002$, *Mann-Whitney test*), retroversion ($p=0.03$) and varus angulation ($p=0.02$). The clinical results at 2 years (total score, pain score) did not differ. Two patients with Options stem are on the waiting list for revision due to pain and femoral osteolysis (1 hip). Further one experienced sudden thigh pain 3 years after the operation. These 3 stems classified as clinical failures displayed -0.48 mm (median, range: -0.70 to -0.30) subsidence at 2 years compared to -0.12 mm (-0.75 to 0.3) in the remaining Option stems ($p=0.003$).

Conclusion: The increasing migration of the Option stem during the second year of observation turned out to indicate clinical failure. The reason for this failure is not known. Implant design including choice of surface finish is probably important. In future studies we recommend that only well-documented cemented implants should be used as control group in clinical trials.

11. Revision surgery of hip and knee facilitated by hypotension through temporary balloon occlusion

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Revision surgery of the hip and knee may involve lengthy operations and are often associated with increased bleeding. We report our experiences from a consecutive group of 9 patients (2 female and 7 male) aged 42 to 74 years. 4 of the patients had an early second step exchange procedure of an infected hip arthroplasty combined with impaction grafting. Three of the patients had a re-revision of a stemmed knee arthroplasty combined with impaction grafting. One case was a knee arthrodesis due to a persistent periprosthetic infection. One patient had a primary hip arthroplasty in the right hip, followed by a revision procedure containing impaction grafting in the acetabulum in his left hip using his

right femoral head as an autograft.

Balloon introduction was accomplished by the interventional radiologist in the afternoon of the preoperative day or in the morning before surgery. A latex occlusion balloon was inserted via the transfemoral ipsi- or contralateral route. A pelvic angiography was performed to visualize the arterial conditions including the collateral circulation. The patient was given low molecular weight Heparin in a dose of 40 mg x 2. In the operating theatre saline was injected in the predetermined volume to inflate the balloon. Immediately after surgery the balloon was deflated. The balloon catheter was extruded after surgery on the postoperative care unit. The time for inflated balloons was from 2 hours 15 minutes to 6 hours. Surgery was performed not in a bloodless field but in a field of reduced bleeding. In two patients the intra-arterial blood-pressure was measured and found to decrease from 120 to 40 mmHg and 155 to 50 mmHg, respectively after balloon inflation. The only complication that could be connected to the method of arterial balloon occlusion was a suggested decrease in arterial circulation of the operated leg (coldness of the foot) during the night after surgery, which however spontaneously recovered. Reduction of blood loss was estimated through a comparison group of three patients having the same kind of early second step hip revision without balloon occlusion. The blood loss was reduced by more than 50% per hour during surgery in the cases with balloon occlusion.

Our experience from these 9 cases has shown introduction of the catheter to be a simple and fast procedure for an experienced interventional radiologist. Occlusion of the main vessel in the lower extremity can be accomplished for several hours without serious complications. Surgery was facilitated and the loss of blood was reduced during surgery. Temporary balloon occlusion should be usable also in the axillary artery when performing major surgery in the upper extremity as well as for persons that for various reasons refuse blood transfusion.

12. Exeter hip surgery with a modified, temporary collar technique improves stem positioning and cementation

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Getting good stem alignment and depth control may be more difficult with a collarless stem like the Exeter hip prosthesis, since a collar docks on the prepared calcar and thereby positions the prosthesis correctly during cementation. Furthermore, the collar acts as a proximal seal for cement pressurisation. Therefore we developed a temporary, height adjustable collar to be applied and used only during stem insertion until the cement has hardened. The method also includes control of the cutting angle of the femoral cervix by means of a cutting jig.

Materials and methods: Stem position was evaluated

from postoperative radiographs of 31 stems positioned with temporary collar technique and 28 with ordinary collarless Exeter technique. In 16 of the patients the pressure in the proximal femur during stem insertion was measured. Maximum and mean pressures were calculated as well as area under curve, representing the total amount of pressure applied.

Results: The use of temporary collar technique resulted in a significantly better stem position both regarding divergence from the exact varus/valgus position ($0.8^\circ \pm 1.0^\circ$ vs. $2.0^\circ \pm 1.4^\circ$, $p < 0.001$) and from the midline in lateral view (quotient anterior/posterior 0.4 ± 0.06 vs. 0.3 ± 0.04 , $p < 0.05$). Furthermore, mean pressure (292 ± 95 vs. 170 ± 110 mmHg) as well as area under the curve (17592 ± 5740 vs. 10279 ± 6632) during the first minute was significantly higher for the temporary collar technique ($p < 0.05$), whereas the maximum pressure was the same for both groups (1232 vs. 1218 mmHg).

Conclusions: The use of a temporary collar technique for otherwise collarless prostheses improves the positioning of the stem as well as the duration of a high proximal cement pressure.

13. No effect of partial weight bearing on implant fixation in total hip arthroplasty

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The indications for restricted weight bearing during a limited period after uncomplicated primary total hip arthroplasty are unclear and its efficacy has even been questioned. We studied the early fixation and femoral head penetration in cemented and uncemented THA, where the patients were randomly allocated to partial weight bearing for 6 weeks (Group A) or were allowed to load the operated side as much as tolerated (Group B).

Patients and methods: 53 patients (26 male, 27 female, median age 56 [45-65] years) with non-inflammatory arthritis have so far entered the study. The patients were stratified to a cemented (Lubinus SP2, $n = 24$) or an uncemented hydroxyapatite coated (ABG, $n = 29$) THA and to restricted weight bearing ($n = 26$) or not ($n = 27$) based on gender and weight. The migration of the socket and the stem and wear were studied with radiostereometric analysis (RSA) postoperatively, at 3 months and 1 year after the operation. To facilitate reduced weight bearing these patients received a pressure sensitive insole which was individually calibrated to deliver a beeping sound if the pre-set pressure level (about 50% of body weight) was reached during activity.

Results: The cup and stem migration and the femoral head penetration were not influenced by restricted weight bearing in neither of the groups. Neither had the type of implant any influence on the recorded values (*non-parametric tests, logistic regression*). After 3 months and 1 year the median

proximal migration of the cup was less than 0.1 and 0.12 mm, respectively. The corresponding values for proximal penetration of the femoral head were less than 0.1 and 0.18 mm and for stem subsidence 0.08 and 0.13 mm. Two ABG stems subsided more than 1 mm after 3 months (2.2 and 4.7 mm, one from each group). One of these stems subsided further up to 1 year (0.25 mm, Group A).

Conclusion: The use of reduced postoperative weight bearing had no measurable effect on the early fixation or the wear in either the ABG or Lubinus SP designs.

14. The CLS acetabular expansion cup—a 6–11-year follow-up study

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Uncemented acetabular cups in total hip replacement can be fixated in different ways. Pressfit fixation—with or without simultaneous screw fixation—has shown to give good results in several studies. The CLS expansion cup relies on a unique form of pressfit fixation, where the metal shell is expanded into the acetabular cavity. The polyethylene liner is fixated to the shell by threading.

Material: During 1987–1992, 65 CLS expansion cups were implanted in 57 patients, 43 men and 22 women. Mean age at operation was 52 (34–62) years. The mean follow up time was 8.3 (6–11) years

Method: All patients were followed in a consecutive, prospective and longitudinal study. The patients were clinically evaluated according to Merle d'Aubigné as modified by Charnley. Radiological the latest radiograph and the first available radiograph were analyzed with respect to migration, radiolucent lines and ectopic bone formation.

Results: During the follow up period 7 patients died, leaving 50 patients representing 58 cups for follow-up. The preoperative Merle d'Aubigné score was according to pain 2.6, function 2.8 and ROM 3.4. At the latest follow up the corresponding scores were for pain 5.8, function 5.7 and ROM 5.0. The radiological analyses showed a low frequency of migration and radiolucent lines. No cup was revised because of loosening. Four cups, however, were revised mainly due to problems related to the femoral component.

Conclusions: Based on this study, we conclude that the uncemented CLS expansion cup in a younger patient group, gives good clinical results with only a few complications and a low revision rate. The clinical and radiological findings indicate that the prosthesis seems to be stable thus giving hope for a long-term survival for the prosthesis.

KNEE ARTHROPLASTY

15. HKA-examinations after total arthroplasty of the knee by the use of an intramedullary technique for femur

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Today the use of an intramedullary technique for femoral prosthesis positioning is most popular after the early initial more common use of only extramedullary instruments. Most commonly, good prosthesis position in the femoral bone is obtained. In practice, though, the technique has limitations by previous femoral fracture treatment with plates and nails, the use of same side hip prosthesis, curved femoral bone etc. In most clinics, the postoperative prosthesis position is evaluated by the use of routine 20 x 40 films of only the distal 20 cm or less of femur and tibia, respectively. We routinely use a 120-cm special cassette to image the whole weight-bearing limb by one single exposure under one-leg standing. This allows us to measure more exactly the prosthesis position in relation to the mechanical instead of anatomical axis of femur.

Method: The prosthesis positions have been measured postoperatively in 139 knees operated on due to noninflammatory osteoarthritis. A standard AGC (Biomet, U.K.) prosthesis was implanted utilizing the recommended intramedullary technique with standard settings of 7°.

The angles, measured from the medial side, were defined as follows:

Fma – the angle on frontal films between the articular surface of the femoral component and the mechanical axis of femur from the center of the hip to the center of said surface distal femur.

Tma – the angle on frontal films between the lower surface of the tibial component and the mechanical axis of tibia from the center of the ankle mortise to the center of said surface proximal tibia.

The inclination of the tibial component was also measured, **Ts** – the angle on sagittal films between the long axis of tibia and the lower surface of the tibial component posteriorly.

Results:

	mean	SD	median	interq. range	min	max
Fma	90.0	2.6	90	2	83	99
Tma	88.2	1.9	88	3	82	93
Ts	88.5	3.5	89	4	81	97

Conclusion: A standard method using femoral intramedullary routine technique for positioning of the prosthesis leads to good results in the majority of cases. In our opinion, an intramedullary technique is, however, not satisfactory enough to avoid significant misplacement of prosthesis components. There is a definitive risk that errors by technique will result in a lifetime bad functional outcome in individual patients. Work is in progress to develop a direct and extraar-

ticular method to relate to the mechanical instead of the anatomical femoral axis intraoperatively for positioning of the prosthesis with less errors.

16. HA-coating not always superior to porous-coating in uncemented fixation of the tibial component in TKA

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Several studies have shown that hydroxyapatite-coating (HA) of the tibial component is beneficial for the fixation of the uncemented tibial component. Fixation of uncemented implants is, however, also dependent on the design of the tibial component undersurface (presence of pegs, stems, etc) and the design of the femoro-tibial articulation. The optimum design as regards minimum migration of the tibial component is still not established. The purpose of this paper was to study the migration of a porous-coated tibial component with 4 pegs and an unconstrained flat on flat femoro-tibial articulation where the use of porous-coating (PC) only, HA-coating, or cement was randomized.

Materials and methods: 68 consecutive patients (20 men, 48 women, mean age 72 [51–86]) with OA were operated with the MG2 TKA with 4 pegs (but no stem). After randomization 23 knees received a tibial component with PC only, 21 knees a component with PC + additional HA-coating (HA/TCP), and 24 knees a cemented (Palacos) PC tibial component. In the PC and HA groups 4 screws were used in addition. The quality of the fixation was studied with RSA during 2 years.

Results: There were no statistically significant differences in migration between PC and HA. At 2 years mean anterior-posterior tilt was 1.0° (HA) and 0.89° (PC), varus-valgus tilt 0.56° (HA) and 0.59° (PC), maximum subsidence 0.98 mm (HA) and 0.72 mm (PC), and maximum migration 1.26 mm (HA) and 1.16 mm (PC). Both uncemented groups displayed larger migration compared to cemented fixation most pronounced during the early months postoperatively.

Discussion: In this study addition of HA-coating to the porous-coated implant did not improve the fixation. In a recently published study using the same prosthesis as in the present study (MG2) but with the addition of a stem, Regnér et al. (1998) found that the HA-coated implants displayed significantly lower magnitudes of migration as compared to the porous-coated ones. Moreover, the magnitudes of migration for both groups of fixation in the study of Regnér were about 50% lower than those of the present study. Positive findings of using HA-coating reported in the literature have all been made using tibial components that have been equipped with a stem. This seems to indicate that the presence of a stem is beneficial for the fixation of the tibial component, and that adjuncts in the design of the implant is needed in order to fully take advantage of the osteoconductive properties of the HA.

17. All-polyethylene tibial component equally as effective as metal-backed and stemmed tibial component in Freeman-Samuelson TKA

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Due to inferior results of all-polyethylene (AP) tibial components during the 70's and early 80's several changes in design were introduced. Based on biomechanical tests both metal-backing (MB) as well as addition of a stem on the tibial component was advocated. Improved results have been presented. However, no randomized studies have so far been presented comparing AP with MB in the same prosthetic design with identical femoro-tibial articulation. The purpose of the present study was to compare if the addition of MB and a stem on the tibial component improved the fixation over AP in TKA:s with otherwise identical design.

Materials and methods: 38 consecutive patients (7 men, 31 women, mean age 69) with OA were operated on with cemented Freeman-Samuelson (F-S) TKA. 18 knees were randomized to MB tibial component and 20 knees to AP tibial component. The design of the F-S TKA as regards joint surface is identical for MB and AP. The femoro-tibial articulation is conforming in the sagittal plane and flat on flat in the coronal plane. The undersurface of the AP has 2 "magic pegs" whereas the MB has 2 metal pegs and a round stem. The thickness of the metal backing itself is 2.5 mm. The quality of the fixation was studied with RSA during 2 years.

Results: Total tibial component thickness (median) was 10.5 mm (MB) and 8 mm (AP) ($p < 0.001$), whereas the effective polyethylene thickness was the same in the both groups (median: 8 mm). Maximum migration (MTPM) at 2 years (median) was 0.72 (MB) and 0.75 (AP) (n.s.). At 24 months there were no statistically significant differences between MB and AP as regards anterior-posterior and varus-valgus tilting, or maximum subsidence. However, MB implants displayed larger internal-external rotation (median: 0.57 vs. 0.22 degrees, $p < 0.05$), and a tendency to (however not statistically significant) larger lift-off from the bone (0.51 vs. 0.32 mm). Knee society knee score and function score did not differ between MB and AP.

Discussion: This study demonstrates that, in spite of what is generally believed, the addition of metal-backing and a stem to the tibial component does not improve cemented fixation when the Freeman-Samuelson prosthesis is used. The reason for the inferior results of AP implants reported previously is probably attributed to poor operative technique. With modern instrumentation leading to normal prosthetic alignment as well as modern cementing technique results on par with metal-backed and stemmed components can be achieved, even in prostheses with highly congruent joint surfaces.

18. All-polyethylene tibial component not inferior to metal-backed tibial component in cemented TKA

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Metal-backed (MB) tibial components in TKA were introduced because studies had shown that a metal tray supporting the tibial polyethylene would place smaller compressive peak stresses on the bone and thereby improve fixation. The higher costs for MB implants, and the wish to maximize the polyethylene thickness for a given tibial cut, have led to a renewed interest in all-polyethylene (AP) tibial components. However, no prospective randomized studies comparing MB with AP in the same prosthetic design have so far been presented. The purpose of this study was to compare, in a prospective randomized manner, MB with AP in cemented TKA with a prosthesis with identical design except for the presence of MB.

Materials and methods: 34 consecutive patients (12 men, 22 women, mean age 71) with OA were operated on with cemented AGC (Biomet®) TKA. 17 knees were randomized to MB tibial component and 17 knees to AP tibial component. The design of the AGC TKA as regards joint surface and undersurface is identical for MB and AP. The femoro-tibial articulation is rather flat on flat, and there is a "H"-shaped stem on the underside. The thickness of the metal backing itself is 3.7 mm. The quality of the fixation was studied with RSA during 2 years.

Results: Total tibial component thickness (median) was 10 mm (MB) and 8 mm (AP) ($p < 0.05$). However, the effective polyethylene thickness was larger in the AP knees (median: 8 mm vs. 6.3 mm, $p < 0.001$). Maximum migration (MTPM) at 2 years (median) was 0.59 (MB) and 0.41 (AP) (n.s.). At 24 months there were no statistically significant differences between MB and AP as regards anterior-posterior and varus-valgus tilting, internal-external rotation, or maximum subsidence. However, MB implants displayed larger lift-off from the bone (median: 0.40 vs. 0.18 mm, $p = 0.01$). Knee society knee score and function score did not differ between MB and AP.

Discussion: All-polyethylene tibial components were abandoned 15–20 years ago due to perceived bad performance as regards fixation. The present study shows that results on par with (or even better than) metal backed tibial components can be achieved with all-polyethylene implants, when modern operation technique as regards knee and implant alignment and cementation is used, even when using a TKA design with flat-on-flat tibio-femoral articulation such as the AGC. For a given thickness of the tibial cut, significantly more polyethylene can be inserted using an AP implant. Metal-backed components displayed larger lift-off from the bone than did AP implants. This is probably attributed to the higher stiffness of the metal. Lift-off is unacceptable since it implies that the area supporting the prosthesis is reduced with a risk for increased stresses and subsequent

subsidence in the future. Lift-off also implies that joint fluid can get access to the cement-bone interface.

19. Contrast-enhanced MRI in preradiographic gonarthrosis

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New methods that detect early pathology noninvasively in osteoarthritis (OA) are needed. Proteoglycans (PG) are abundant negatively charged molecules in the cartilage matrix. Magnevist™ (Gadolinium -DTPA²⁻) is a charged compound used in contrast-enhanced magnetic resonance imaging (MRI). In vitro experiments have shown a relationship between MRI-assessed Gd-DTPA²⁻ uptake in the cartilage and charged molecules in the matrix.

Material and methods: To study the Gd-DTPA²⁻ uptake assessed by MRI in human knee joint cartilage, 8 healthy volunteers (5 male and 3 female, 22–30 years) and 8 patients with preradiographic osteoarthritis (OA) and knee pain were included. The patients were 6 male, 35–47 years, and 2 female, 38 and 50 years. All patients had normal weight-bearing radiography and arthroscopically verified cartilage degeneration in one of the femorotibial compartments (medially in 7 patients). MRI was performed before and repeatedly after an intravenous injection of Gd-DTPA²⁻ (0.3 mmol/kg bw). A 5-mm sagittal image with 5 different inversion times was used in both femoral compartments. Results are expressed as T1-relaxation rates ($=1/T1$ -relaxation time) in regions of interest in the weight-bearing femoral cartilage.

Results: The contrast medium diffused into all examined cartilages. The maximum uptake was received within ≈100 minutes in all examined cartilages. In the healthy volunteers there was no difference between the medial and lateral femoral cartilage. In the patients there was a higher uptake in the degenerated compared with the healthy compartment ($p < 0.008$). In contrast to the cartilage in the healthy compartments and in the volunteers, there was a notable decrease in uptake in the degenerated cartilages after ≈170 minutes compared with ≈80 minutes ($p < 0.016$). Group analysis showed higher T1-relaxation rate in degenerated cartilage compared with cartilage in the healthy volunteers ($p < 0.006$).

Discussion: The higher Gd-DTPA²⁻ uptake in fibrillated cartilage compared with non-fibrillated, suggests a lower PG content in such cartilage. However, a greater general diffusibility in degenerated cartilage can not be ruled out.

Conclusion: Contrast-enhanced MRI seems promising as a new diagnostic tool for the detection and monitoring of preradiographic OA.

20. In vivo kinematics of total knee replacement with constrained vs posterior stabilized tibial polyethylene tray

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In a previous study we compared standard with constrained tibial insert with filmexchanger technique and radiostereometry during weight bearing. In the present series, patients with more advanced deformities ($>5^\circ$ varus/valgus or $>10^\circ$ extension defect) were randomized to a constrained or posterior stabilized (PS) component. The PCL was resected in all cases.

Patients and methods: 16 patients (8 male, 8 female, median age 70 [60–81] years) with arthrosis of the knee operated on with an AMK (DePuy) total knee replacement (TKR) 1 year earlier were studied. The polyethylene insert was stratified to a constrained ($n=9$) or a PS ($n=7$) configuration. The normal knee in 11 patients (median age 25 [18–41] years) was used as controls. Tantalum markers were inserted in the distal femur and proximal tibia at the TKR or during arthroscopy (control cases). At the examination the patients ascended a platform (approximately 1 dm high) corresponding to an extension of the knee from 40–60 degrees of flexion. During the extension 2 film-exchangers simultaneously exposed serial stereoradiographs with a frame rate of 3 or 4 exposures/s. Tibial rotations and translations and femoral anterior-posterior translation were evaluated. The expectations of the patients on the results of the surgical procedure and the HSS scores were recorded preoperatively and after 1 year. The study was approved by the local ethics committee.

Statistics: Repeated measures ANOVA.

Results: The internal-external rotation, varus-valgus tilt and the medial-lateral translations of the center of the tibial plateau did not differ between the two designs of joint area. The constrained design displayed a more proximal ($p=0.02$) and posterior displacement ($p=0.02$) of the center of the tibial plateau and a corresponding more anterior translation of the center of the femoral condyles ($p=0.01$). At 40 degrees of flexion the mean differences were 3–4 mm.

Compared with the normal knees the TKR (both designs) showed less internal rotation (difference at 40° of flexion: 5° , $p<0.004$) and a more distal (diff. at 40° : 2–5 mm, $p<0.002$) and posterior position (diff. at 40° : 12–15 mm, $p<0.0005$) of the tibial plateau during the extension. Compared with the normal knees both designs of TKR showed a more anterior position of the center of the femoral condyles ($p<0.0005$). One year after the operation the HSS scores (C and PS) were 86 (75–96) and 84 (61–95), respectively. 11 patients (7C, 4PS) reported that their knees had been as stable as expected or still better, 4 (2C, 2PS) noted an improvement but not according to expectations and 1 (PS) reported no change. Four patients (2C, 2PS) felt that their operated knee functioned as a normal knee, 9 (6C, 3PS) that their knee almost could be regarded as normal and 3 (1C, 2PS) that their knee function was definitely abnormal.

Discussion: The use of a posterior stabilized design reduced the anterior-posterior translations in the knee, but not to normal values. Absence of the cruciate ligaments and joint area design can probably explain this finding. The AP-translations of the constrained design did not differ from those recorded in a previous study where the PCL had been retained indicating that the function of this ligament can be questioned in this design of TKR.

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21. A comparison of one generic and two disease-specific measurements of pain and physical function in patients with osteoarthritis of the knee.

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Both disease-specific and generic health status instruments are used to assess different, but complementary aspects of patients' quality of life (QOL). The aim of this study was to compare the characteristics of one self-administrated, validated generic knee questionnaire, and two commonly used disease-specific knee assessment scales in patients suffering from knee osteoarthritis included in a clinical trial.

Patients and methods: The generic health assessment tool, the Short-Form (SF)-36 was compared with two disease-specific measures; the patient-based WOMAC osteoarthritis index and the investigator-administrated Lequesne index of pain and physical function were completed at baseline. Furthermore, the evaluation obtained in SF-36 was compared with a Swedish normal aged-matched population ($n=941$). The comparisons were performed in 203 male and female patients, with a mean age of 70.5 years, suffering from knee osteoarthritis. The Kendall's tau rank correlation coefficient was used to evaluate the correlations.

Results: The most noticeable differences in the study population compared with the published Swedish normal aged-matched population in SF-36 Health Status Profile scores were in the categories physical function ($p<0.001$) and pain ($p<0.001$). There was a much more pronounced correlation between the SF-36 pain index and the SF-36 physical function and the WOMAC index (-0.39 and -0.37 ; $p<0.0001$) compared with the Lequesne index (-0.21 and -0.28 ; $p<0.0001$).

Conclusion: The stronger correlation between the SF-36 pain index and the SF-36 physical functioning and the WOMAC index compared with the Lequesne index might be an effect of the administration. These three scales assess different aspects of patients' health. The results of this comparison support the inclusion of both a generic and a disease-specific health-related quality of life measure to assess pa-

tients' outcomes fully. Furthermore, our data indicate that the patients suffering from osteoarthritis of the knee experience a marked impairment in quality of life compared with a Swedish normal aged-matched population.

22. Osseointegrated transfemoral amputation prostheses—preliminary results from a 3-year follow-up study

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The concept of direct skeletal anchorage of an amputation prosthesis according to the osseointegration principle was originally developed by P-I Brånemark and co-workers in Göteborg following extensive experience since the 1960's with osseointegrated implants in the treatment of edentulism. In a multidisciplinary team-approach, osseointegrated implants have been used for direct, transcutaneous skeletal anchorage of amputation prostheses in upper and lower extremities in a limited number of patients since 1990. The results obtained in the first 16 transfemoral amputees, with a minimum follow-up time of 3 years, are presented. Function according to the score system introduced by Enneking et al. (1993) improved from a preoperative mean value (for socket prostheses) of 37% to a postoperative value (with osseointegrated prostheses) of 68%. The patients experienced improved comfort, especially when sitting and due to easy attachment and detachment of the prostheses. An increased sensory capability was noted (osseoperception), which serves to improve function and physiological acceptance. Superficial infections were frequent. Deep infections led to loosening of the implant in 4 patients, of which 3 had a new implant installed, one had a shortening of the skeleton and no implant reinstalled. Two patients have chronic fistulae, which does not prevent one of them from using his osseointegrated prosthesis. At follow-up 76% were free of complications.

Osseointegrated amputation prostheses represent a promising development in the rehabilitation of amputees. The infection rate is gradually decreasing following improvements in surgical techniques. Especially transfemoral amputees with socket problems seem to benefit from this treatment.

HIP FRACTURE

23. Risk factors for hip fracture—a prospective study of 30,000 men and women

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Hip fractures are one of the Western world's health care problems, and occupy a large part of the available economic and social resources. The last decades we have seen an increasing number of fractures, which cannot be explained by an ageing population. It is of utmost importance to identify the existing risk factors, to be able to stop the fracture trend. If we could identify them at the age of 50, preventive measures would be possible. The earlier published prospective studies of risk factors for hip fracture have all been done in higher age groups and mainly in women.

In the middle of the seventies a prevention study was started in Malmö, 22,000 men and 11,000 women participated. The mean age at screening was 44 years for the men and 49 years for women. Medical as well as social data was collected. The population was followed prospectively with a follow up time after screening of 17 and 13 years for men and women, respectively. In this population 210 hip fractures occurred, 119 among the men and 91 among the women.

The data has been analyzed with multivariate analysis and age adjusted logistical regression.

Numerous risk factors were significant in both men and women. A selection of the clinically important factors are:

- Low body weight
- Low BMI
- Elevated resting pulse
- Low FEV 0.5 s
- Diabetes
- > 20 cigarettes a day
- Anemia more than twice the last 5 years
- Early retirement

With these risk factor as a basis we are able to create a risk score for hip fracture that can be used for selection for screening of patients at 50 years of age. Our intention is to identify high-risk patients and with early prevention be able to prevent future hip fractures.

24. Methods to operate hip fracture in Sweden—an enquiry comparing 1982, 1985, 1990 and 1998

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Three enquiries to Swedish hospitals in 1982, 1985 and 1990 where previously published in *Läkartidningen* 1983, OP-

MEAR 1988 and Acta Orthop Scand 1993.

Material and methods: A forth enquiry was sent to 84 hospitals. We received 74/84 written answers, the remaining hospitals was interviewed by telephone. In 1982, 90 hospitals performed operations on hip fracture patients compared to 72 hospitals in 1998.

Results: Of all cervical fractures, the Olmed subchondral screw was the most common implant in 1998 followed by LIH-pinning. Single nail and von Bahr screws had been abandoned. Primary prostheses has become more common compared with the results of the previous enquiries.

Regarding the trochanteric fracture the sliding screw and plate now is the most common method but the Medoff plate and the short intramedullar nail are new methods that are gaining market shares.

The percentage of the methods, divided in cervical and trochanteric fractures

Year	1982	1985	1990	1998
CERVICAL				
Single nail	34	11	<1	<1
V Bahr	37	39	19	<1
LIH	7	22	34	35
Multiple pins	18	23	16	5
Olmed	-	-	27	46
Primary prothesis	1-2	2	2	10
TROCHANT.				
Ender nailing	60	46	11	<1
Slid. screw/plate	34	49	86	79
Medoff	-	-	<1	6
Intramed. nail	-	-	<1	6

25. A new double sliding screw and plate system (LE-plate) versus standard sliding screw and plate system (DHS) in the treatment of trochanteric hip fractures—minimum 12 months follow-up of 31 patients in a randomized prospective study—preliminary report

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The LE-plate system is a new method, where 2 Olmed screws are used as double sliding screws in a 2-cap plate in the treatment of trochanteric hip fractures.

Method: 41 patients from two hospitals (Arvika and Kristinehamn) were randomized to either DHS-plate or LE-plate. The fractures were classified as stable or unstable. 12 different surgeons operated on the 41 patients.

Results: Despite the fact that a new method was introduced there was no difference in operation time, blood loss or postoperative in-patient time. 6 patients (4 DHS + 2 LE) died in the postoperative period. Another one (DHS-patient) died at 4 months. 2 were lost for follow up. Thus 32 patients (15 DHS and 17 LE) were followed up at minimum 12 months.

In the DHS group 12 had healed according to radiography

and another 2 clinically. One had a suspected pseudarthrosis. In the LE-group 15 had healed according to radiography and another 2 clinically.

Conclusion: This preliminary report does not show any difference in the analyzed parameters between the DHS-plate system and the LE-plate system, although the material is too small for statistical analysis. The study is going on and today further 37 patients are included.

26. The influence of augmentation with bone mineral substitute or cement on the maximum torque and holding power of femoral neck fracture implants in artificial bone

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An adequate grip in the femoral head is crucial for successful fixation of femoral neck fractures. To overcome the reduction in strength in the cancellous bone caused by osteoporosis implants have been developed where the characteristics have been altered by changing screw thread design or by addition of a barb or a hook. Another alternative to achieve a better grip for the implant is by augmentation around the screw threads using cement. The purpose with this in vitro study was to measure the maximum torque and pull-out resistance for different implants used for femoral neck fracture fixation and quantify the effect of augmentation with a resorbable bone mineral substitute (Norian SRS®) or traditional cement (Palacos®).

Material and methods: The tested implants were the AO cancellous screw, Olmed screw, LIH hook-pin, Hybrid screw and Hansson screw. Testing was done using a servo-hydraulic testing machine (Mini-Bionix 858, MTS, MN, USA). Axial pullout was applied with 0.5 mm/sec while anti clock-wise torsion at 40/sec. Low density foam cubes sized 50 mm were chosen to model osteoporotic femoral heads (polyurethane foam, General Plastics, Tacoma, WA, USA). In the first series implants were inserted according to the manufacturers guidelines with (AO, Hybrid, LIH) or without (Olmed, Hansson) predrilling. In the second and third series predrilling was done in all blocks after which Norian SRS® or Palacos® was inserted in the drilled channel before inserting the implant. All implants were inserted to a depth of 40 mm.

Results: Without cement there was a significant difference in maximum torque between the implants. The Hansson screw system had the highest maximum torque (1.06 Nm) followed by the LIH hook-pin (0.91 Nm) and the Hybrid screw (0.84 Nm). The AO (0.48 Nm) and Olmed (0.66 Nm) screws had significantly lower maximum torque compared with the former three. Norian SRS® increased the maximum torque 5% (AO), 46% (Olmed), 93% (Hybrid), and 151% (LIH) while in the Hansson screw system the maximum torque decreased slightly when compared to torque without cement. Palacos® increased the maximum

torque 162–468% when compared without cement. Maximum holding power with or without cement was significantly higher for the Hansson screw system when compared with all the other implants. It was followed by the AO, Olmed and Hybrid. The LIH system had significantly less maximum holding power compared with the other implants. Augmentation with Norian SRS® increased pull-out resistance by 15–94% while Palacos increased the holding power by 49–311% compared to without cement.

Conclusion: The thread design in the Hansson screw system combined with no predrilling provided a torque and pull-out resistance that was significantly higher than the other two screw systems as well as the systems utilizing a hook-pin (LIH) or a barb (Hybrid) to enhance the grip. Adding Norian SRS® or traditional bone cement like Palacos® around the implant created a substantial gain in both maximum torque and pull-out resistance especially in implants with a hook or a barb. Augmentation around the metal implant might become an attractive way to enhance the grip in the femoral head when fixing femoral neck fractures.

27. Augmentation of femoral neck fracture fixation with resorbable cement (Norian SRS) and its effect on early postoperative stability measured with RSA

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There is a positive correlation between fracture stability and uneventful healing of internally fixed displaced femoral neck fractures. Unfortunately bone strength is often reduced due to osteoporosis which counteracts the desire for stability. In recent in vitro studies improved stability was achieved when internally fixed femoral neck fractures were augmented with resorbable bone cement. The purpose with this study was to find out whether such augmentation might provide additional stability during the early rehabilitation period when used in vivo.

Patients and methods: 24 ambulatory patients above 65 years of age with a displaced femoral neck fracture (Garden III–IV) were randomized to internal fixation with either two cannulated screws (Olmed) or screws combined with injection of resorbable bone cement (Norian SRS) around the screw threads and for filling of the fracture void. The cement is biocompatible and hardens under physiologic conditions in a non-exothermic reaction. It appears to be remodeled through the same mechanism as normal bone. Radiostereometric analysis (RSA) was done within 24 hours after surgery, before weight bearing, after which all patients were allowed free mobilization. Two additional RSA examinations were done at 1 and 6 weeks.

Results: All patients could be followed according to the study protocol and there were no reoperations during the observation time. At 1 week the fractures augmented with Norian SRS had moved significantly less when compared with

fractures fixed with conventional screws alone. For rotational movements the differences were especially pronounced in rotation about the sagittal axis. In translation the improved stability was most evident in movement along the longitudinal and the sagittal axes. At 6 weeks the accumulated fracture movement was still lower in fractures augmented with cement although the differences were less pronounced when compared with the results at 1 week.

Conclusion: The findings are in accordance with previous in vitro results with improved fracture stability when using Norian SRS for augmentation of internally fixed femoral neck fractures. The concept to enhance the strength of the compromised bone around the metal implant by injecting resorbable cement might become a useful method for fixation of fractures in osteoporotic bone. Future studies will show whether the improved early stability shown in the present study will last over time and whether it will lead to an improved clinical outcome when compared with traditional fixation using metal implants alone.

28. Primary treatment of displaced femoral neck fractures

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A randomized study was carried out to compare internal fixation of two von Bahr screws with a bipolar Variokopf prosthesis in displaced cervical hip fractures, type Garden 3–4. At the follow-up after 4–6 years, 2/3 of the patients had been reoperated for implant removal or secondary prosthesis in the screw-fixed group. 15% of the patients had early dislocations of the prosthesis. Disability to co-operate postoperatively calls for special attention. Bipolar prosthesis may be a relevant alternative in the primary treatment of displaced femoral neck fractures.

29. Internal fixation vs primary total hip arthroplasty for dislocated femoral neck fractures—preliminary results

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The traditional treatment in Sweden for dislocated femoral neck fractures in elderly is internal fixation although healing complications are very common. Earlier studies on THR has shown a high complication rate, especially dislocations.

Material and methods: Patients (>70) with acute dislocated femoral neck fracture—and normal walking capabili-

ty, without severe cognitive dysfunction (SPMSQ > 3), from independent living—were randomized to internal fixation (IF) with 2 Olmed screws, or to primary THR (Exeter stem and OGEE cup, 28 mm head) through a Hardinge approach. The patients were summoned at 4, 12, and 24 months. This is the 12-month result of the first 46 patients.

In the THR group (n = 23), 6 patients were excluded (2 refused, 2 had aortic valve stenosis contraindicating major surgery, 1 developed sepsis before surgery, and 1 got the diagnosis rheumatoid arthritis (RA) during follow-up). In the IF group (n = 23) 1 patient was excluded (RA diagnosis during follow-up). It thus remained 39 patients (5 men), mean age 81 (70–96). The 2 groups had similar background data.

Results: One IF patient had a myocardial infarction at 2 weeks. One THR patient had a suspected superficial infection (negative cultures, antibiotics for 2 weeks), apparently healed at 4 and 12 months. In the IF group 7 patients got a secondary hip arthroplasty (6 redislocations/ pseudarthrosis and 1 avascular necrosis), a 32% reoperation rate. One THR patient died (not surgery related) at 10 months. There were no other complications.

At 12 months the IF group, even when excluding the patients with healing complications, fared worse than the THR group: Pain (VAS) at rest: IF 13, THR 5; pain at walking: 25, 10. Walking aids: 67%, 31%. ADL (Katz) independent: 73%, 75%. Quality of life estimated with SF-36 and Euro-Qol was more than 10% higher in the THR group at 4 and 12 months. Total hospital days during the first postoperative year were 36 days in the IF group and 26 days in the THR group.

Conclusion: There is a high complication rate after IF in dislocated femoral neck fractures. Often, it is claimed that many patients do not need further surgery, because of their poor general condition. This was not our experience, perhaps because we had cognitive state among the inclusion criteria. Using an anterior approach and modern modular THRs preserving an adequate offset, dislocation rate can be decreased, and here the patients' mental state no doubt also is important. Today, hip fracture patients are often treated in a routine, not to say schematic way. Many surgeons do not even follow-up these patients. The encouraging preliminary results with primary THR in elderly healthy patients with dislocated femoral neck fractures may be due to surgical technique and strict indications.

30. Nail or arthroplasty—a randomized study of displaced cervical hip fractures with 1-year results

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In surgical treatment of displaced, cervical hip fractures internal fixation with nails/screws or arthroplasty are the main alternatives. The method of choice in Scandinavia has been internal fixation. The aim of our study is to compare the two

methods regarding complications, mortality, functional outcome etc.

Material: During 1995–1997, 420 patients aged 70 and older with hip fractures graded Garden 3–4 were included in a 2-year prospective multicenter study consisting of 12 Swedish hospitals (Halmstad, Ängelholm, Helsingborg, Landskrona, Lund, Malmö, Ystad, Hässleholm, Kristianstad, Karlshamn, Karlskrona and Ljungby). Patients with mental confusion or rheumatoid arthritis were excluded, as well as bedridden or institution dwelling persons. The patients were randomized to either internal fixation or arthroplasty.

Results: Preliminary 1-year results shows that the failure rate in the group with internal fixation is 40% (most often caused by pseudarthrosis), compared to 3.5% in the arthroplasty group (recurrent dislocations). The arthroplasty group has better walking ability and less pain. There is no difference in mortality between the groups.

31. Osteosynthesis versus total hip arthroplasty for displaced femoral neck fractures—results after 4 years of a prospective randomized study

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Patients sustaining a femoral neck fracture are currently treated by closed reduction and osteosynthesis or by a hip arthroplasty. In Scandinavia, osteosynthesis is the most common method whereas arthroplasty is favored in many other countries. The aim of this study was to compare the relative mortality, morbidity and mobility of patients treated with either osteosynthesis (OS) or total hip arthroplasty (THA).

Patients and methods: From February 1990 to December 1994, 100 patients with a displaced femoral neck fracture (Garden III–IV) with an age over 65 years and admitted from their own homes and with no concurrent joint disease or previous hip fracture were included in the study. The patients were randomly allocated, depending on the day of the week, to either osteosynthesis (Olmed screws) or total hip arthroplasty (Bimetric). All patients were followed with clinical examination (Harris hip score) and radiography at 3, 12, 24 and 48 months or until death.

Results: 57 patients (41 women and 16 men) were operated on with osteosynthesis and 43 patients (38 women and 5 men) with total hip arthroplasty. The mean age was 78 (65–88) years in the THA group and 79 (66–90) years in the OS group. 16 patients treated with OS died during the study period and 8 in THA group.

In the OS group 30 patients (53%) have been reoperated at least once at the 4 year control; 19 patients with THA and one with a hemiarthroplasty because of nonunion or avascular necrosis and 1 patient because of infection. 8 patients had only the screws extracted and in 2 patients a Girdlestone arthroplasty was performed. 6 patients in the OS group had avascular necrosis or nonunions, but are not planned for

reoperation.

In the THA group 6 (14%) patients had postoperative dislocation of the prosthesis but only one with recurrences after closed reduction. 1 patient in the THA group has been reoperated because of mechanical loosening. The median Harris hip score for the OS group was 79 and for the THA group 88.

Conclusion: In this selected group of healthy patients, an unacceptable high complication and reoperation rate was observed after osteosynthesis, whereas total hip arthroplasty showed fewer complications. The patients in the THA group had better clinical outcome after 4 years.

32. Femoral neck fractures—fewer secondary hip arthroplasty procedures with a differentiated treatment protocol

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In Sweden femoral neck fractures are usually treated with closed reduction and screw or nail fixation. The complication rate is, however, high and many secondary hip arthroplasty procedures are required. In other countries, on the other hand, primary hip arthroplasty is the standard procedure in displaced fractures. We implemented a differentiated treatment protocol in 1997 at the Karolinska Hospital, which leads to a greater number of primary hip arthroplasties.

Material and methods: All fresh nonmalignant femoral neck fractures with cranial displacement of the femoral shaft (the tip of the greater trochanter was used as a landmark) no further than to the joint line and/or with a posterior angulation < 60° were treated by screw fixation provided that a satisfactory reduction (no varus and dorsal angulation < 30°) could be obtained. Otherwise a primary hip arthroplasty was performed. The requirement for a secondary hip arthroplasty was compared during a period before and after the new treatment protocol had been implemented. From Jan. 1988 to Dec. 1989, 252 femoral neck fractures were treated according to the opinion of the surgeon and from July 1997 to Nov. 1998, 282 fractures were treated according to the protocol.

Results: During the former period 93% of the fractures were treated with screw fixation (v. Bahr) and 7% with hip arthroplasty. During the later period 71% were treated with screw fixation (Olmed) and 29% with hip arthroplasty. The requirement for a secondary hip arthroplasty among all fractures due to a complication was reduced from 18–7% ($p < 0.0002$). Of the fractures treated with screw fixation the rate of secondary hip arthroplasties was reduced from 20–10%.

Conclusion: By the practice of a protocol based on radiological assessment of the preoperative radiographs and the results of fracture reduction in the operation theatre the need for secondary hip arthroplasties was markedly reduced. The results suggest that treatment of femoral neck fractures should be differentiated and fewer screw or nail fixations should be performed. The radiological criteria need, however, to be refined.

BASIC SCIENCE

33. Release of cytokines by cultured monocytes in patients with and without osteolysis after uncemented THR

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We have addressed the possibility of constitutional differences in cytokine production among patients with and without osteolysis after total hip replacement (THR).

Materials and methods: 19 patients, operated on with uncemented PCA hip replacements 11–13 years previously, were studied. 7 patients (group 1) showed radiographic signs of focal osteolysis in the femur and/or acetabulum, and 12 patients (group 2) were completely free of osteolysis. Peripheral blood was drawn from all 19 patients and monocytes were isolated by centrifugation. The cells were cultured and then stimulated with lipopolysaccharide (LPS). The release into the supernatant of cytokines (IL-1, IL-6, TNF-alpha and GM-CSF) by the monocytes was measured pre- and post stimulation.

Results: There was no difference in the release of IL-1 and IL-6, either between groups or patients. There was either a high or low release of TNF-alpha and GM-CSF (a difference of 2 orders of magnitude), but no difference between the groups in the distribution of high- and low-responders (c-2 test; $p > 0.05$).

Discussion: Osteolysis after THR remains enigmatic. It has been shown that the release of cytokines from cultured, particle-stimulated monocytes differs between patients with stable and loose hip prostheses (1). Similar results have been obtained when comparing normal volunteers and patients with THR (2). These findings indicate either an influence on the cells by the implant material(s) or a constitutional variation in the reactivity of phagocytic cells. In this preliminary study we have looked at the latter question by stimulating monocytes unspecifically rather than with wear particles. We have not found systematic differences in the release of bone-associated cytokines by monocytes from patients with and without radiographic signs of osteolysis. However, these results alone do not rule out the existence of constitutional factors, and further study is in progress.

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34. A comparison of two hyaluronan drugs and placebo in patients with mild to moderate osteoarthritis of the knee—a controlled, randomised, parallel-design multicenter study

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We have previously reported the first part (26 weeks) of this controlled, randomized, parallel-design multi-center trial. The first part showed that three weekly intraarticular injections produced a significant reduction of weighted pain, resting pain, maximum pain, Lequesne index and WOMAC index score, without significant differences between hyaluronan treatment and placebo during 26 weeks. Neither there was any difference between the two active hyaluronan drugs.

The objective of this study was to compare the duration of efficacy and safety of three injections of Artzal®, Synvisc® or placebo in patients with mild to moderate osteoarthritis of the knee. The study was a randomized, double-blind, placebo-controlled, multicenter trial with parallel groups.

Patients and methods: 210 patients were included in the study. The following inclusion criteria were employed; age 60 years or above, Lequesne index of 10 or above, weighted pain according to Visual Analogue Scale (VAS) of 40 mm or above, radiologically verified osteoarthritis in the knee joint (Ahlbäck grade I–II), dominating pain in one knee only due to osteoarthritis and general physical examination normal. A total of three injections, once weekly of the two active drugs or the placebo were used. For this part of the study the efficacy parameter was “time to clinical failure”. “Clinical failure” was defined as concomitant treatment for the study knee, i.e. analgesics (more than 4 g paracetamol/day), surgical alternative or new injections. If the patient needed more than the permitted treatment due to other reasons than the study knee he/she was withdrawn from the efficacy analysis from that date, but not regarded as a clinical failure. The patients were followed for 52 weeks. The duration of clinical benefit after hyaluronan treatment was analyzed with the Kaplan-Meier technique during 52 weeks.

Results: The intraarticular injections produced a significant reduction in weighted pain, resting pain, maximum pain, Lequesne index and WOMAC index score after 26 and 52 weeks. The cumulative percentage of patients still satisfied with treatment after 52 weeks of treatment estimated from the Kaplan-Meier curves was 60% in the Artzal® group, 59% in the Synvisc® group (59.5% in the combined group receiving active treatment) compared with 48.5% in the placebo group. Test of equality over strata was performed with Wilcoxon and comparisons were made between the placebo and Artzal® groups ($p = 0.06$), the placebo and the Synvisc® groups ($p = 0.134$) and placebo and active group ($p = 0.05$). Active treatment had a significantly longer duration and clinical benefit compared with placebo ($p < 0.05$).

Conclusion: After 52 weeks, active treatment had a significantly longer duration and clinical benefit compared with

placebo. Intraarticular injections with hyaluronan into the knee joint were shown to be a safe treatment and well tolerated by the patients.

35. Cartilage repair in a rabbit model using hyaluronic acid-based biopolymers

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Articular cartilage in adults has a limited ability for self repair. The methods devised to augment its natural healing response allow some regeneration of hyaline-like cartilage but this response is often accompanied for variable amounts of fibrocartilage and the reparative tissue fails. We have used hyaluronic acid (HA)-based polymers to facilitate the natural healing response by mimicking an embryonic-like milieu where endogenous progenitor cells can regenerate the injured tissues.

Standard 3 mm diameter x 3 mm deep osteochondral defects were made on the weight-bearing surface of the medial femoral condyle of 4-month-old rabbits. The defects were either left untreated or treated with ACP™ or HYAFF®11 sponges provided by Fidia Advanced Biopolymers (Abano Terme, Italy). Rabbits were sacrificed 4 and 12 weeks after surgery and the condyles fixed in formalin, decalcified, embedded in paraffin, sectioned and stained with Toluidine Blue. All 12-week defects were scored with a modification of O'Driscoll's 24 point scale. Scores were compared with a Mann-Whitney rank sum test.

The repair tissue of untreated defects was similar at both time points. Most were filled with bony tissue up to or beyond the tidemark and the non-calcified top layer varied from undifferentiated fibrous to more hyaline-like tissue. No empty defect repaired completely with hyaline-like cartilage. Four weeks after surgery, the defects treated with ACP™ exhibited endochondral bony filling to the level of the tidemark and the top layer was composed of hyaline-like cartilage which showed impressive integration with the adjacent cartilage. The 12-week specimens exhibited bone up to or beyond the tidemark level and the non-calcified layer was mainly hyaline-like cartilage which was half as thick as the normal cartilage. Four weeks after surgery, the HYAFF®11-treated defects presented a rim of chondrogenic cells at the interface with the host tissue, while only empty sponge material was present in the center of the defect. The top layer was variable with fibrocartilage in some cases and hyaline-like cartilage in others. Importantly, the defect tissue was always integrated with the adjacent cartilage. At the 12-week time point, most of the defects exhibited bony fill with an area in the center that was either unfilled or filled with fibrous tissue. In some defects, some areas of hypertrophic cartilage were still present. The non-mineralized surface lay-

er was composed mainly of hyaline-like cartilage with, in some cases, cracks and fissures. The histologic scores revealed that ACP™-treated defects presented better repair than both HYAFF®11-treated ($p < 0.05$) and empty, untreated defects ($p < 0.002$). The differences found between HYAFF®11-treated and empty defects were not significant ($p = 0.3$).

The introduction of a biocompatible and biodegradable porous material into the defects provides the scaffolding and micro-environment for the reparative cells to regenerate and integrate. HA-based polymers are excellent cell-delivery vehicles and possess the unique chemical composition to recreate an embryonic-like milieu that is favorable for the regenerative process. Further work is required to fully assess the value and different dynamics of the two materials used, and also the long-term outcome of osteochondral defects treated with these biopolymers.

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36. Relationship between the integrity of small proteoglycans and the cleavage of type II collagen

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Osteoarthritis (OA) is a degenerative disease leading to the destruction of joint cartilage. Type II collagen is a major matrix component providing a fibrillar network which retains large aggregating proteoglycans (PGs). Small PGs (decorin, biglycan and fibromodulin) are known to interact with fibrillar collagens along with other molecules forming a sheath around such fibrils^{1,2}. Thus far, the only known matrix metalloproteinases (MMPs) which can cleave intact type II collagen are MMPs 1, 8 and 13 at near physiological pH³. An antibody directed against this cleavage site (COL2 3/4C) will allow us to monitor the initial breakdown of type II collagen⁴. The destruction of small PGs by other known MMPs may precede the cleavage of collagen, suggesting that these molecules are important in protecting the collagen fibril from attack by MMPs.

Methods: Bovine and human cartilage explants were cultured in Dulbecco's Modified Eagle Medium (DMEM) with or without Interleukin-1 (IL-1) for 15 days. Explants were extracted with Guanidinium-HCl (GuHCl) for 48 hours. The residue was washed in water and treated with Cyanogen Bromide (CNBr)⁵. CNBr digests were electrophoresed on polyacrylamide gels and transferred onto nitrocellulose

membranes^{6,7}. Membranes were probed for the presence of the collagenase cleavage site using antibody COL2 3/4C⁴. Small PGs found in the GuHCl extracts were treated in the same manner though were visualised using antibodies specific for their core proteins.

Results: In IL-1 treated cultures, decorin and biglycan contents were observed to decline throughout the culture period. In contrast, the amount of type II collagen varied little throughout the 15 days of culture. Amounts of fibromodulin remained constant over the entire culture. Contents of the small PGs and collagen in control cultures remained constant.

Discussion: The use of sequential CNBr digestion following GuHCl extraction permitted the analysis of both collagen and small PGs from the same piece of cartilage. The loss of decorin and biglycan observed over the period of culture coupled with the minimal loss of type II collagen suggests a temporal difference between these sequences of events. It is known that decorin is cleaved by different MMPs than collagen⁸ and an upregulation of these enzymes prior to that of the collagenases could explain such a result. Fibromodulin would be expected to vary in the same manner as decorin, both being intimately associated with collagen albeit binding to different sites on the fibril. That this was not observed may again be related to differences in enzyme expression or activation.

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37. Disease modifying drugs in OA—inhibition of joint cartilage Collagen degradation—a future treatment?

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Joint cartilage is a composite tissue where type II collagen, its major constituent, forms the fibrillar network. Trapped in this fibrillar meshwork is the large aggregating proteoglycan. By the hydration of these proteoglycans, a swelling pressure is achieved. To provide its functional properties, like compressive stiffness, the joint cartilage is critically dependent of the integrity and interaction of aggrecan and type

II collagen. In osteoarthritis (OA), type II collagen is excessively degraded by enzymes (collagenases).

Methods: Femoral knee articular cartilage, obtained at joint replacement in eleven OA patients, or at autopsy in five non-arthritic patients, were cut into pieces, mixed, weighed and placed in culture wells for 14 days. Triplicate cultures were treated with synthetic enzyme inhibitors (Roche): either a preferential collagenase 3 inhibitor (MMP 13), or a broader spectrum collagenase inhibitor. Media were examined by immunoassay (ELISA) for fragments produced by cleavage of the type II collagen by collagenase. Proteoglycan release into the culture media was analyzed as glycosaminoglycan (GAG) by the DMMB assay.

Results: Analysis of normal versus OA cartilage showed an increased total release of the collagenase-generated fragment from the OA cartilage. Both types of collagenase inhibitors significantly decreased the release of these fragments from the OA cartilage. Interestingly, only the preferential collagenase 3 inhibitor decreased the cleavage of type II collagen in non-arthritic cartilage. These inhibitors did not inhibit the GAG release. Unexpectedly, the release of GAG was similar in OA compared to non-arthritic cartilage.

Conclusions: This study provides evidence for an increased enzymatic cleavage of type II collagen by collagenase in cultured OA cartilage that was not accompanied by increased proteoglycan degradation. The decreased release of the collagenase-generated fragment in OA and non-arthritic articular cartilage treated with collagenase inhibitors, indicate a role for these enzymes in the physiology and pathophysiology of articular cartilage. Inhibition of type II collagen degradation, may prove of value as treatment of progressive degeneration of cartilage in OA.

38. The epidemiology of vertebral deformation in Swedish men and women

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Vertebral fracture-deformation is a common feature of osteoporosis with age, sex and geographical variation. The purpose of this study was to investigate the prevalence and incidence of vertebral deformation in a Swedish population.

Subjects and methods: Spine radiographs of 797 men and women, age 50-92, participating in two population-based studies, were analysed for the occurrence of vertebral deformation. After three years in one study and seven years in the other those subjects still alive were asked back for a new spine radiograph, altogether 443 responded.

On lateral radiograms including Th4-L4 the four corners of each vertebral body and the midpoint of each endplate were marked. The marked points were recorded on a digitizing table and the anterior/posterior and midvertebral/posterior ratios were calculated as well as the ratio between the pos-

terior height and the posterior height of the adjacent vertebra.

The definition of a prevalent deformation on the baseline radiograms is based on a comparison between the observed and the expected ratios in non-deformed vertebrae. A vertebra is deformed if any of the three ratios representing that vertebra is reduced 3 SD or more from the normal mean. The definition of an incident vertebral deformation is based on a comparison between the baseline and follow-up radiographs of the same subject. A new deformation has occurred if any of the three heights of a vertebra is decreased 20% or more.

Result: The prevalence of subjects with vertebral deformation increased significantly with age in both sexes. Adjusted for age women had a significantly higher prevalence of deformation as compared with men, OR 1.5; 95%CI 1.1-2.0, using the deformation criterion -3SD. 43% of the women and 30 % of the men had vertebral deformation. The vertebrae most commonly deformed were L1, Th12 and Th11 in both sexes. In subjects with vertebral deformation the number of vertebrae showing deformation increased with age, however statistically significant only for women. The incidence of subjects with new vertebral deformation increased with age in both sexes.

Conclusion: The prevalence of vertebral deformation is high, both for men and women, and increases with age.

39. Serum antibodies against glycosphingolipids in patients with acute severe sciatica

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Glycosphingolipids are composed of ceramide and a carbohydrate chain and mainly expressed on the cell surface, making them accessible to antibodies. They are most frequently expressed in the nervous system. Different neurological disorders are associated with increased titers of serum antibodies against carbohydrate epitopes of glycosphingolipids. The leakage of nucleus pulposus into the epidural space and the mechanical and/or chemical nerve root damage in disc herniation may lead to exposure of substances not normally encountered by the immune system, or may present them in an abnormal way. The aim of this study was to investigate whether production of autoantibodies to glycosphingolipids occurs in patients with sciatica, and if glycosphingolipid-antibodies correlates to clinical findings and imaging results.

Material and methods: 68 patients with acute severe sciatica were investigated by clinical examination and CT. A 10 mL fasting blood sample was collected from the patients within 24 hours of admission. Samples were analyzed by a Microtiter-ELISA method for the presence of autoantibodies

in serum against a number of glycosphingolipids (GM1, GA1, LK1, GM2, GD1a, GD1b, GQ1b, 3'LM1, 3'isoLM1 and Sulphatide) and correlation between the individual antibodies and imaging, SLR, pain below the knee, and neurological tests were evaluated. All the samples were analyzed in duplicate. Since these autoantibodies may be present at low titers in normal individuals and there is no clear limit for pathological levels in serum, we used pooled serum from 50 blood donors as a negative reference. The ratio of optical absorbance of patient serum to the absorbance of pooled negative control serum was computed. An absorbance ratio of greater than 2 was classified as positive.

Results: Elevated titers for the different antibodies were found in between 3-38 % of the patient sera. The most frequently found antibodies were directed against 3'LM1 (34% IgM, 15% IgG), GD1b (38% IgM, 9% IgG), and GM1 (31% IgM, 7% IgG). 3'LM1 is the major ganglioside in peripheral nerve myelin and GD1b and GM1 are both present in nerve cells of peripheral nerves. Antibodies (either IgG or IgM) against GM1, GA1, or GD1b antibodies which have the same sugar epitopes were grouped together and the frequency of patients with any of these antibodies in elevated levels in sera was found to be 53%.

Positive neurological test results were associated with 3'LM1 (IgM) (95% CI 0.91-9.12, $p=0.068$), 3'LM1 (IgM+IgG) (95% CI 1.22-10.89, $p=0.023$), and GD1A (IgM) (95% CI 1.2-18.5, $p=0.017$). No correlation was detected to imaging, SLR, pain below the knee.

Conclusion: The increased frequency of some of the antibodies indicate that these may be involved in the pathophysiological mechanisms behind sciatica but did not prove to be helpful in the diagnosis of a single patient.

40. Inhibition of inducible nitric oxide synthase reduces the effects of nucleus pulposus on spinal nerve roots

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Cytokines are present at the site of a disc herniation. Cytokines may induce production of inducible nitric oxide synthase (iNOS) which catalyzes the conversion of L-arginine to nitric oxide (NO). NO is primarily implicated in vasoregulation and neurotransmission but large amounts of NO have cytotoxic effects on neurons. The aim of this study was to investigate if systemic treatment with aminoguanidine (AG), a selective iNOS inhibitor, can reduce the negative effects on vascular permeability and nerve conduction velocity (NCV), previously observed after nucleus pulposus (NP) exposure to spinal nerve roots.

Material and methods: Two sets of randomized, controlled and blinded experiments were performed in the pig.

1. S2 and S3 nerve roots were exposed unilaterally for autologous NP. In the AG group ($n=7$), aminoguanidine (20 mg/kg in 50 ml NaCl) was injected intravenously immedi-

ately before NP application. The control group ($n=8$) received the same amount of NaCl. The animals were kept anaesthetized for 2 hours, subsequently perfused with Evans blue solution (50 mg/kg) and sacrificed. After 10 minutes of *in situ* fixation with 5 % Karnowsky solution, the nerve roots were harvested and snap frozen. Five sections from each specimen were investigated by fluorescent microscopy. The edema in the nerve root was graded as none/slight, moderate or severe.

2. Spinal nerve roots at the level of cauda equina were exposed to autologous NP. In the AG group ($n=5$) aminoguanidine (20 mg/kg) was injected intravenously prior to application of NP and repeated intramuscularly the day after surgery. The control animals ($n=7$) did not receive AG and served as controls. Seven days after surgery, NCV over the exposed area were measured.

Results:

1. In the AG group, a severe spinal nerve root edema was observed in one of the animals (12%). In the control group, four of the animals (57%) had severely damaged nerve roots. Moderate edema was observed in three of the animals (38%) in the AG group and in two animals (29%) in the control group. Four of the animals (50%) in the AG group and one (14%) in the control group showed none or only slight nerve root edema.

2. Nerve conduction velocity were significantly higher in the aminoguanidine treated animals than in control animals (71 ± 18 vs 48 ± 18 m/s, $p < 0.05$).

Conclusions: Inhibition of inducible nitric oxide synthase reduces nucleus pulposus-induced edema and prevents the reduction of nerve conduction velocity. NCV in the AG group was similar to what previously has been in observed after fat exposure to nerve roots (76 ± 11 m/s).

The results suggest that nitric oxide is involved in the pathophysiological effects of nucleus pulposus in disc herniation. Furthermore, the results may suggest a new approach for treatment of disc herniation.

TUMOR

41. Morphological diagnosis of unknown skeletal lesions—analysis based on cytology in 110 cancer patients

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We have previously shown that cytologic diagnosis based on fine needle aspiration biopsy (FNAB) is a safe and efficient method for the discrimination between benign, primary malignant and metastatic bone lesions. In this study, we address metastatic lesions specifically to assess the diagnostic accuracy and to ascertain whether FNAB permits identification of the primary lesion.

Patients and methods: Between 1990 and 1997, 444 patients were referred to the Department of Orthopedics, Karolinska Hospital for diagnosis of skeletal lesions of unknown type. Patients who had undergone prior biopsies or had been operated were not included. 116 of these patients proved to have metastatic disease or myeloma/lymphoma. In 6 patients the medical records could not be retrieved leaving 110 consecutive patients with metastatic carcinoma (80), myeloma (16) or lymphoma (14). All were investigated with FNAB and none had a previous history of malignancy.

Results: A correct diagnosis of metastatic carcinoma, lymphoma or myeloma was achieved by FNAB in 101 of the 110 patients (92%), it was misleading in 4 and inconclusive in 5. The four misleading diagnoses were of no clinical consequences. In 5 patients the FNAB was inconclusive. In all these patients the final diagnosis was made on histological material from surgical biopsy specimens. FNAB correctly diagnosed 15 of 16 patients with myeloma, 12 of 14 with lymphoma, and in 75 of 80 patients with metastatic carcinoma. Furthermore, the site and type of malignancy was correctly suggested in 2/3 of the patients with metastatic carcinoma.

Conclusion: FNAB is a safe and reliable method for the diagnosis of metastatic carcinoma, lymphoma and myeloma. Time consuming and costly investigations can be limited by choosing FNAB as the initial diagnostic method in the search for the primary tumor. Hence, the choice of radiological examinations, laboratory tests and biopsies can be efficiently guided by the result of FNAB of the skeletal lesion.

42. Anterior decompression and reconstruction in metastatic spinal disease

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Decompression and stabilization with rods through a posterior approach has been our routine treatment for cancer patients with epidural compression. Since 1994, selected patients have been operated with removal of the vertebral body and reconstruction with cement and anterior.

14 patients, accounting for 10% of patients operated for epidural compression, were operated by an anterior approach. The most common sites of primary tumor was the kidney (5) and breast (4). Preoperative neurological function (Frankel), showed that 3 patients were non-walkers (C), 8 could walk with aid (D), and 3 had minimal neurological symptoms and were operated because of pain (E). The operated level was thoracic in 8 patients, lumbar in 5 and both (Th10 and L1) in 1. The vertebral body and discs were removed, the spinal cord or cauda equina was decompressed. Reconstruction was achieved with cement and a Z-plate. The median operative time was 180 (135–420) min and blood loss was 1700 (900–5500) ml.

There were 2 systemic complications. A 70-year-old patient with metastasis of kidney cancer died in respiratory failure 2 weeks postoperatively. One 78-year-old man with prostate cancer developed septicemia but recovered. There were 2 local complications, 1 postoperative bleeding requiring reoperation and 1 patient had a pleural effusion.

3 patients died within 3 months of surgery, but 6 have survived more than a year. 4 patients are still alive a median of 1 year after surgery. Neurologically, 9 of 10 evaluable patients with neurological compromise were improved, 2 from Frankel C to D, 7 from D to E. 2 patients were reoperated because of local tumor progression at 16 and 34 months, respectively.

We conclude from this limited experience that anterior decompression and stabilization affords lasting neurological and functional improvement. The morbidity was not higher compared to posterior approaches. The patients selected for anterior decompression had less advanced disease leading to a twice as high chance of surviving 1 year after operation. My indications for anterior decompression are pathological fracture of the vertebral body with neurological symptoms or severe pain in cancer patients with limited disease and good prognosis for 1-year survival.

TRAUMA

43. Fracture registry—is it worth the effort?

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Registers for orthopedic diagnosis are by now well established and useful for the treatment particularly for patients with arthroplasties. This study aimed to evaluate if a corresponding prospective registration of patients with diaphyseal fractures in the lower extremities would be beneficial.

Material: During a period of 12 months 81 patients (53% male, age 49 ± 22 years) with a shaft fracture of the tibia ($n=64$) or the femur ($n=17$) were identified by a study nurse and included. All patients were operatively treated according to the protocol at our institution. All patients filled out questionnaires regarding demographics, details about the injury and the SF-36. The patients were followed up at 6 months (questionnaire) and at 12 months (questionnaire, clinical examination, radiographs).

Results: 31% of all fractures were caused by high energy accidents. Femur fractures were AO-classified as 32A (44%), 32B (50%) and 42C (6%). 13 patients were treated with an IM nail (6 AO, 6 long Gamma, 1 retrograde) and 4 patients with a plate fixation. All fractures healed and there were no major complications. Tibial fractures were classified as 42A (61%), 42B (30%) and 42C (9%). 68% of the patients were treated by IM nailing, 16% with plate and 16% with a plaster fixation. 4 patients suffered from a compartment syndrome and one patient had a superficial wound infection. In 3 cases, the proximally locked tibial IM nail had migrated proximally >1 cm. Several patients with IM-nailed tibial fractures complained of knee pain and reported a lower quality of life than prior to the fracture.

Discussion: There were no severe complications among patients treated with IM-nail confirming that nailing is a safe procedure. Migration of the tibial nail, even if locked proximally, was a new finding. Knee pain after IM-nailing of the tibia was a frequent complication. There were several difficulties in retrieving data to this registry. We feel that running this registry seems to be too high an effort for the limited value it has in clinical practice.

44. Trauma registry—one year experience

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Trauma registries are designed for collecting information on nature and severity of injuries, treatment and mortality. This study aimed to evaluate the benefits of a trauma registry among an urban population.

Material: During a period of 12 months (July 1995 to June 1996) injured patients admitted to Stockholm Söder

Hospital were included into a trauma registry. Elderly patients with osteoporotic fractures were excluded. Demographic and pre-hospital data, vital parameters, acute treatment, surgical procedures, diagnosis and in-hospital mortality were recorded. The Injury Severity Score (ISS) and the T-Revised Trauma Score (T-RTS) were calculated.

Results: A total of 992 patients (54% male, mean 49 ± 22 years) were entered into the database. Pre-hospital data was recorded for 47% of the patients. The injury mechanism was a simple fall in 35%, fall from a high level in 21%, traffic in 17%, assault and battery/self-inflicted injuries in 9% and various injury mechanisms in 18% of the cases. During the first 24 hours 49% of the patients had an acute operation. Five per cent (54/992) of the patients scored an ISS >10 and one per cent (12/992) scored ISS >16 . T-RTS was <12 in 3% (32/992). A total of 4 patients died.

Discussion: Data collection for trauma registration takes time, money and enthusiasm. The results showed that even if about half of the patients had had a high energy accident the number of severely injured patients was small. We believe that for hospitals like Stockholm Söder Hospital with a large number of patients, but a few severely injured, this type of general registration is of a limited value.

45. Closed intramedullary nailing versus cast treatment of displaced tibial shaft fractures—a prospective randomized study

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Materials and methods: This is a prospective study of 53 unilateral, displaced and closed or grade one open tibial shaft fractures, stratified in two treatment groups. 27 patients (group I) were randomized to treatment with an unreamed nail and 26 patients (group II), to treatment with a plaster of Paris with or without minimal internal fixation. The two groups were not significantly different in terms of age, gender, smoking habits, addiction, energy type, nor the severity of soft-tissue damage, fracture morphology and localization. All patients were assessed for union, and complications were documented. All patients completed the Nottingham Health Profile questionnaire (NHP). They also assessed their pain intensity at rest and during walking on visual analogue scales.

Results: The mean time to union was 19 weeks (SD = 8.2) for group I, and 25 weeks (SD = 9.4) for group II ($p < 0.005$). The time to full weight-bearing was 14 weeks (SD = 4.6) for group I and 22 (SD = 10.8) for group II ($p < 0.005$). Six patients in group I and 15 patients in group II demonstrated healing with delayed union (union after 20 weeks) ($p < 0.01$). One patient in group I, and 2 patients in group II developed non-union. The NHP index scores on physical mobility, social isolation, work ability, and sexual life were all significantly better for group I compared with group II, at

three months after the injury ($p < 0.05$). Patients in group I had significantly higher pain intensity on walking during the first two months ($p < 0.05$).

Conclusions: From this study can be concluded that 1) intramedullary nailing is an efficient treatment method for displaced, closed tibial shaft fractures, there the persistent knee pain is a troublesome and common complication, 2) nailed patients had better quality of life during the first 3 months after the injury, and 3) delayed union, malunion, and restricted range of motion at the ankle joint can be common complications if these fractures are treated by cast.

46. Low-intensity ultrasound and healing of intramedullary fixed tibial fractures

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During the last years two clinical studies have been published describing a substantial reduction in healing time for cast treated tibial fractures as well as for fractures of the distal radius following daily use of low-intensity ultrasound. In the present study we wanted to find out whether a similar acceleration of healing could be obtained in fresh tibial fractures when treated with surgery.

Patients and methods: 32 patients with a diaphyseal tibial fracture treated with a reamed and statically locked intramedullary nail (AO Universal) were included. The study was prospective, randomized, double-blind and placebo-controlled. All patients were equipped with a coded ultrasound (US) device. US was started within three days after surgery consisting of 20 minute sessions every day for 75 days. All devices were identical except that only half of the devices emitted an active ultrasound signal. Neither the patient nor the investigator was aware of the status of the device. Codes were not broken until all radiographic reviews had been completed. After surgery the patients were followed every third week until healing and at 26 and 52 weeks. At each visit standardized radiographs were taken. Furthermore, serum samples were obtained at each visit for analysis of serum markers for bone resorption (ICTP) and bone formation (bALP and osteocalcin).

Results: All fractures healed. The average time until the first callus could be seen on the radiographs was 39 ± 3 days for the ultrasound group and 37 ± 3 days for the placebo group. The average healing time defined as bridging of three cortices was 155 ± 22 days (median 112 days) in the ultrasound group while 125 ± 11 days (median 114 days) in the placebo group. The shorter healing time in the placebo group was not significant.

All three serum markers increased for all patients with ICTP reaching a maximum at 1–4 weeks and bALP and osteocalcin at 10–16 weeks. At 1 week the level of ICTP was significantly lower in the ultrasound group compared with placebo. There was no significant difference in the levels of

bALP and osteocalcin at any time point between patients treated with ultrasound and placebo.

Conclusion: Ultrasound does not shorten healing time in fresh tibial fractures treated with a reamed and statically locked intramedullary nail. The findings are not in accordance with previous studies reporting considerable reduction of the healing time of non-operatively treated tibial fractures. The serum bone markers indicate that ultrasound might slow down early bone resorption while there was no effect of ultrasound on bone formation as given by serum markers.

47. Torque of the knee joint and center of pressure after healed tibial fracture—a prospective randomized study

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We have measured muscle strength as torque of the knee joint during knee extension and balance as center of pressure in patients with healed tibial fracture 1 year after injury.

Method: 24 patients with a tibial shaft fracture were randomized for intramedullary nailing (group 1) and for treatment by plaster cast (group 2). Knee extension torque was measured during isometric and concentric muscle action with a velocity of 60° per sec. by an isokinetic dynamometer (Kin Com II). Center of pressure was measured on a force plate (AMTI).

Results: Torque was 84 (SD = 45) Nm in group 1 patients and 57 (SD = 27) Nm in group 2 patients during static contractions ($p < 0.05$). Torque values were not significantly different between groups during dynamic testing. Torque values were not significantly different between injured and uninjured legs. Center of pressure was directed more towards the healthy leg in patients who had been treated by a plaster cast compared to intramedullary nailing.

Discussion: Patients treated by intramedullary nailing had more anterior knee pain. We believe this was the reason for the lower torque values during dynamic knee extension. Patients treated by intramedullary nailing forced their injured leg more than patients treated by a plaster cast.

48. Helix wire fixation of dislocated surgical neck fractures of the humerus—preliminary results

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Operative treatment of dislocated fractures through the surgical neck of the humerus in elderly patients is controversial.

Closed reduction gives usually good preliminary results but secondary re-dislocation is common. Percutaneous pinning after closed reduction (Jaberg et al 1992, Ebraheim et al. 1996, Chen et al. 1998) is a demanding procedure with a high degree of local complications from the pin sites. Kristiansen (1987, 1989) presented a concept of closed reduction and external fixation but his results have been difficult to reproduce. Some authors claim that operative treatment of proximal humerus fractures in the elderly offers no advantage over nonsurgical treatment (Zyto et al. 1997, McQueen 1998). Laminger (1998) has presented a surgical procedure by fixation of the main fracture fragments with an elastic spiral wire (the Helix wire®) after closed reduction. The wire is inserted through a small lateral incision in the upper part of the diaphysis and passed intramedullary up through the fracture line and anchored in the head of the humerus. This gives a semiflexible fixation which is intended to prevent re-dislocation.

Materiel: The indication for operation was displaced, unstable, extra-articular, uni- or bifocal proximal fractures of the humerus. We have performed 33 Helix wire fixations on 32 patients during 1998 and January 1999. 25 women and 7 men with a median age of 78 (29–92) years were included. The operation was performed the 2nd (0–18) day after the injury.

Results: The median operation time was 30 (10–71) minutes. Early reoperations were performed in 7 cases. The radiological and preliminary clinical results have been followed until April 1999.

Conclusions: Our preliminary experience is that fixation of displaced surgical neck fractures by the Helix wire technique combined with two to three weeks in a Camp arm support is a fast and reliable method to prevent redislocation of the head of the humerus. A prospective study of the long-term clinical outcome compared to nonsurgical treatment is necessary for a conclusive evaluation of the method.

49. Is the predictive ability of a bone mineral measurement for fracture wearing off with time after measurement?

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Several prospective studies have shown that bone mineral density has a good predictive ability of fractures later in life. A meta-analysis shows that for a 1 SD decrease in BMD the relative risk was 1.6–2.6 depending on site and fracture. The question is whether the predictive ability decreases with time after measurement.

Method: 1,730 individuals were measured with the SPA technique during 1970–1976. The measurements were performed in the forearm, 1 cm and 6 cm from the joint space of the wrist. All individuals have been followed and all fractures have been registered as well as death and causes of

death. In the present study we have included those who have died in Malmö and have been living in Malmö (n = 1,328). The mean follow-up was 16.25 years with a maximum of 26 years. A Poisson model was used and especially the effect of interactions with time after measurement and age, absolute value of BMD was calculated.

Results: Interaction between BMD and other variables is presented in Table I.

Table 1

Interaction with	BMD 1 cm All fract.	BMD 6 cm All fract.	BMC 1 cm All fract.	BMC 6 cm All fract.
Time period	p<0.001	p<0.001	p<0.001	p<0.001
Age	p=0.13	p<0.01	p<0.30	p=0.23
Sex	p<0.30	p<0.30	p<0.30	p<0.30
Previous fractures	p<0.30	p<0.30	p<0.30	p<0.30
BMD	p<0.30	p<0.30	p<0.30	p<0.30

The relative risk for a 1SD decrease was at the time of measurement 1.66 and after 10 years 1.45, after 20 years 1.27 for fragility fractures. For hip fractures the corresponding figures were 1.85, 1.55 and 1.30, respectively. Thus, the predictive ability decreases slightly with increasing age. For hip fractures there was also a significant interaction with time after measurement, both for BMC 1 cm and 6 cm. In all models previous fracture was independently significant.

Conclusion: The predictive ability of a bone mineral measurement decreased slightly over time and this effect should be included in outcome models. A previous fracture was also predictor for new fractures, also after adjustment for bone mineral density (relative risk 1.9 for hip fractures).

50. Comparison of a fluid filled and a transducer-tipped catheter for measuring intramuscular pressure (IMP)

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The microcapillary infusion technique (Myopress® catheter) and a transducer-tipped catheter (Codman®) were compared for measuring intramuscular pressure.

Method: IMP was measured at rest and during exercise in nine volunteers in the tibialis anterior muscle, with both catheters inserted side by side. The pressure was measured in 18 different test situations including external compression of the muscle, with a plaster cast on the leg, and during venous stasis.

Results: IMP at rest was 5.7 mmHg (SD = 2.7) with the infusion technique, and it was 5.5 mmHg (SD 3.3) with the piezoelectric technique. It was 91 (SD 5.6) and 89 (SD 4.9) mmHg, respectively during external compression by an in-

flatable cuff. No signs of catheter occlusion were observed. No significant differences in IMP between the methods were discovered in any of 18 test situations. The correlation between IMP by the two methods was 0.998.

Conclusion : We conclude that both methods are suitable for measuring IMP at rest and during exercise. The transducer-tipped system was not prone to any hydrostatic artefacts, which all fluid filled systems are.

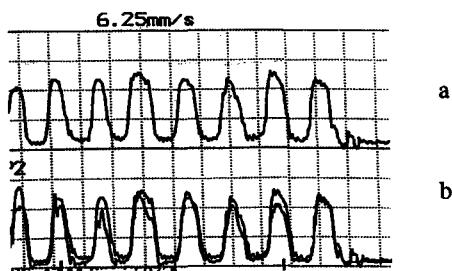


Figure. The pressure curves from the tibialis anterior muscle during external compression. a. IMP by the microcapillary infusion technique. b. IMP by the transducertipped catheter, with the infusion curve (above) superimposed.

Methods: Sure-Closure is a device for dermal traction. The device consists of two 7.5 cm long metal pins and a tensiometer that is graded from 1–3 N. Intramuscular pressures were measured with a Myopress catheter. Leg perfusion pressure was calculated as the difference between mean arterial blood pressure and IMP.

Results: IMP was 8.3 (SD = 1.7) mm Hg at rest. It increased to 14.6 (SD = 2.3) mm Hg when one N was applied. IMP increased to 21.4 (SD = 2.7) and 30.4 (SD = 3.2) mm Hg when 2 N and 3 N were applied, respectively. At maximal tension IMP increased to 36.8 (range 34 - 41) mm Hg, and local perfusion pressure decreased by 47% from 78 mm Hg to 41 mm Hg. The wound diastasis decreased from 12 cm to 6 cm intraoperatively when a tensile force of 3 N was used.

Conclusion: Dermatraction by Sure-Closure, with a tensile force of up to 3 N increases local IMP to levels that preserve an adequate limb perfusion pressure in normotensive patients. The maximum value of tensile force should be used only intraoperatively. Sure-Closure, is a suitable device to be used for up to 6–12 hours of dermatraction. However, for practical reasons it is less suitable for dermatraction during longer time periods.

51. Dermatraction by Sure-Closure, and intramuscular pressure (IMP) after fasciotomy for acute compartment syndrome

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Intramuscular pressure (IMP) was measured in 7 patients (mean age 36 years) during secondary wound closure by Sure-Closure, five days after they had been treated by fasciotomy for acute compartment syndrome. The aim was to study the relationship between intramuscular pressure and the tensile force applied by the traction device intra-operatively.

SPINE

52. Hydroxyapatite coating improves fixation of loaded pedicular screws—an experimental study in sheep

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Loosening of the pedicular screws is a frequent problem in spinal instrumentation, and may result in non-union due to lack of stability. Coating of pedicular screws with plasma-sprayed hydroxyl apatite (HA) has been used in a clinical pilot study where a significant increase of removal torques could be shown. Since pull-out has been described to be the failure mode of pedicular instrumentations, an experimental study was performed to investigate the effects of HA coating on the pull-out resistance.

Methods: 9 sheep were operated on with destabilizing laminectomies at two levels, L2–L3 and L4–L5. Two instrumentations with 4 pedicular screws in each were used for stabilization (Posterior Fixator MiniSystem, Nordopedic, Uppsala, Sweden). Standard screws (stainless steel), or the same type of screws coated with plasma-sprayed HA were used in either the upper or the lower instrumentation in a randomized fashion. 3 sheep were killed at 6 weeks and 4 sheep at 12 weeks. 2 sheep were euthanized early due to complications.

The pull-out resistance was recorded in two HA-coated and two standard screws in each animal. Axial pull-out was applied with 0.5 mm/sec using a servohydraulic testing machine (Mini-Bionix 858, MTS, MN, USA). Values given as mean $\pm$ SEM.

Results: In the 6 week group, the maximum pull-out load was 1547 ± 351 N for the standard screws and 2084 ± 163 N in the HA group (N.S.). In the 12 week group, the maximum pull-out load was 1363 ± 427 N in the standard group, and 2424 ± 234 N in the HA group ($p < 0.05$). 5 of the 28 screws were judged to be loose before the mechanical testing. All of these were standard screws, and the pull-out loads were below 510 N for these screws. None of the HA coated screws were considered loose, and the pull-out loads exceeded 1440 N. Thus, 5/14 screws were loose in the standard group, and 0/14 screws in the HA group ($p < 0.05$).

Conclusion: HA coating improves fixation of loaded pedicular screws, with increased pull-out resistance and reduced risk of loosening.

53. Removal of transpedicular spinal implants—is it worthwhile?

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With the increasing use of spinal instrumentation, removal

of spinal implants is not uncommon. We have in a retrospective study evaluated indications for removal of transpedicular spinal implants and results of the procedure.

Methods: All patients who underwent removal of spinal instruments between 1992 and 1998 were identified. The indication for instrumentation was categorized into either fracture or degenerative disease.

Time between application and removal of the device was registered. The indications for plate removal were grouped into 5 different categories: soft tissue problems; hardware-failure; low patient age; attempt at pain relief and further treatment/evaluation of fractures. In patients where the implantation was removed with the aim to obtain pain reduction, the surgical results were evaluated using a 5-grade scale.

Results: 61 patients, 37 men and 24 women had removal of transpedicular implants. The indication for spinal instrumentation was fracture in 33 patients and degenerative disease in 28. The implants were removed after mean 28 (7–66) months. Two thirds of the patients had their spinal implants removed in order to obtain pain relief and the other indications for plate removal were equally distributed.

Pain relief after plate removal was related to diagnosis: in patients with fractures pain relief was common, while in patients with a “degenerative” diagnosis the majority had none or only minor effect of the procedure.

Conclusions: In patients with back pain after a surgically treated spinal fracture, implant removal seems worthwhile, whereas for patients with a “degenerative” disease, removal only rarely yields lasting pain relief.

54. Prediction of outcome in whiplash associated disorders (WAD) using multidimensional pain inventory (MPI)

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The Multidimensional Pain Inventory (MPI) is a widely used instrument to assess cognitive, emotional and behavioural aspects of clinical states of pain. Our aim was to find out if MPI could predict the prognosis in patients with WAD.

Methods: 164 patients who fulfilled specific criteria entered the study. They answered the MPI questionnaire within 4 weeks after the accident. One year later they answered the questionnaire on the consequences of the accident. The main outcome was determined by the question “Do you have residual neck pain which you attribute to your accident?”

Results: The follow-up was completed by 150 (91%) patients. 31 (21%) patients were symptom free. The following subset of the MPI variables differed significantly between the group with residual symptoms and the group with no symptoms; pain severity, pain interferens, life control, affect-

tive distress, support, punishing responses. In a regression analysis MPI variables were found to correctly classify 92% of the patients reporting pain one year after the accident. On the basis of the answers of the MPI, 3 clusters were identified as in other studies; interpersonally distressed, adaptive copers and dysfunctional. Patients classified as interpersonally distressed or dysfunctional reported pain more frequently one year after the accident than those classified as adaptive copers.

	Pain	No pain
Cluster 1 (Interpersonally distressed)	18	0
Cluster 2 (Adaptive Coper)	36	19
Cluster 3 (Dysfunctional)	31	0

Conclusion: MPI may be used at an early stage to identify patients who may develop chronic neck pain following traffic accident.

55. Reduced pain after surgery for cervical disc protrusion/stenosis—a controlled 2-year clinical follow-up with Sickness Impact Profile and Visual Analogue Scales

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The objective of the study was to follow the clinical outcome after surgery for cervical rhizopathy caused by disc protrusion and/or stenosis.

Material and methods: 43 patients (24 male and 19 female, 30–66 years of age) all awaiting surgery were studied prospectively. A control group of 41 conservatively treated patients was chosen, matched for gender and age, due to the reluctance among patients with longstanding pain to accept randomization between surgical and conservative treatment. The patients in the control group all had long-standing pain radiating from the neck into one or both of the arms and where a clinical suspicion of cervical radiculopathy had led to a MRI. All patients rated their quality of life (Sickness Impact Profile, SIP) and pain (VAS) and were clinically examined by unbiased observers day one (preoperatively) and 3, 9 and 24 months later. 29 patients were followed at the Dept. of Rehabilitation Medicine and 55 patients at the National Social Insurance Hospital.

Results: The VAS marked by the patients which had been operated indicated a statistically significant pain reduction postoperatively, from mean 6.6 ± 2.5 in the neck and 6.4 ± 2.7 in the arm preoperatively to 4.8 ± 2.4 respectively 4.6 ± 2.3 three months postoperatively and 5.4 ± 2.8 / 5.2 ± 2.9 after 24 months. No corresponding change in pain intensity could be

shown in the control group. Among the operated patients, SIP showed a temporary improvement of the total index (at 9 months), psychosocial index and for the independent factors sleep and rest at 3 respectively 9 months as well as home management (3 m.). The only factor that remained improved after 24 months was mobility. The control group's SIP indicated a temporary improvement of the factors sleep and rest at 9 months. No other changes in their SIP response was observed. Among the operated patients followed at the Dept. Rehabilitation Medicine, there was a statistically significant improvement of SIP after 24 months for the total and physical indexes, as well as for the factors recreation/pastimes and sleep/rest. The group of operated patients followed at the National Social Insurance Hospital showed only temporary improvement of their SIP. This group of patients had a higher proportion of associated diagnoses, e. g. whiplash associated disorder (WAD). Clinical examination 24 months after surgery showed improved sensory function and reduction of reflex disturbances.

Conclusion: Surgically treated patients experienced a statistically significant pain reduction in the neck and in the arm at 3 respectively 24 months after surgery. A sustained improvement in the quality of life measured by SIP was observed among the operated patients that were directly referred to us by the local hospitals.

56. Clinical experience with a new implant system (CerviFix.) enabling the use of both hooks and screws for posterior stabilisation of the cervical spine

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Instability of the cervical spine whether traumatic, degenerative or metastatic may need internal fixation. Although several methods are available for posterior stabilisation of the occipito-cervical junction and the cervical and upper thoracic spine, few implant systems allow optimal screw insertion and the use of sublaminae hooks. The aim was to evaluate safety and efficacy of a new implant system for posterior stabilisation of the cervical and upper thoracic spine.

Patients and methods: The series consisted of 25 consecutive patients (male/female 16/9) operated between August 1996 and July 1998. Indications for surgery were fracture dislocation (13 patients), spinal stenosis with cervical myelopathy (2 patients), osteomyelitis of the spine (1 patient) and metastasis (9 patients). Combined anterior and posterior stabilisation was performed in three patients. Occipito-cervical junction was stabilised in three patients and a cervicothoracic fixation with a long construct connecting CerviFix, with a thoracolumbar implant (Universal Spine System,) was used in two patients. In 16 cases the lower cervical and upper thoracic spine was included in the stabilisation. The patients were clinically and radiographically evaluated.

Results: Three patients; a patient with cervical spondylitis, a patient with C6/C7 fracture and pelvospondylitis and a

patient with cervical metastasis died 4 days to 1.5 months after surgery due to gastrointestinal bleeding and/or heart failure or myocardial infarction.

The remaining 12 patients with fracture-dislocation were followed 8-16 months. At that time the fusion appeared solid and no signs of implant failure were seen. The two patients with degenerative diseases and myelopathy were fused with no signs of implant failure 14 to 18 months after surgery. Eight of the nine patients with cervical metastases were followed 1.5 to 9 months (mean 4) and during the follow-up time no radiological or clinical sign of implant failure were seen.

Conclusion: The CerviFix implant system seems to be safe and efficient. It is easy to handle constructs with solely screw fixation and hook /screw constructs with few fixation points. Several claw constructs was time consuming mainly due to the lack of an appropriate hook holder.

57. A prospective randomised study of the outcome of the Cloward procedure and the Brantigan Cage in the cervical spine

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The purpose of the study was to determine whether the use of a carbon fibre intervertebral cage, the Brantigan Cage (BC) results in an improved outcome compared to the traditional Cloward procedure (CP) in patients with neck pain and radiculopathy of degenerative origin.

Patients and methods: 80 consecutive patients were randomised to surgical decompression and autograft fusion

with the BC or the CP. The inclusion criteria were > 6 months duration of neck pain and radiculopathy of degenerative origin, with compatible MRI and clinical findings. Exclusion criteria were myelopathy, psychiatric disturbance, drug abuse, and previous spine surgery. Pain was quantified by VAS, and function by the Cervical Spine Functional Index (CSFI, VAS: Average of 14 activities) as well as by the Oswestry neck score, before treatment and at one year post-operatively.

Results: 38 patients were randomised to the CP and 42 to the BC. All 80 patients were followed for 1 year. The results were as follows:

	CLOWARD		BRANTIGAN CAGE	
	Preop	1 year	Preop	1 year
Pain				
right now (0-100)	67	29	66	39
worst last week (0-100)	78	39	78	49
CSFI (0-100)	57	33	53	38
Oswestry score (0-100)	36	26	34	27

The improvements in pain and function with both methods, measured by all outcome variables, were all significant ($p < 0.001$). The improvements of all scores were more pronounced with the CP than with the BC procedure, although not statistically significant.

Conclusions: The use of the BC and the CP in the degenerative cervical spine both result in a significant improvement of pain and functional disability. No improvement in outcome with the carbon fibre cage compared to the traditional Cloward procedure could be demonstrated. Thus, despite the potential advantages with the BC, i.e. less donor site morbidity, prevention of graft collapse with foraminal narrowing, and restoration of physiologic lordosis, the outcome of the two methods is similar.

SHOULDER

58. Arthroscopic lavage speeds up reduction of effusion in the glenohumeral joint after primary anterior shoulder dislocation—a controlled randomized ultrasound study

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Recent studies have shown that arthroscopic lavage of the glenohumeral joint within 10 days following a primary anterior shoulder dislocation significantly lowers the recurrence rate when compared with a non-operative regime. The purpose with this study was to find out whether the lavage causes a faster reduction of the joint effusion when compared with the speed of reduction seen after traditional non-operative treatment.

Patients and methods: Using ultrasound (US), we assessed the hemarthrosis in the glenohumeral joint weekly in 16 consecutive patients (17–31 years) after traumatic primary anterior shoulder dislocation. The patients were randomized into two groups for treatment with either arthroscopic lavage or a non-operative regime. Except for the lavage both groups followed an identical rehabilitation programme including free mobilization. Transversal dorsal US of the glenohumeral joint was performed, in which the joint effusion was assessed as the distance between the humeral head and the glenoid.

Results: Prior to the lavage both groups had a similar amount of excessive joint effusion. The effusion declined to a steady state level within 3–7 weeks.

The arthroscopic lavage did not preserve a normalized joint as shown by fluid that had accumulated on the first US after the lavage. Still, the speed of reduction was faster (33%) in the group treated with lavage compared with patients treated non-operatively ($p = 0.02$).

Conclusion: These results indicate that one possible reason for the effect of arthroscopic lavage on the recurrence rate after shoulder dislocation might be a faster reduction of the amount of joint effusion. This increased speed of reduction might indirectly facilitate healing of the soft tissue injury due to the joint and capsule being less distended.

59. A clinical and radiographic comparison of absorbable and non-absorbable suture anchors in open shoulder stabilization

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The aim of this study was to compare the clinical and radiographic results using either absorbable or non-absorbable implants in patients with recurrent unidirectional, post-traumatic shoulder dislocations. All patients had a Bankart lesion.

Patients and methods: 33 consecutive patients, 27 male and 6 female, were operated on by one surgeon. Group A comprised 15 shoulders which underwent a standardized open Bankart reconstruction using absorbable 3.7 mm TAG[®] suture anchors. Group B comprised 18 shoulders (9 dominant, 9 non-dominant) which underwent the same procedure using non-absorbable 3.7 mm TAG[®] suture anchors. The median number of dislocations before the reconstruction was 6 (2–45) in Group A and 8 (3–60) in Group B (n.s.). The median age of the patients was 28 (16–45) years in Group A and 25 (16–35) years in Group B (n.s.). Two patients in Group B were lost to follow-up, one died and the other was not possible to locate. The follow-up examination was performed by independent observers after a median of 31 (25–48) months in Group A and 26 (22–72) months in Group B (n.s.). Contralateral, healthy shoulders ($n = 26$) from the same cohort were used as a control for the ROM and strength measurements. An independent radiologist without any knowledge of the surgical procedure evaluated all the radiographs.

Results: There was one re-dislocation in each group. In Group B one patient had signs of subluxation when the apprehension test was performed. During the follow-up period 2 patients in Group A were re-operated. 1 underwent an arthroscopy and forceful manipulation due to severe restriction in ROM and 1 a subsequent arthroscopic upper labrum fixation due to persistent pain in external rotation. In Group B, 1 patient was re-operated on with the same technique 2.5 years after the first reconstruction due to recurrent instability. Furthermore 1 patient in Group B suffered a septic arthritis and was therefore excluded from the radiographic evaluation. In Group A, the Rowe and Constant scores were 89 (69–98) and 89 (76–99) points, respectively. The corresponding values in Group B were 87 (44–98) (n.s.) and 90 (71–100) points (n.s.). The strength measurements revealed 8.1 (3.8–12.3) kg in 90° abduction in Group A and 10.0 (6.7–12.0) kg in Group B. The value for the controls was 10.2 (4.5–13.2) kg; (n.s. A and B v controls). The external rotation in abduction was 70° (40–90) in Group A and 80° (40–100) in Group B. The controls had 90° (80–120); ($p < 0.001$ (A v controls), $p < 0.05$ (A v B) and $p < 0.001$ (B v controls)). The radiographs revealed that 9/15 (60%) in Group A and 10/15 (66%) in Group B had visible drill-holes or cystic formations in conjunction with the drill-holes (n.s). Furthermore, 11/15 (73%) in Group A and 10/15 (66%) in Group B showed signs of minor degeneration (n.s.).

Conclusions: In terms of the stability as well as the clinical results no differences were found between the study groups. Both groups revealed a restriction in external rotation as compared with healthy shoulders from the same cohort. On the radiographs visible drill-holes or cystic formations in conjunction with the drill-holes were seen in equal frequency, regardless of whether absorbable or non-absorbable suture anchors were used.

KNEE AND ANKLE LIGAMENTS

60. Anatomical reconstruction versus tenodesis for the treatment of chronic antero-lateral instability of the ankle joint—a 2–10-year follow-up—a multi-center study

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The objective of this study was to compare the results of anatomical reconstructions with tenodeses for chronic antero-lateral ankle instability with a 2–10-year follow-up.

Patients and methods: At five centers, a total of 324 ankle ligament reconstructions were performed. 152 patients underwent anatomical reconstruction and 172 underwent tenodesis. The inclusion criteria in this retrospective study were: 1) age at operation between 14 and 60 years; 2) no history of previous fracture of the affected ankle; 3) no prior surgery of the affected ankle; and 4) no generalized neuromuscular disorder. At the follow-up, two-to-ten years after the operation, patient characteristics and the preinjury Tegner activity level were recorded. The review protocol consisted of the administration of postoperative complications, the Tegner activity level, and the Karlsson and Sefton scores. At the physical examination, range of motion (ROM), swelling, pain on palpation and the anterior drawer sign were determined. Standard and stress radiographs were taken. 97 patients were lost to follow-up and 11 patients did not meet the inclusion criteria. Of the 216 patients included, 106 underwent anatomical reconstruction and 110 underwent tenodesis.

Results: A significantly higher number of reoperations were performed in the tenodesis group ($p = 0.008$). At the physical examination 36 patients in the tenodesis group had a restricted range of ankle motion compared with 11 in the anatomical reconstruction group ($p=0.009$). Significantly more patients in the tenodesis group demonstrated medially located osteophytes as seen on standard radiographs. When it came to the stress radiographic examination, the mean talar tilt ($p=0.001$) and anterior talar translation ($p<0.001$) were significantly higher in the tenodesis group. There was no difference in the mean Karlsson score between the groups, but significantly more patients in the anatomical reconstruction group had an excellent result according to the Sefton score ($p=0.011$).

Conclusion: Unlike anatomical reconstructions, tenodeses do not restore the isometricity of the ankle ligaments. This results in a restricted range of ankle motion, less stability, a higher number of reoperations and less satisfactory overall results for the tenodeses.

61. Hip-, knee- and ankle-joint load during squatting exercise

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The squatting exercise, performing a knee bend while carrying a weight on the shoulders, is an often used and important method for lower limb muscle training to maximize strength but also during rehabilitation training. Little is however known about the loads produced on the hip, knee and ankle joints during this type of exercise.

Material and methods: 8 young national class olympic weight lifters performed squatting exercise to four different knee flexion angles; 45°, 90°, thighs parallel to the floor and deepest possible squat. They held a bar-bell across their shoulders with a weight of 65% of their one-repetition maximum. The loading moments of force about the hip, knee and ankle joints were calculated using a semidynamic biomechanical method with a video system for motion recording and force data from a Kistler force plate.

Results: The hip joint load increased significantly between the 90° and the parallel squat ($p < 0.001$) but there was no significant difference between the parallel and the deep squat. For the knee joint there was no significant difference between the 45°, 90° and parallel squats, but there was great difference between these three and the deep squat ($p < 0.001$). The loading moment on the ankle increased significantly from the 90° squat to the parallel ($p < 0.001$), and between the parallel and deep squats ($p < 0.001$). The 45° squat produced an ankle joint load in level with the parallel squat and significantly higher than for the 90° squat ($p < 0.001$).

Discussion: This study shows that the 90° squatting depth is optimal to reduce the joint loads during squatting training, which is of importance in a rehabilitation situation. According to our previous studies, the 90° squat still creates a good muscular training effect.

62. Can local anesthesia be recommended for routine use in elective knee arthroscopy?—a comparison between local, spinal and general anesthesia

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Local anesthesia (LA) for outpatient knee arthroscopy is not used as a standard procedure at most hospitals. To evaluate the local anesthesia technique for knee arthroscopy on medically healthy patients with a minimum range of motion 0–90° this study compared three anesthesia techniques. 400 pa-

tients were randomized to either local (n = 200), general (n = 100) or spinal (n = 100) anesthesia.

Evaluated outcomes included the patient's subjective view of the procedure, nausea and pain at rest and during active movement. All parameters were recorded peri- and postoperatively.

In addition the performing surgeon's opinion of the degree of patient pain and the technical difficulty of the procedure were noted. 342 patients completed the study. In the group receiving local anesthesia (N=180), the median VAS pain score during surgery was low, 6 mm (SD 23.2, range 0–100 mm).

We found that elective knee arthroscopy can be performed under local anesthesia in the majority of patients. From the surgeon's point of view, technical problems are to be expected in 5% of the LA patients, and if excess synovitis is present, as in 3 % of our LA patients, an alternative anesthesia method should be considered. Thus, this study shows that elective knee arthroscopy can be performed under local anesthesia in 92 % of the patients from a technical point of view.

If the patients that do not want local anesthesia, and the patients with excess knee joint synovitis are excluded, knee arthroscopies can be performed as safely and effectively under local anesthesia, as in any other form of anesthesia. Consequently, local anesthesia can be recommended as the standard procedure for outpatient knee arthroscopy.

63. Analysis of subjective, objective and functional examination tests after anterior cruciate ligament reconstruction

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The aim of this study was to assess outcome and function after arthroscopic anterior cruciate ligament (ACL) reconstruction using bone-patellar tendon-bone autografts and interference screw fixation. Furthermore, the aim was to evaluate the subjective and objective results and to analyze the correlations between the evaluation systems that were used.

Patients and methods: 527 patients (178 female and 349 male) with a unilateral ACL rupture were included in the study. The follow-up examination was performed by independent observers a median of 38 (21–68) months after the index operation.

Results: At the follow-up, the Lysholm score was 86 (14–100) points, the Lysholm instability sub-score was 22 (0–25) points and the Lysholm pain sub-score was 19 (0–25) points. The Tegner activity level was 6 (1–10). The one-leg-hop quotient was 91 (0–167)% of the non-injured knee. The difference in the anterior side-to-side laxity as measured with the KT-1000 arthrometer at 89 N was 1.5 (minus 5–13) mm and the total KT-1000 side-to-side laxity difference at 89 N

was 2 (minus 7–11) mm. Using the IKDC evaluation system, 177 (33.6%) patients were classified as normal (Group A), 211 (40%) as nearly normal (Group B), 109 (20.7%) as abnormal (Group C) and 30 (5.7%) as severely abnormal (Group D).

The highest correlation coefficients were recorded between the IKDC evaluation system and the Lysholm score (Rho = 0.66), the patients' subjective evaluation (Rho = 0.53), the Tegner activity level (Rho = 0.34), all the laxity tests (Rho $\geq$ 0.34) and the one-leg-hop test (Rho = 0.28). The resumption of sports activities and work as evaluated by the Tegner activity level correlated with the patients' subjective evaluation (Rho = 0.34) but did not correlate with the laxity tests, i.e. the manual Lachman test (Rho = - 0.06) and the total or anterior KT-1000 tests (Rho = - 0.06). None of the laxity tests correlated with the functional tests or the patients' subjective evaluation. However, the correlation between the laxity tests, manual Lachman test and total KT-1000 side-to-side difference was good (Rho = 0.44).

Conclusion: We conclude that the IKDC evaluation system is a reliable and useful tool for evaluating the post-operative outcome after ACL reconstruction. Furthermore, we conclude that the laxity tests correlated with neither the subjective nor the objective function.

64. Goretex anterior cruciate prosthesis, a radiological, clinical and arthrometrical evaluation

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We report preliminary results on a study of 22 patients (12 men), reconstructed in our clinic through the years 1985 to 1987, with Goretex anterior cruciate ligament prosthesis. This artificial cruciate ligament prosthesis gave good stability to the operated knees but were abandoned due to unacceptable problems with aseptic effusions and pain. During the past 13 years 8 patients have been reoperated with explantation of the cruciate ligament prosthesis and 7 of them has had a new reconstruction performed with autogenous grafts. Of these 8 patients we have reoperated 5 due to effusion / pain and 3 because of traumatic rupture of the Goretex ligament. Another 4 patients have had complaints of pain and swelling but not to the extent as to go through a reoperation.

Other authors have reported osteolytic lesions, seen on plain radiographs or MRT, surrounding Goretex ligament. When we have performed the reoperation our impression have been that there has been no bone ingrowth in the tibial tunnel, the ligament have been surrounded by a fibrous tissue and the bone tunnel have sometimes seemed widened. Because of this we have decided to perform a follow up of all the patients operated with the Goretex prosthesis at our clinic.

Material and methods: All patients are evaluated with: CT measurements of sagittal and coronar tibial tunnel diameters. K-1000 arthrometry at 89 N and maximal manual displacement. Lachman and pivot shift tests. IKDC score. Lysholm and Tegner scores. Painscore with VAS scale. All the patient had the tibial tunnel drilled with a 7.9 mm drill at the Goretex reconstruction.

Results: Patient #1: Reoperated with a Kennedy LAD reconstruction after 2 years because of painful effusions and instability, the Goretex ligament was not ruptured. Lysholm: 80, IKDC: abnormal, KT 1000: ≥ 3 mm, Tegner: 5, Lachman / pivot shift tests: positive. No CT measurements because pt. is pregnant. # 2: No reoperation. Recurrent effusions, no in-stability. Lysholm: 87, IKDC: abnormal, KT 1000: < 3 mm, Tegner: 3, Lachman / pivot shift: neg. CT: sclerotic margins in the tunnel, diameter: 95 x 80 mm (sag. x cor.). # 3: Reoperated with Kennedy LAD because of graft rupture after 1.5 years. New tibial tunnel drilled at reop. converging with the old Goretex tunnel proximally. Lysholm: 92, IKDC: abnormal, KT 1000: > 3 mm, Tegner: 4, Lachman / pivot shift: pos. CT: sclerotic margins in LAD tunnel, diameter: 70 x 70 mm. Lytic margins in the Goretex tunnel, diameter: 80 x 80. Lytic margins in the combined part of the tunnel, diameter: 110 x 140 mm. # 4: No re-operation. Lysholm 100, IKDC: normal, KT 1000: < 3 mm, Tegner 3, Lachman / pivot shift: neg. CT: Lytic margins in the tunnel, diameter: 230 x 220 mm. # 5: Reop with Kennedy LAD after 2 years because of rupture, same tibial tunnel used after thorough curettage. Lysholm 100, IKDC: normal, KT 1000 < 3 mm, Tegner 4, Lachman / pivot shift: neg. CT: sclerotic margins, diameter: 120 x 110 mm. # 6: No reoperation. Lysholm: 97, IKDC: abnormal, KT 1000: > 3 mm, Tegner: 5, Lachman / pivot shift: pos. CT measurements not available yet. # 7: Not reoperated at the beginning of this study. Lysholm: 65, IKDC: gravely abnormal, KT 1000: > 3 mm, Tegner: 5, Lachman / pivot shift: pos. CT: lytic margins, diameter: 210 x 180 mm. Is now operated with explantation of the Goretex graft and autogenous bonegrafting into the tunnel.

Discussion: The Goretex graft has been showed to evoke reactions (sterile effusions) in some patients, it also seems to sometimes induce lytic bone lesions. Our preliminary results show that these can be asymptomatic and also not found in clinical examination or at arthroscopy (pt. # 7). This may pose a problem at secondary surgery because of osteoarthritis (eg. high tibia osteotomy, uni / total knee arthroplasty), a problem with higher incidence in this group than the normal population. Our recommendation is to perform regular a follow up including CT scans, in at least, all patients operated with an artificial graft. These examinations should go on until we know the natural course of an artificial graft implanted into the knee of these young individuals

65. A comparison of results after anterior cruciate ligament reconstruction in patients with a high or a low activity level

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The aim of this study was to compare the subjective and objective results after Anterior Cruciate Ligament (ACL) reconstruction in individuals with either a high or a low activity level.

Patients and methods: From our database of 865 patients who had undergone ACL reconstruction, we selected two subgroups of individuals. One group with a low activity level (recreational athletes, Group A; n=47; Tegner activity level 2–5) and one group with a high activity level (elite athletes, Group B; n=209; Tegner activity level 9–10). The groups were matched in terms of surgical technique (bone-patellar tendon-bone) and uninjured contralateral knee. The follow-up examination was performed by independent observers a median of 32 (23–52) months after the reconstruction in both groups. The follow-up was based on the Lysholm score, Tegner activity level, IKDC classification, evaluation of the total side-to-side difference using the KT-1000 laxity meter, knee-walking ability, measurements of range of motion (ROM) and the one-leg-hop test. Furthermore, the patients' subjective evaluation and expectations in terms of the final outcome of the reconstruction were registered.

Results: The Lysholm score at follow-up was 86 (37–100) points in Group A, as compared with 90 (34–100) points in Group B (n.s.). In Group A, the Tegner activity level before the injury was 5 (2–5), as compared with 4 (1–6) at follow-up ($p = 0.0001$). The desired level was 5 (2–6). In Group B, the Tegner activity level before the injury was 9 (9–10), as compared with 7 (2–10) at follow-up ($p = 0.0001$). The desired level was 9 (9–10). The KT-1000 measurement showed a side-to-side difference of 2.0 (–2.5–8.5) mm in Group A and 1.5 (–7.0–11) mm in Group B (n.s.). Using the IKDC classification, there was no difference between the groups. Nor was there any difference between the groups in terms of the patients' subjective evaluation and expectations, or their one-leg-hop and knee-walking ability.

Conclusion: In this study, we were not able to demonstrate any difference in either the subjective or the objective results after ACL reconstruction between individuals with a preinjury high or a low activity level using the patellar tendon autograft. We therefore conclude that recreational athletes who have ACL insufficiency and suffer from repeated giving-way symptoms should also be offered ACL reconstruction.

66. Osteoarthritis after surgical or conservative treatment of the acutely torn anterior cruciate ligament—a randomized study with 15 years follow-up

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Material and Methods: Between 1980 and 1983, 105 patients with an acute anterior cruciate ligament injury were randomized to conservative treatment ($n = 67$) or surgical treatment with augmented primary ACL suture ($n = 38$). All patients underwent diagnostic arthroscopy, which revealed a total rupture of the ACL. The patients were 14–30 year old at the time of injury, with an average age of 21.8 years. The average follow up time was 15.1 years.

Results: Of the initially conservatively treated patients, 21 (33%) underwent secondary anterior cruciate ligament reconstruction due to instability of the knee, and 22 (35%) patients underwent meniscectomy (totally 35 meniscectomies). Only 3 (9%) of the primarily surgically treated patients underwent meniscectomy (totally 5 meniscectomies) during the follow-up period. Tegner Activity Level, Lysholm score or KOOS (Knee Osteoarthritis Outcome Score) did not differ between the two groups. 96 patients were examined radiographically. The degree of osteoarthritis was classified according to Fairbank and Ahlbäck. 17 (50%) of the 34 surgically treated patients, showed significant changes due to osteoarthritis, and 20 (48%) of the 42 patients in the conservatively treated group, showed similar changes (n.s.).

Summary: 1/3 of the initially conservatively treated patients underwent later ACL reconstruction due to instability symptoms of the knee. The conservatively treated patients had significantly more meniscal injuries during the 15 years follow-up period. No difference in level of activity, patient estimation of residual symptoms or osteoarthritis was detected. We could not find any evidence that an ACL reconstruction would decrease the risk for late osteoarthritis.

pose of this study was to compare early range of motion with immobilization, which was the former standard postoperative routine. The principal evaluation variable was sagittal knee laxity. The sample size analysis was based on a wish to detect a side to side difference between groups of 1.5 mm with 90% power.

Patients and methods: Between May 1995 and September 1996, 50 patients, undergoing an ACL-reconstruction with a bone-patellar tendon-bone graft and interference screw fixation, were postoperatively randomly allocated to either a plaster cast for 5 weeks (Group 1) or a brace for 6 weeks and range of motion exercises from day 7 (Group 2). Activity level, age and sex distribution was similar for the two groups. ROM was monitored each week for 6 months, isokinetic strength was measured at 4, 6, 12 and 24 months, sagittal stability using the Stryker Laxity tester was measured at 6, 12 and 24 months, and Lysholm score together with Tegner activity level were established at 12 and 24 months.

Results: The commencement of ROM exercises were postponed 4 weeks for Group 1 compared to Group 2, but progressed subsequently with equal speed. At 12 months there were 3 patients with an extension lag $\geq 5^\circ$ in Group 1 and 1 patient in Group 2. There were 9 patients in Group 1 and 5 in Group 2 with a flexion deficit of $\geq 5^\circ$ compared to the non-injured side. These results were not significantly different. There was no difference between the groups regarding muscle-strength (absolute values and side to side differences) at 4, 6, 12 and 24 months. There was no difference in Tegner activity level or Lysholm score at 12 and 24 months. Further, there was no statistically significant difference in side to side knee laxity at 12 and 24 months, 0.6 ± 1.7 mm for Group 1 and 1.5 ± 1.7 mm for Group 2.

Discussion: The overall stability result for both groups fares well in a comparison with previously published studies. Early range of motion seems to give satisfactory stability. Surprisingly, no major disadvantage with plaster casting was detected in a 2 year follow-up time. Possible differences regarding adverse cartilage effects may be detected in a future long term follow-up. The authors now routinely use early ROM.

67. Early range of motion vs. immobilization after ACL reconstruction, a prospective randomized comparison with a 2 years follow-up

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Early motion exercises after ACL reconstruction are almost universally employed today. Several uncontrolled reports have indicated a favorable outcome following such a regimen, but no prospective randomized comparison with previous routines has to our knowledge been published. The pur-

68. Effect of preconditioning the mid-third patellar tendon autografts in arthroscopic anterior cruciate ligament reconstruction

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The aim of this study was to evaluate the effect of preconditioning patellar tendon autografts before implantation and fixation during anterior cruciate ligament (ACL) reconstruction.

Patients and methods: This is a prospective randomised study including 53 patients with ACL rupture, who were op-

erated on by one surgeon. One group had their patellar tendon autograft preconditioned by stretching (Group P). A constant load of 40 Newtons was put on the graft during ten minutes immediately prior to the implantation. The other group underwent no preconditioning before implantation of the graft (Group NP). Group P consisted of 25 patients, 15 males and 10 females with an age of 27 (16–52) years. Group NP consisted of 28 patients, 19 males and 9 females with an age of 28 (14–50) years (n.s.). The reconstruction was performed 11 (2–184) months after the rupture in Group P and after 19 (3–192) months in Group NP. The follow-up examination was performed by independent observers after 26 (23–29) months in Group P and after 25 (23–30) months in Group NP (n.s.).

Results: The KT-1000 test revealed a total side-to-side difference of 2.5 (–1.5–8.5) mm in Group P and 3.0 (–7–6.5) mm in Group NP (n.s.). The Lysholm score was 86 (47–100) points in Group P and 94 (44–100) points in Group NP (n.s.). The Tegner activity level in Group P was 6 (2–9) and in Group NP 7 (3–9) (n.s.). The one-leg-hop test in Group P was 95% (68–132) and in group NP 93% (53–126) (n.s.). The IKDC classification revealed no significant difference between the study groups. No difference in the knee walking ability was demonstrated. Patient evaluation graded as excellent/good/fair and poor was 8/11/5/1 in Group P and 9/13/3/0 in Group NP (n.s.).

Conclusion: Patients who underwent ACL reconstruction using a preconditioned patellar tendon autograft, did not have any advantages, in terms of stability or clinical outcome at the two year follow-up. For this reason, we have discontinued to precondition the patellar tendon autografts in patients undergoing ACL reconstruction.

69. Traditional or subcutaneous patellar tendon harvest?—a prospective study of donor-site problems after anterior cruciate ligament reconstruction

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The aim of the study was to compare the results after anterior cruciate ligament (ACL) reconstruction using either the traditional one-incision or the subcutaneous two-incision technique to harvest the central third of the patellar tendon. Special attention was paid to the disturbance of anterior knee sensitivity and the knee-walking ability.

Patients and methods: A consecutive series of 124 patients with unilateral ACL rupture and no previous incisions in the anterior knee region were included in the study. The patients underwent reconstruction by one surgeon using the arthroscopic transtibial technique and interference screw fixation. The traditional graft harvesting technique was used in 66 patients (Group T) and the subcutaneous technique in

58 patients (Group S). Pre-operatively the groups were comparable in terms of gender, age, time period between injury and reconstruction, as well as subjective and objective clinical assessments. The pre- and post-operative assessments were made by independent observers. All patients were rehabilitated according to an accelerated protocol and no post-operative brace was used. In Group T 55/58 patients and in Group S 64/66 patients returned to the follow-up control after 24 (22–36) and 25 (23–30) months respectively.

Results: The Lysholm score was 86 (22–100) points in Group T and 91 (47–100) points in Group S (n.s.). The Tegner activity level was 6 (1–9) in Group T and 7 (3–9) in Group S ($p = 0.03$). The KT-1000 total side-to-side difference was 2.5 (–7–11) mm in Group T and 3 (–2.5–11.5) mm in Group S (n.s.). In terms of the IKDC classification and the one-leg-hop test no significant differences were found. The disturbance of anterior knee sensitivity was 24 (0–200) cm² in Group T and 0 (0–285) cm² in Group S ($p = 0.02$). In Group T 36/55 (65%) and in Group S 30/64 (47%) of the patients subjectively classified the knee walking test as difficult or impossible to perform (n.s. $p = 0.04$).

Conclusions: The subcutaneous graft harvesting technique rendered less disturbance of anterior knee sensitivity and less discomfort during knee walking than the traditional technique. Otherwise the subjective and objective results were comparable.

70. A radiographic and histologic evaluation of the patellar tendon after harvesting its central third

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The aim of the study was to evaluate the radiographic and histologic appearance of the patellar tendon after its central third had been harvested as a graft for anterior cruciate ligament reconstruction.

Patients and methods: Nineteen consecutive patients were included in the study. The age of the patients at the index operation was 27 (16–43) years. Magnetic Resonance Imaging (MRI) was performed 6 (5–10) weeks, 6 (6–8) months and 27 (24–29) months after the index operation. Ultrasonography examinations and obtaining of biopsies were performed 27 (24–29) months after the index operation. Normal control tissue from the patellar tendon of 11 age matched patients, was obtained, at the time of an anterior cruciate ligament reconstruction.

Results: At the follow-up the Tegner activity level, Lysholm score, International Knee Documentation Committee (IKDC) evaluation system and one-leg-hop test revealed a significant improvement as compared with the preoperative

values. The serial MRI evaluations revealed that the donor-site gap (area corresponding to non-tendinous-like tissue signal) decreased with time during the study period. Both the thickness and the width were significantly increased ($p < 0.01$) compared with the non-harvested contralateral tendon regardless of when the MRI were done. Ultrasonography examinations at 27 months revealed that the thickness of the patellar tendon at the donor-site was significantly ($p < 0.001$) increased as compared with the non-harvested contralateral patellar tendon. Histologic evaluation of the central part of the tendon, and the tissue in the peripheral part of the patellar tendon at the donor-site showed significantly increased ($p < 0.01$) cellularity and vascularity, as compared with normal control tendon. Both the cellularity ($p < 0.01$) and vascularity ($p < 0.001$) were significantly increased in the biopsies obtained from the central repair tissue, as compared with the peripheral part of the donor-site. No increase was registered in the content of glycosaminoglycans (GAGs) or the amount of collagen type III. The absence of GAGs in the biopsies of the present study suggests, that other factors than retained water contributed to the increased cross-sectional area of the patellar tendon. Our inability to demonstrate increased amounts of collagen type III, in the central as well as the peripheral part of the patellar tendon indicates that there was no early collagen synthesis present 27 months after the harvest procedure.

Conclusion: Serial Magnetic Resonance Imaging revealed that the donor-site gap filled with tendinous-like tissue with time. The patellar tendon, 27 months after the harvesting procedure, showed significant radiographic abnormalities, i.e. increased thickness and width. The histological correlate to these findings included an increased cellularity and vascularity in the central repair tissue as well as the peripheral part of the tendon.

71. Radiographic imaging and obtaining of ultrasonography guided biopsies from the patellar tendon after central third harvest

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The aim of the study was to compare the results of Ultrasonography (US) and Magnetic Resonance Imaging (MRI) examinations of the patellar tendon after anterior cruciate ligament (ACL) reconstruction using central third patellar tendon autografts. Furthermore, to assess the possibility to obtain consistent US-guided biopsies from the patellar tendon.

Patients and methods: 19 consecutive patients (7 female and 12 male) underwent MRI, US and US-guided obtaining of biopsies 27 (24–29) months after ACL reconstruction using central third patellar tendon autografts. Two experienced radiologists blinded from each other evaluated the MRI and

US examinations respectively. To obtain biopsies a Tru-cut Monoply[®] instrument was used under local anesthesia.

Results: The results of the MRI and US examinations are shown in the Table 1.

Significant correlations between the MRI and US examinations were found for the donor-site gap (area of non-tendinous like tissue signal/echo) ($r = 0.80$; $p < 0.001$) and the width of the contralateral side ($r = 0.47$; $p = 0.04$). A tendency of correlation was found for the thickness of the contralateral side ($r = 0.44$; $p = 0.06$). No significant correlations were found for the width and the thickness of the donor-site patellar tendon. Altogether 76 biopsies were obtained and 72/76 (95%) contained sufficient amounts of tissue to be evaluated. None of the patients felt discomfort during the biopsy procedure.

Conclusion: In this study MRI and US were found to be comparable methods for the evaluation of the patellar tendon after central third harvest. US-guided biopsies from the patellar tendon using the Tru-cut Monoply[®] instrument under local anaesthesia is a safe and reproducible method and gives sufficient tissue for histologic evaluation in a high percentage of patients.

Table 1

	Donor-site patellar tendon	Contralateral patellar tendon
MRI donor-site gap	2 (0–5) mm	No gap
US donor-site gap	3 (2–7) mm	No gap
MRI width	30 (24–38) mm	28 (20–33) mm
US width	30 (24–36) mm	29 (24–37) mm
MRI thickness	6 (5–8) mm	5 (3–8) mm
US thickness	6 (5–7) mm	5 (3–6) mm

72. Semitendinosus tendon graft ingrowth in tibial tunnel following ACL reconstruction—a case report

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One of the crucial factors concerning successful anterior cruciate ligament (ACL) reconstruction is the potential of graft integration with the bone tunnels. When using hamstring graft (gracilis and/or semitendinosus tendon) one has to rely on osseointegration of the tendon graft in the surrounding bone. Pinczewski published in 1997 a report of two cases with graft rupture within 3 months following ACL reconstruction with hamstring graft fixed by interference screws. While performing revision surgery he obtained biopsies of the graft-bone interface for histological studies which showed continuity between collagen fibres of the graft and surrounding bone. When using quadruple semitendinosus graft with endobutton fixation technique no interference screws are used and the graft is secured with mersilene tapes

and ethibond sutures tied around screws distally. Thus, in contrast to the interference screw fixation no compression of the graft in the bone tunnels is created.

To our knowledge there are no earlier reports showing the histology of semitendinosus graft integration in bone tunnels with endobutton fixation technique.

Materials and methods: A 24 year old male primarily ACL reconstructed with a quadruple semitendinosus graft and endobutton fixation suffered 6 months postoperatively a graft rupture while playing soccer. Revision surgery was performed using BTB graft from the ipsilateral side. At this operation the whole previous tibial bone tunnel was extracted as a core biopsy. The biopsy consisted of a full thickness graft remnant within the tibial tunnel including the surrounding bone, allowing histological examination of the graft bone interface.

Results: The quadruple semitendinosus graft, examined histologically at various levels in longitudinal and transverse sections, was fused to one continuous tendinous cord. In several segments of the tunnel the tendinous cord showed a complete integration with the surrounding bone forming structures closely recapitulating that of a normal tendon-bone attachment: continuity of collagen fibers of the tendon with that of an outer layer of woven bone, segments of chondroid differentiation, and a deeper zone of compact lamellar bone.

Conclusion: The four stranded semitendinosus graft has the potential of fusing into one tendinous cord in the bone tunnels. Further on our results illustrate that osseointegration of tendon grafts not requires anchoring by interference screws.

POSTERS

P 1. Median nerve latency measurement—agreement between portable and conventional techniques

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We compared a portable nerve conduction testing device with conventional EMG technique in the measurement of distal motor and sensory latencies of the median nerve.

Methods: In a population-based study, a health questionnaire was mailed to a random sample of 3000 subjects (25–74 years). Of the 2466 responders, 262 subjects who reported numbness and/or tingling in the median nerve distribution in the hands, and 125 non-symptomatic responders underwent clinical and electrophysiological examination. Median nerve distal motor and sensory latency measurements were performed using the portable Nervepace (NeuMed, Lawrenceville, New Jersey) nerve conduction testing device, as well as a conventional EMG apparatus.

Results: Median nerve distal motor latency measured with the portable device was on average 0.1 milliseconds (ms) lower than distal motor latency measured with the conventional method (95% limits of agreement, -0.8–0.6 ms).

Median nerve distal sensory latency (wrist-to-index finger) measured with the portable device was on average 0.3 ms lower than distal sensory latency (long finger-to-wrist) measured with the conventional method (95% limits of agreement, -0.7–0.1 ms).

Strong correlations were found between the portably and conventionally measured latencies (correlation coefficient, 0.90–0.93).

Conclusion: The agreement between the portable and conventional methods in measuring median nerve distal motor and sensory latencies appears to be acceptable for clinical purposes. The cut-off value for abnormal distal sensory latency might need to be lower for the portable than the conventional method if the present measurement techniques are used. Portable nerve conduction testing can be a useful tool in the diagnosis of carpal tunnel syndrome.

P 2. Risk factors for carpal tunnel syndrome—a population-based study

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The purpose was to investigate the association of medical and occupational factors with carpal tunnel syndrome (CTS).

Methods: In a population-based study designed to estimate the prevalence of CTS, a sex and age-stratified random sample of 3000 subjects (age, 25–74 years) was selected from the population register of the southern Swedish region of Nordöstra Skåne (population, 170000).

A questionnaire inquiring about general health, medical history, symptoms (pain, numbness and tingling), employment, and work activities was mailed to the subjects.

All responders who reported numbness/tingling in the median nerve distribution experienced weekly during the preceding four weeks were invited to the hospital. A clinical examination was performed by a hand surgeon who diagnosed each symptomatic subject as having clinically certain or clinically uncertain CTS. This was followed by nerve conduction studies performed by blinded EMG technicians. Median-ulnar sensory latency difference ≥ 0.8 milliseconds was used as a criterion for the diagnosis of median neuropathy. Hands with previous carpal tunnel surgery were excluded.

Results: The response rate was 83% for the survey and 81% for the examination. Among the subjects with clinically certain and electrophysiologically confirmed CTS, and among the remaining responders, diabetes was reported in 3.0% and 3.2%, respectively, thyroid disorder in 3.0% and 3.0%, rheumatoid arthritis in 4.5% and 1.9%, and overweight/obesity (body mass index ≥ 25 kg/m²) in 70% and 47% ($P < 0.001$).

Clinically and electrophysiologically confirmed CTS was present in 25 of 710 active blue-collar workers (prevalence, 3.5%), and in 12 of 712 active white-collar employees (prevalence, 1.7%) ($P < 0.03$). The prevalence of CTS among working subjects who reported >1 hour/day use, and those reporting less frequent or no use of excessive force with the hand during work was 5.4% and 1.8%, respectively ($P < 0.001$). In a similar analysis of other work-related activities (ie, >1 hour/day vs less frequently), CTS prevalence in the two groups was, for working with excessively flexed or extended wrist 3.8% and 1.7% ($P < 0.02$), for repetitive hand or wrist motion 2.4% and 2.7%, and for use of hand-held vibratory tools 5.5% and 2.4% ($P = 0.05$).

Conclusion: Overweight and work-related factors appear to be associated with CTS.

P 3. Physical activity and its relationship to bone mass—a population-based study on 277 children aged 11–16 years

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In order to investigate the effect of physical activity on bone mass within the limits of a normal lifestyle, we performed bone mineral measurements in a population-based setting on 277 children aged 11–16 years (131 girls and 146 boys) from a small rural area in southern Sweden. The examination was done with ultrasound (QUS) of both heels, single-energy X-ray absorptiometry (SXA) of the non-dominant forearm and a total body scan followed by a separate scan of the left hip with dual-energy X-ray absorptiometry (DXA). Physical activity was determined by a questionnaire and in 213 children the 20-meter shuttle test was used to determine their maximal oxygen uptake (VO_{2max}).

We found a significant correlation between the level of self-reported physical activity and bone mass in the skeletal sites measured, both for girls ($r = 0.19$ – 0.29) and boys ($r = 0.15$ – 0.36). The correlations between VO_{2max} and bone mass were significant both for girls ($r = 0.09$ – 0.40), and boys ($r = 0.27$ – 0.45). The correlation with bone mass was higher in loaded areas both for physical activity and VO_{2max} . Boys reported higher levels of physical activity and more weight-bearing activities than girls ($p < 0.001$ for both).

Comparing the level of physical activity with bone measurements we found significant differences, between the low and high activity groups, both for boys and girls, with higher values in the high activity group. For boys the difference between the groups in lumbar spine BMD was 6.0%, in the hip between 9.6–10.9%, QUS of the heels 6.9% and for the distal radius 6.0–8.0%. These differences were still significant after adjustment for age, height, and weight. For girls these differences between low and high activity group were similar, but disappeared after adjustment for age, height, and weight.

We conclude that within the limits of a normal lifestyle there is a significant correlation between physical activity and BMD, and for boys this is of clinical value concerning increase in bone mass. For girls of this age group the benefit is smaller and perhaps not of clinical importance. This may be due to the lower levels of physical activity, lower magnitude and shorter duration of activity for girls than boys.