J Bone Miner Metab (2000) 18:245–257

Review and perspectives

Journal of
Bone and
Mineral
Metabolism

Regular joint loading in youth assists in the establishment and strengthening of the collagen network of articular cartilage and contributes to the prevention of osteoarthrosis later in life: a hypothesis

Heikki J. Helminen[1], Mika M. Hyttinen[1], Mikko J. Lammi[1], Jari P.A. Arokoski[2], Tuomo Lapveteläinen[1], Jukka Jurvelin[3], Ilkka Kiviranta[4], and Markku I. Tammi[1]

[1] Department of Anatomy, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland
[2] Department of Physical and Rehabilitation Medicine, Kuopio University Hospital, Kuopio, Finland
[3] Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland
[4] Department of Surgery, Jyväskylä Central Hospital, Jyväskylä, Finland

Key words Articular cartilage · Cartilage diseases · Joint diseases · Osteoarthrosis · Osteoarthritis · Primary prevention · Collagen · Proteoglycans · Exercise

Introduction

Advancement in knowledge of the basic biological and biomechanical properties of articular cartilage and the increasing understanding of the principles governing the development and molecular biology of cartilage have opened new views and possibilities for the prevention of osteoarthrosis (OA) [1,2]. The fact that many details of the molecular mechanisms of cartilage breakdown are now solved has further encouraged researchers to tackle the problem of OA prevention [3,4]. In practice, deciphering realistic and effective strategies for prevention of OA is a necessity for modern societies because the number of individuals reaching old age continues to increase simultaneously with their greater risk to fall ill with OA. Today the most effective cure of severe OA of weight-bearing joints is total joint replacement. The operation relieves pain effectively and restores joint mobility. However, the costs of the operation and treatment are high. Before surgery the patient has usually suffered from pain and disability for years, or even decades, and the ailment has caused both social handicap and economical losses to the individual and society. Therefore, it is understandable that effective strategies for elimination of the risk factors and the prevention of OA are needed [5].

In this communication we present the prevailing principles of the prevention of OA and a hypothesis of the importance of regular joint loading in young age for the development of a well-organized and strong articular cartilage collagen network, which contributes to the prevention of OA later in life. The load-bearing properties of articular cartilage as well as the main features of the metabolism and turnover of proteoglycans (PGs) and collagen are briefly reviewed, especially in relation to joint loading.

Offprint requests to: H.J. Helminen
Received: February 2, 2000

Prevention of OA

The knowledge of the pathogenesis of OA and its risk factors is today supplemented at an increasing pace, which makes the prospects for prevention of the disease more and more realistic [2–8]. OA is a disease with a multifactorial etiology. It affects not only the articular cartilage but the whole synovial joint organ. This implies that in addition to articular cartilage, the properties of the subchondral bone and ligaments, the weight-bearing conditions including the biomechanical alignment of the joint, the weakness of the shock-absorbing and weight-bearing muscles, and the integrity and proper function of the neuromuscular system must be taken into regard [9]. Even though the OA process in the joint structures is accomplished by biochemical signals, i.e., cytokines, growth factors, proteins and enzymes, the disease appears to be primarily driven by the local mechanical factors in the joint. Thus, the mechanical etiology of OA deserves ongoing close scrutiny [9].

The *primary prevention* of OA emphasizes hindering the disease from affecting healthy persons [2,5]. Large epidemiological studies on OA have pointed out several risk factors that can be influenced by adjusting our lifestyles. For example, obese persons are instructed to reduce body weight and to carry out exercises to strengthen their lower limb muscles to reduce stress at

the surface of articular cartilage [10,11]. Inadequate neuromuscular fitness has been observed to result in greater impact upon heel strike [10]. Avoiding knee injuries and eliminating jobs that require bending of the knees and squatting are also measures that prevent OA [2,5]. *Secondary prevention* focuses on screening of persons, groups of people, or families who are at risk of developing early OA and a manifest disorder. Persons with a defect in a cartilage-specific molecule, such as results from a mutated type II procollagen gene, for example, may show familial inheritance of severe OA or chondrodysplasia [12–14]. These persons and families may benefit from an early intervention, even though it is not exactly clear what would be the preventive measures. Gender, age, and race are demographic variables that affect the development of OA. The disease profiles are different for white, black, and Asian people [2]. Secondary preventive measures are, in principle, applicable to these people, as well as to those with congenital and developmental deformities [2,15]. In principle, all individuals who have deformed bones and altered weight-bearing conditions in joints would benefit from the secondary prevention of OA.

Tertiary prevention of OA refers to hindering of further damage and disability in persons who already have the disease. Unfortunately, little is known about the factors affecting progression of the disease [2,5]. Several nonpharmacological and pharmacological approaches have been suggested for this purpose, the emphasis being on nonpharmacological treatments [10].

Load-bearing properties of articular cartilage

The basic principles of the biomechanical properties in relation to structure and function of articular cartilage have been reviewed recently [16–18]. Articular cartilage is a biological composite material consisting of interacting solid matrix and interstitial water. The solid matrix is composed mainly of the collagen fibrils and PG molecules, which are responsible for the tensile, shear, and compressive properties of articular cartilage [16]. Electrostatic interactions between PGs and the electrolytes of interstitial water produce swelling pressure, which is transmitted to and constrained by the collagen network [19]. Interstitial fluid pressurization prevents excessive strains in the cartilage, also upon the collagen fibril network, and shields the collagen–PG matrix against mechanical failure.

Elastic modulus, which designates the "stiffness" of articular cartilage matrix, is typically 0.5–1.0 MPa in compression [20,21]. In principle, the low modulus cannot account for successful mechanical function during dynamic joint stresses with peak values of up to 18 MPa [22]. However, due to the relatively small permeability of the tissue, the interstitial water is pressurized and supports most of the load during dynamic loading. Therefore, cartilage stiffness increases effectively during dynamic loading and can be tenfold higher than the intrinsic modulus of the matrix [23,24].

Under physiological loading conditions, interstitial compressive, tensional, and shear stresses are created in the cartilage matrix. Collagen is primarily responsible for the cartilage properties in tension and shear. Under high rate loading, the shape change of the cartilage matrix is restricted by the collagen fibrils [25]. Water flow through the porous matrix takes place during prolonged loading. This stage of deformation depends significantly on cartilage permeability, which is primarily controlled by the PGs [20].

The structure and composition of the superficial zone of articular cartilage affect significantly the mechanical response of the tissue [17]. The superficial zone properties vary in different topographical regions of the joint. For example, in canine cartilage the mean thickness of the superficial zone and its proportion to the total uncalcified articular cartilage is significantly greater in the femoral than in the tibial cartilage. At the same time, the elastic modulus, i.e., stiffness, of the femoral cartilage is markedly higher than in the tibia even though the PG concentration is higher in the tibial cartilage [17]. In OA, some of the first detectable histological abnormalities are the separation and disorganization of the superficial collagen fibrils, decrease of the superficial PG concentration, and increase in water content [26].

In aging cartilage and in OA, the earliest damage to type II collagen starts in the matrix around the superficial chondrocytes and extends into deeper tissue with progressive damage [6–8]. The simultaneous loss of PGs leads to decreased cartilage stiffness [27,28]. In fact, articular cartilage softening may be the first sign of the OA process while the cartilage surface still appears intact [6]. Disturbance in the content, properties, or interactions of structural components (collagen, PGs, water, and electrolytes) impairs the mechanical properties of the tissue and renders it susceptible to further damage during joint loading.

Joint loading and articular cartilage

Increased joint loading and weight-bearing

Early studies on animal models suggested that running, even when strenuous, caused no untoward changes in the articular cartilage [29–31]. Later, however, running was reported to exert harmful effects also on articular cartilage in mice, rabbits, and dogs [32–34]. Nevertheless, the prevailing view is that normal physiological

loading does not impair the articular cartilage. It also appears that properties of cartilage and its responses to loading are very site specific [35]. Differences in the magnitude and type of joint loading, e.g., degree of shear or weight-bearing, probably explain the site-dependent cartilage responses to loading.

We have systematically studied the response of articular cartilage to loading in the knee (stifle) joint of young beagles after three different training programs. Running exercise of 4 km/day on a treadmill inclined 15° uphill, 5 days per week for 15 weeks, increased the thickness and PG content (16%–26%) in the femoral cartilage, whereas collagen content remained practically unaltered (Fig. 1) [35–37]. A slight stiffening of the cartilage occurred in the proximal part of the patellar surface of the femur and tibial cartilages. The rate of cartilage deformation during compression decreased [38]. Running exercise of either 20 km/day or 40 km/day for up to 15 weeks reduced the glycosaminoglycan (GAG) content in the superficial zone of femoral and tibial condylar cartilages [39,40], increased water content, and decreased the concentration of collagen in the cartilage of lateral femoral condyle [41]. However, the overall PG content of the cartilage did not change significantly during 40 km/day running [42]. Running exercise of 20 km/day did not improve the biomechanical properties of articular cartilage observed after the 4 km/day running program [43], and running exercise for 40 km/day reduced the stiffness of articular cartilage [44]. Running exercise of 40 km/day generally decreased (24%–34%) the collagen birefringence of the superficial zone cartilage at the weight-bearing sites of the femoral and tibial condyles (Fig. 2) [45]. It was anticipated that a derangement, or even a disorganization, of the superficial collagen network would be the reason for the birefringence decline and would also explain the softening of cartilage. Histomorphometric parameters of the subchondral bone showed marked signs of remodeling in all sites examined [46].

It is not known whether the negative changes after long-distance running represented early and true degenerative changes or, alternatively, adaptation of the articular cartilage and the subchondral bone to long-term joint loading. Our hypothesis is that the changes were degenerative in nature. On the other hand, the observed peripheral thickening of the cartilage with increased bone remodeling can also be considered to represent a compensatory and an adaptive mechanism aiming at improving congruence between contacting articular surfaces. For example, the centrally observed depletion of GAGs and softening of the cartilage after a 40 km/day running program may serve this purpose instead of denoting early changes of OA.

Most clinical and epidemiological studies have failed to detect any correlation between running training and OA [47–52]. However, Marti et al. (1989) found radio-

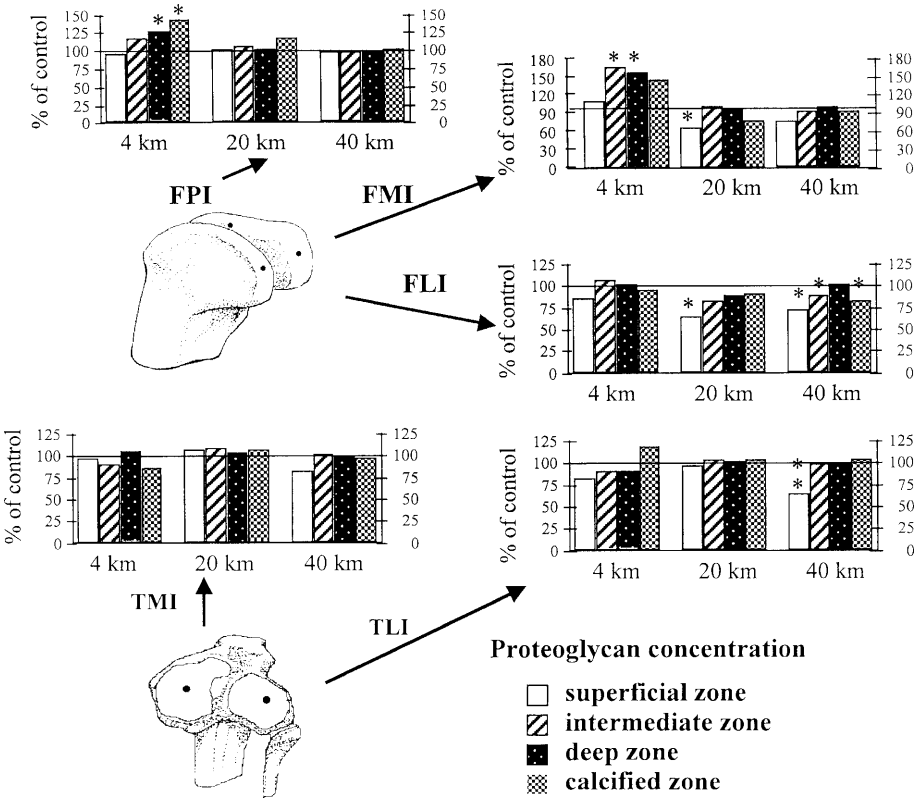

Fig. 1. Zonal changes of proteoglycan concentration in five regions of the knee joint (stifle) articular cartilage of beagle dogs after different running programs on treadmill inclined 15° uphill (*4 km*, 4 km/day; *20 km*, 20 km/day; *40 km*, 40 km/day, for 15 weeks). *Numbers* represent the ratios of the mean values of the runner (n = 5–10) and control (n = 5–10) groups. *FPI*, inferior section (point) of the patellar surface of femur; *FMI* and *FLI*, intermediate sections (points) of the medial and lateral condyles of femur, respectively; TMI and TLI, intermediate sections (points) of the medial and lateral condyles of tibia, respectively. * $P < 0.05$, ** $P < 0.01$ (Wilcoxon matched-pairs signed-rank test). For further details, see text and Kiviranta et al. [35]

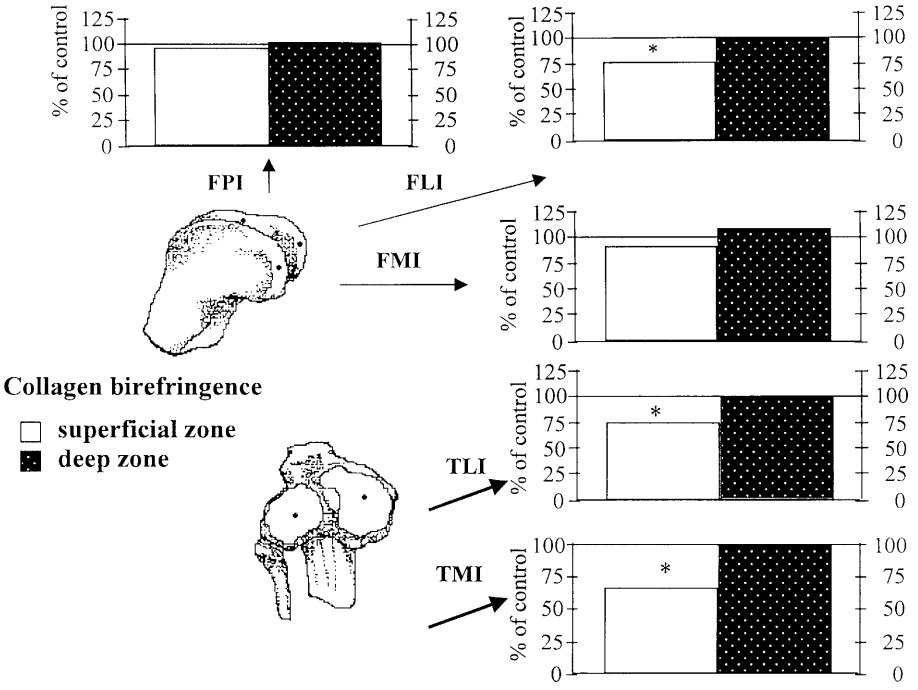

Fig. 2. Effect of running 40 km/day on collagen-induced birefringence of beagle knee joint articular cartilage. See legend for Fig. 1 and Arokoski et al. [45]

logically more degenerative changes in the hip joints of former national team long-distance runners than in bobsleigh competitors and the reference population [53]. Also, runners who had sustained injuries, or who had anatomical abnormalities but continued running training, showed accelerated development of OA in affected joints [54]. Different types of exercise or sports activities, which repetitively expose joints to high levels of impact or torsional loading, are associated with increased prevalence of OA [55–60]. However, habitual recreational physical activity of moderate degree seems not to increase the risk of OA [55,61].

Few studies have been published on the interrelationship between exercise, aging, and the articular cartilage. Rats who ran on a treadmill between the ages of 6 and 24 months showed more severe OA in the knee joints than did the control animals [62]. Lifelong moderate running (1 km/day) on a treadmill between 2 and 18 months of age increased the incidence and severity of OA in the knee joints of C57BL mice [63]. However, lifelong moderate running of beagle dogs showed no evidence of knee articular cartilage injury after 4 km/day exercise on the treadmill, 5 days/weeks, for a total of 550 weeks [64].

Immobilization and remobilization

Several studies have shown that lack of load-bearing and restriction of movements in a casted joint cause atrophic changes in articular cartilage [65]. Mechanical forces seem to be more important than motion in supporting the properties of articular cartilage because movements of the joint in the absence of loading initiate and maintain atrophic changes [66]. On the other hand, rigid fixation of the joint, which increases the contact forces between articular surfaces, produces local destruction of cartilage at the site of contact area [67].

Immobilization of the knee (stifle) joints of beagle dogs in 90° flexion for 11 weeks reduced the glycosaminoglycan (GAG) concentration of articular cartilage by 20%–48% (Fig. 3) [68]. The GAGs were depleted mainly in the superficial zone of articular cartilage, and immobilized cartilage was more immature in nature [65,69]. However, total PG synthesis was not significantly changed after immobilization [69]. Birefringence of the collagen fibril network showed no significant changes, but the amount of collagen cross-links was reduced [70]. An 11-week immobilization of the canine knee femoral and tibial articular cartilage decreased cartilage stiffness by 25% (Fig. 4) [71]. Also, the flow rate of interstitial fluid under compression increased in articular cartilage of immobilized dogs. Normal cartilage stiffness remained in the contact area between the patella and the patellar surface of femur, probably as a consequence of sustained, but not totally static, compressive patellofemoral load during 90° joint flexion.

After remobilization, PGs of articular cartilage in adult dogs seemed to return to the level of the contralateral limb 3 weeks after removal of the cast [66,72], whereas rigid external fixation of the joints for 6 weeks prevented the recovery almost totally [73]; this indicates that articular cartilage is able to recover from immobili-

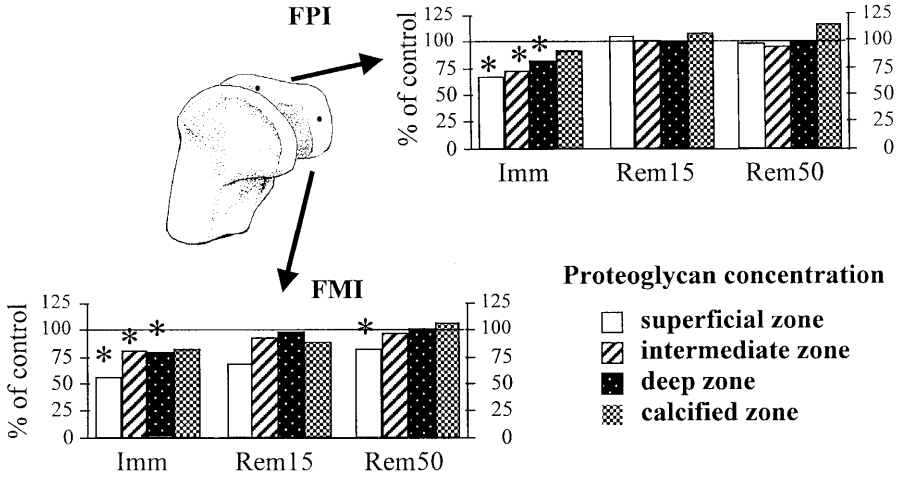

Fig. 3. Zonal changes of proteoglycan concentration in three regions of the knee joint of beagle dogs after joint immobilization in flexion and subsequent remobilization up to 1 year. *Imm*, after 11 weeks of immobilization; *Rem15*, after 15 weeks of remobilization; *Rem50*, after 50 weeks of remobilization

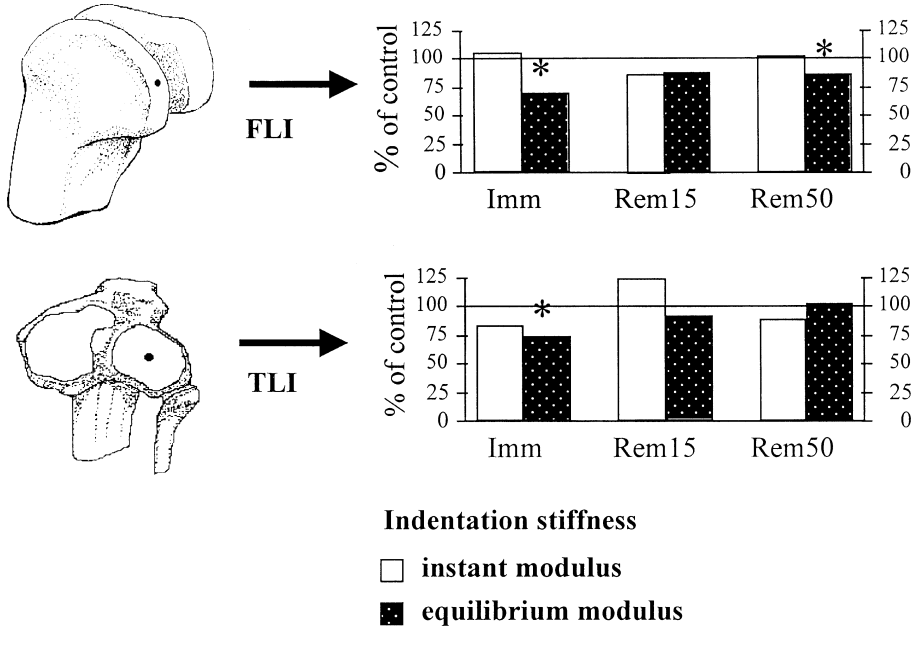

Fig. 4. Effect of joint immobilization and subsequent remobilization on the biomechanical properties of beagle dog articular cartilage expressed as indentation stiffness

zation. However, the situation is probably more complicated. Remobilization of young beagle dogs for 15 weeks, after a prior 11-week immobilization period, restored the GAG content of articular cartilage in the patellofemoral region and in condyles of tibia, while on the summits of femoral condyles the GAG concentration remained below the control level (see Fig. 3) [69,70,74]. Also, the equilibrium shear modulus of cartilage remained at a lower level and the cartilage permeability at a higher level than in controls (see Fig. 4) [75]. The reduced content of PGs and the decreased CS-6/CS-4 ratio that resulted from immobilization were restored within 15 weeks of remobilization close to the level of control dogs. However, even after 50 weeks of remobilization there were cartilage areas where the PG concentration of the articular cartilage remained low,

especially in the superficial zone (Fig. 3). The arrangement of collagen fibrils was not different from controls after 50 weeks of remobilization [70]. In some regions the stiffness of cartilage also remained below the control level (Fig. 4) [76]. These results indicate that the immobilization-induced atrophic changes of articular cartilage are for the most part reversible, even though some joint regions may recover incompletely. It is also worth noting that vigorous running exercise inhibits the reversal of atrophic changes in the canine knee after prolonged immobilization [77,78]. Moderate exercise seems to exacerbate OA lesions in cartilage produced by meniscectomy [78,79].

Articular cartilage loading in vitro

During joint loading, the collagen fibrils of articular cartilage exhibit zone-specific deformation that is dependent on the magnitude and type of loading [80]. Vigorous cyclic loading (0.5 Hz, 4.1 MPa) of cartilage plugs increases the thickness and collagen orientation in the superficial zone, probably on account of tissue compression [81]. Repeated compressive loading may cause reduction in tensile strength of cartilage in vitro [82]. PG synthesis decreases during static pressurization of cultured articular cartilage explants [83,84]. Dynamic compression of cartilage explants has yielded different results. Cyclic loading at frequencies of 0.01–1.0 Hz increases PG synthesis [85–88], but this effect is no longer evident after low-frequency loading (<0.001 Hz) [85,86]. Cyclic (0.5 Hz, 5 MPa) short-term (1.5 h) hydrostatic pressure applied to cartilage explants stimulated PG synthesis but inhibited it when applied to chondrocyte cultures [89]. Thus, the magnitude and frequency of pressure and the length of pressurization have an influence on the outcome as well as whether the chondrocytes are embedded in the extracellular matrix.

Proteoglycan synthesis and turnover in young age, aging, and OA

The normal function of articular cartilage requires a balance between continuous biosynthesis of extracellular matrix molecules and their catabolic pathways. Aggrecan is the PG that is responsible for most of the elastic properties of cartilage, and its metabolism plays a key role in the health of the joint. PG synthesis rate increases toward the deep zones [90,91], and the synthesis varies in different locations of the joint cartilage; this has been observed especially in the superficial zone of articular cartilage [91]. Factors such as soluble mediators, mechanical stress, aging, and OA can influence the balance and overall rate of turnover and change the extracellular matrix protein gene expressions [92].

Within the extracellular matrix of adult cartilage, aggrecan appears to be present in two pools. The first is a pericellular (territorial) pool. Retention and maturation of newly synthesized aggrecan molecules takes place in this pool before their sequestration as PG aggregates into the second pool, which resides in the interterritorial load-bearing matrix [93]. In this interterritorial metabolically inert pool, the PG aggregate degradation may occur over long time periods, perhaps even periods approaching the lifetime of an individual [94]. Dynamic compression stimulates PG synthesis and deposition of the PG aggregates [95], while static loading causes a decline in the tensile load-carrying capacity of the collagen matrix, presumably associated with a mechanical breakdown of the tissue and elevated rate of PG turnover, especially in the pericellular matrix. This change involves both an increased release of PG aggregates and their breakdown, resulting in a spectrum of degradation products [96]. The loss of aggregating PGs can also be partly due to a decreased synthesis of link protein, which may lead to a disproportionate relationship between aggrecan and the link protein [97]. The approximate mean life of articular cartilage PGs in young rabbits has been estimated to be 90 to 130 days but slows down to 340 days in adulthood [98]. In adult human femoral cartilage the average mean life of PGs was estimated to be about 1000 days, i.e., 3 years [98].

A major cleavage site for aggrecan is located in the interglobular domain between the two globular domains G1 and G2 [99], a region susceptible for both matrix metalloproteinases and aggrecanase [100]. Aggrecanases 1 and 2 are members of the ADAM (a disintegrin and metalloproteinase) family and were recently cloned [101,102]. Aggrecanases are supposed to be the key enzymes in cartilage degradation, interleukin 1 being a major mediator. In murine OA, cleavage products of aggrecanase were observed in the early phase of PG depletion, while those typical for matrix metalloproteinases were present in increased amounts in severely damaged cartilage [103]. The small PGs decorin, biglycan, and lumican are increased rather than decreased in content in OA and, in contrast to aggrecan, they are resistant to interleukin-1-induced catabolism of cartilage [104].

Collagen metabolism and turnover in relation to young age, aging, and OA

Collagen types II, VI, IX, and XI are synthesized by normal articular cartilage, type II being the major collagen of cartilage. Type II procollagen synthesis is relatively low in the newborn, and negligible in the adult, when compared to fetal synthesis levels [105], whereas

synthesis activity is again markedly increased in early OA [103,104]. In advanced OA, type II collagen synthesis in the superficial zone decreases [105,106], whereas in the deeper zones synthesis can be increased, even though some differences are observed between the local mRNA quantities and the level of procollagen synthesis [105,107]. Once incorporated into the matrix, collagen molecules have a very long lifetime (200–400 years) [108,109].

It is the collagen network integrity that is essential for the normal functioning of articular cartilage, and this integrity is lost in OA [110,111]. The collagen network is broken down by the extracellular collagenases. Collagenase activity appears to be a more probable cause for degradation of the collagen network than, mechanical damage due to overloading of the joint, for example [112]. Therefore, medical treatments increasing collagen biosynthesis and inhibiting the enzymatic activity of collagenases could be of therapeutic value in OA [113]. However, we do not know at present how to restore a deranged collagen network, including the broken interfibrillar collagen cross-links.

Cross-linking plays a key role in the regulation of the tensile stiffness and strength of collagen fibrils [108]. During aging, the amount of mature cross-linking residues/triple helix stays very stable but nonenzymatic glycation increases, leading to an increased formation of pentosidine cross-links with age [108]. Zonal variations in the amount of lysyl cross-links suggests that maturation of cartilage begins in the upper half of the cartilage and occurs last in the deep zone close to the bone [108]. Impaired cross-linking of collagen appears to interfere with pericellular collagen deposition and causes an upregulation of collagen synthesis by impaired cell–matrix interactions [114]. This finding further stresses the importance of a balanced maintenance of extracellular matrix around chondrocytes for the health of articular cartilage.

Response of articular cartilage to regular joint loading in young and old guinea pigs

We have studied the response of articular cartilage to joint loading in young adult (28-week-old) and adult mature (62-week-old) Dunkin–Hartley guinea pigs, a breed prone to develop OA typically in the medial compartment of the knee, particularly in the tibia. The animals ran on a treadmill up to 2500 m/day with a speed of 0.33 m/s for 18 weeks. The first signs of progressive, degenerative lesions appeared at the age of 3 months [115].

In the young adult guinea pigs, collagen birefringence increased in the superficial zone of both the femoral and tibial cartilages after running (Fig. 5). In adult mature articular cartilage, the reaction was the opposite: running reduced significantly collagen birefringence in the superficial zone, suggesting an early derangement or disintegration of the collagen network (Fig. 5). In the tibia, both the absolute and the relative thickness of the superficial, tangentially oriented collagen zone was thinner than in the femur. Simultaneously with the collagen changes in the knee joint, ^{35}S-sulfate incorporation in the PGs of the humerus head cartilage showed significant changes. Running reduced ^{35}S-sulfate incorporation in PGs in the young, but not in the adult mature, runners (Fig. 6). In the adult mature runners and controls, the ^{35}S-sulfate distributions did not differ except in the most superficial tissue, where an increased ^{35}S-sulfate incorporation was detected in runners. In young adult animals, the most active area of ^{35}S-sulfate incorporation was in the deep zone, whereas in adult mature guinea pigs the most active area was in the intermediate and superficial zones (Fig. 6); this took place in both runners and controls.

The running program did not increase overall OA prevalence in either the young or older guinea pigs. The highest OA prevalence was found in the tibia. The thicknesses of collagen fibril zones oriented tangentially, obliquely, and perpendicularly to the cartilage surface did not change as the result of running. In conclusion, the superficial zone of articular cartilage showed a unique response of birefringence in the young adult and adult mature guinea pigs. The birefringence of the collagen network increased in the young adult and decreased in the adult mature animals. Compared to the young adult animals, the area of the most active PG synthesis was closer to the cartilage surface in the adult mature guinea pigs.

Hypothesis: regular joint loading in youth assists in the establishment and strengthening of the collagen network of articular cartilage, which prevents osteoarthrosis in middle and old age

It is well established that bones exposed to different types of loading, such as immobilization, normal locomotion, or strenuous exercise, respond to the stress to which they are exposed by altering the internal architecture and composition of the bone. This phenomenon, known as Wolff's law, was observed a century ago [116]. This review indicates that the articular cartilage of diarthrodial joints is also a dynamic tissue, responding actively to various joint loading conditions. Accordingly, articular cartilage also obeys Wolff's law.

In many respects, articular cartilage is similar to bone. Bone tensile strength is provided by type I collagen fibrils, which are reinforced by covalent cross-links as in articular cartilage with the exception that type II

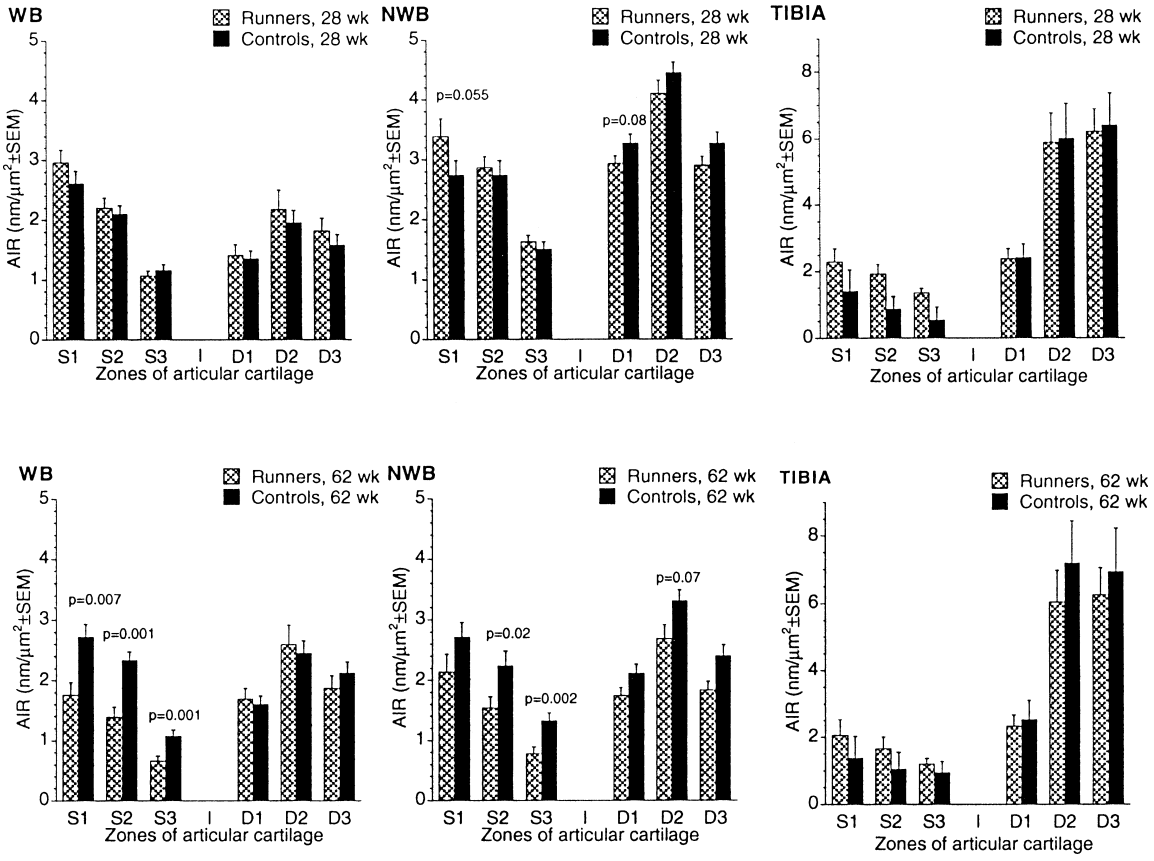

Fig. 5. Effects of running on collagen-induced birefringence in the knee joint articular cartilage of young adult (age 28 weeks) and adult (age 62 weeks) guinea pigs. The guinea pigs, all females, ran on a treadmill up to 2500 m/day, 5 days a week, for 18 weeks at 0.33 m/s, starting at the age of 10 or 44 weeks. Specimens were cut perpendicularly to the joint surface, from both the femur and tibia. *WB*, weight-bearing region; *NWB*, nonweight-bearing region of the medial condyle of femur; *TIBIA*, central area of medial condyle of tibia, not covered with meniscus; *S1–S3*, superficial zone layers, S1 the most superficial and S3 the deepest layer; *D1–D3*, deep zone layers, respectively. Birefringence of collagen is expressed quantitatively as an area-integrated retardation (*AIR*, μm/μm²) of the polarized light (see Arokoski et al. [45]) (Mann–Whitney U test used for statistical analysis)

collagen dominates in articular cartilage. Compressive strength in bone is provided by inorganic hydroxyapatite crystals, whereas PGs serve this purpose in cartilage [117]. The mineral crystals of bone are deposited in holes between the type I collagen fibrils, and PGs fill the spaces between the thinner type II collagen fibrils. Furthermore, it is interesting to note that regular exercise at a young age, especially around puberty, is the prerequisite to obtain maximum bone mineral content in the human skeleton [118], in addition to proper nutrition with sufficient calcium intake and supply of vitamin D. As in articular cartilage, regular exercise and mechanical strain appear to affect the organization of bone collagen [119,120]. So, both in bone and in cartilage, regular loading of the musculoskeletal system seems to optimize the collagen network frame within which either the PGs of cartilage or the mineral of bone are deposited.

Joint movements and muscular activity are needed in the development of the synovial joint. The gross forms of articular structures can develop in vitro [121,122]. This fact is a proof of the participation of an "intrinsic" guidance, i.e., genetic control, during the early stages of joint development. However, the "extrinsic" mechanical factors, generated by muscle contractions and joint movements, are needed for the development and maintenance of the joint cavity and for the acquisition of final form and size of the articular surfaces. Drachman and Sokoloff [123] paralyzed muscular contractions in chick embryos and found that joint cavities did not form in these animals and that the articular surfaces became flattened and distorted. Postnatally, during growth and adulthood, it is the interplay between the influences of joint function and gene expression by the chondrocytes that governs the development of joint surfaces and cartilage composition [124]. The production of extracellu-

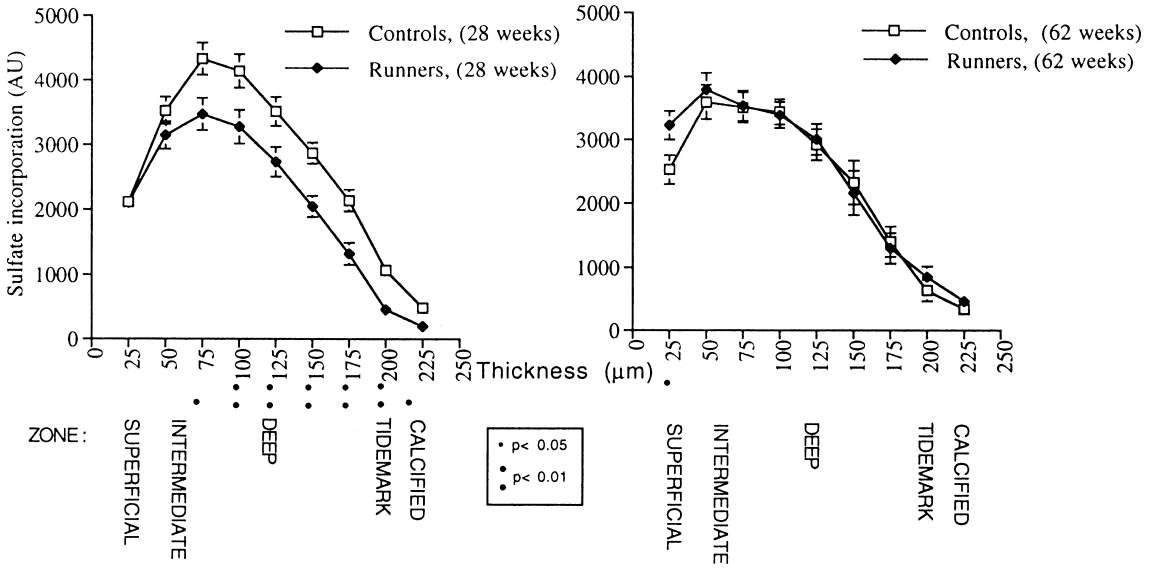

Fig. 6. Effect of age and treadmill running on ^{35}S-sulfate incorporation by the chondrocytes in the different zones of guinea-pig articular cartilage from caput of humerus determined by quantitative autoradiography (Mann–Whitney U test)

lar matrix molecules, PGs and collagen, is higher in the weight-bearing areas than in the areas not carrying load. During growth, the chondrocytes undergo mitoses and the articular cartilage increases in thickness. Simultaneously, the calcified zone in the basal layer of articular cartilage enlargens and becomes invaded by blood vessels from the underlying subchondral bone. Resorption cavities appear and new bone is formed. The result is that both the articular surface and the subchondral bone grow gradually toward the joint cavity, while the intervening uncalcified articular cartilage roughly maintains its thickness. It has been estimated that articular cartilage adds as much as 25 mm to the length of the femur during the first 15 years of life [125]. Many details of this development are still obscure. For example, it needs to be elucidated to what extent the mechanical forces or genetic factors are responsible for the development of the so-called Benninghoff's arcades made up by the collagen fibrils [126].

In articular cartilage, PG synthesis and metabolism react more actively than collagen metabolism and fibril deposition to alterations of joint loading [34–41]. Depending on the mechanical stimulus, either more or less the "filling material," the PGs, is synthesized. PGs imbibe water and regulate the swelling pressure within the constraints of the collagen fibril network. The collagen fibril network forms the "backbone" of cartilage. The assembly of collagen fibrils appears to react slowly to alterations of joint loading. Nevertheless, the collagen fibril network appears to be prone to considerable alterations, especially at a young age when the growth of an individual takes place. On this basis, and based on the observations already presented, we put forward the hypothesis that regular joint loading in youth contributes to the establishment and strengthening of the articular cartilage collagen fibril network and helps in prevention of OA in middle and old age of an individual.

Based on the investigations on the accumulation of nonenzymatic glycation products, i.e., pentosidine, by the collagens in the human articular cartilage, it has been confirmed that collagen turnover in articular cartilage beyond the age of 20 years is negligible. The pentosidine levels are low before age 20 but then increase linearly after this time point. It was suggested by Bank et al. that in young age even extensive remodeling takes place in the articular cartilage with a considerable turnover rate of collagen, whereas in adult individuals the turnover is extremely slow, if at all detectable [108,109].

There seem to exist at least two pools of both PGs and collagens in articular cartilage. These pools show different velocities of turnover. The fast pool molecules with short turnover times seem to be localized in the vicinity of chondrocytes, whereas the more permanent structures, like collagen fibrils and mature PG aggregates, are located in the interterritorial matrix of cartilage further away from the chondrocytes [94,127]. It appears as if the normal adult human cartilage were tuned to operate with a low metabolic activity. When necessary, however, the cartilage is able to respond to increased mechanical demands with vigorous synthetic capacity, as happens after joint loading and during early OA [128]. Taken all this into consideration, it is reasonable to suggest that regular load bearing directs the

development and fate of the collagen fibril network of articular cartilage in the synovial joints, especially in young age. These effects probably contribute to the establishment and strengthening of the network and prevent OA in middle and old age. In this context it is interesting to note that Otterness et al. [129] observed a protective effect of exercise against articular cartilage degeneration in young hamsters. Daily wheel running (6–12 km/day) for 3 months was found to prevent fibrillation of the femoral articular cartilage. In the group of sedentary hamsters, all the animals showed articular cartilage fibrillation, pitting, and fissuring.

Concluding remarks

Exercise in young age can prevent articular cartilage fibrillation and degeneration in experimental animals. In this communication, we introduce the hypothesis that regular joint loading in youth assists in establishing and strengthening the collagen fibril network of articular cartilage, which contributes to the prevention of OA later in life. The importance of the growth period for the foundation of the cartilage collagen network is crucial because remodeling of cartilage and the turnover of collagen cease after the individual reaches maturity.

This hypothesis rests on the observation that articular cartilage obeys Wolff's law. The law implies that the structure, biological properties, and composition of a tissue, in this case the articular cartilage, are regulated by the mechanical forces to which the joints are exposed. The results from experimental work confirm that this requirement is met. In young and old experimental animals, the responses of the collagen network to loading are different. In the articular cartilage of young guinea pigs, regular joint loading appeared to improve the collagen network properties in comparison to older individuals, which after similar exercise showed signs of degeneration of the collagen fibril arrangement.

Acknowledgments. We thank the Finnish Research Council for Physical Education and Sports, Ministry of Education in Finland; Sigrid Juselius Foundation; Academy of Finland; and Kuopio University Hospital (EVO-grant 5103) for support.

References

1. Archer CW, Caterson B, Benjamin M, Ralphs JR (eds) (1999) Biology of the Synovial Joint. Harwood, Amsterdam
2. Felson DT, Zhang Y (1998) An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 41:1343–1355
3. Brandt KD, Doherty M, Lohmander LS (eds) (1998) Osteoarthritis. Oxford University Press, Oxford
4. Reginster J-Y, Pelletier J-P, Martel-Pelletier J, Henrotin Y (eds) (1999) Osteoarthritis. Clinical and Experimental Aspects. Springer, Berlin
5. Dieppe P (1993) Strategies for the prevention of osteoarthritis. Int J Tissue React 15:93–97
6. Buckwalter JA, Mankin HJ (1997) Articular cartilage. Part II. Degeneration and osteoarthrosis, repair, regeneration, and transplantation. J Bone Jt Surg [Am] 79A:612–632
7. Poole AR (1999) An introduction to the pathophysiology of osteoarthritis. Front Biosci 15:D662–D670
8. Martel-Pelletier J, Alaaeddinne N, Pelletier J-P (1999) Cytokines and their role in the pathophysiology of osteoarthritis. Front Biosci 15:D694–D703
9. Dieppe P (1999) Osteoarthritis: time to shift the paradigm. Br Med J 318:1299–1300
10. Brandt KD (1998) The importance of nonpharmacologic approaches in management of osteoarthritis. Am J Med 105(1B): 39S–44S
11. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzucca SA, Braunstein EM, Byrd D (1998) Reduced quadriceps strength relative to body weight. A risk factor for knee osteoarthritis in women? Arthritis Rheum 41:1951–1959
12. Prockop DJ, Kivirikko KI (1995) Collagens: molecular biology, diseases, and potentials for therapy. Annu Rev Biochem 64:403–434
13. Williams CJ, Jimenez SA (1999) Genetic and metabolic aspects. In: Reginster J-Y, Pelletier J-P, Martel-Pelletier J, Henrotin Y (eds) Osteoarthritis. Clinical and Epidemiological Aspects. Springer, Berlin, pp 134–156
14. Cicuttini FM, Spector TD (1996) Genetics of osteoarthritis. Ann Rheum Dis 55:665–667
15. Hochberg MC (1991) Epidemiologic considerations in the primary prevention of osteoarthritis. J Rheumatol 18:1438–1439
16. Mankin HJ, Mow VC, Buckwalter JA, Iannotti JP, Ratcliffe A (1994) Form and function of articular cartilage. In: Simon SR (ed) Orthopaedic Basic Science. American Academy of Orthopaedic Surgeons, pp 1–44
17. Arokoski JPA, Hyttinen MM, Helminen HJ, Jurvelin JS (1999) Biomechanical and structural characteristics of canine femoral and tibial cartilage. J Biomed Mater Res (Appl Biomater) 48:99–107
18. Jurvelin JS, Arokoski JP, Hunziker EB, Helminen HJ (2000) Topographical variation of the elastic properties of articular cartilage in the canine knee. J Biomech 33:669–675
19. Lee RC, Frank EH, Grodzinsky AJ, Roylance DK (1981) Oscillatory compressional behavior of articular cartilage and its associated electromechanical properties. J Biomech Eng 103:280–292
20. Mow VC, Holmes MH, Lai WM (1984) Fluid transport and mechanical properties of articular cartilage: a review. J Biomech 17:377–394
21. Jurvelin J, Kiviranta I, Arokoski J, Tammi M, Helminen HJ (1987) Indentation study of the biochemical properties of articular cartilage in the canine knee. Eng Med 16:15–22
22. Hodge WA, Fijan RS, Carlson KL, Burgess RG, Harris WH, Mann RW (1986) Contact pressures in the human hip joint measured in vivo. Proc Natl Acad Sci USA 83:2879–2883
23. Jurvelin J, Kiviranta I, Säämänen A-M, Tammi M, Helminen HJ (1990) Indentation stiffness of young canine knee articular cartilage—influence of strenuous joint loading. J Biomech 23:1239–1246
24. Jurvelin JS, Buschmann MD, Hunziker EB (1997) Optical and mechanical determination of Poisson's ratio of adult bovine humeral articular cartilage. J Biomech 30:235–241
25. Mizrahi J, Maroudas A, Lanir Y, Ziv I, Webber TJ (1986) The "instantaneous" deformation of cartilage: effects of collagen fiber orientation and osmotic stress. Biorheology 23:311–330
26. Muir H, Carney SL (1987) Pathological and biochemical changes in cartilage and other tissues of the canine knee resulting from induced joint instability. In: Helminen HJ, Kiviranta I,

Säämänen A-M, Tammi M, Paukkonen K, Jurvelin J (eds) Joint Loading. Biology and Health of Articular Structures. Wright, Bristol, pp 47–63
27. Kempson GE, Spivey CJ, Swanson SAV, Freeman MAR (1971) Patterns of cartilage stiffness on normal and degenerate human femoral heads. J Biomech 4:597–609
28. Armstrong CG, Mow VC (1982) Variations in the intrinsic mechanical properties of human articular cartilage with age, degeneration, and water content. J Bone Joint Surg [Am] 64:88–94
29. Lanier RR (1946) The effects of exercise on the knee-joints of inbred mice. Anat Rec 94:311–319
30. Sääf J (1950) Effects of exercise on adult articular cartilage. An experimental study on guinea-pigs with relevance to the continuous regeneration of adult cartilage. Acta Orthop Scand 7 (Suppl):1–86
31. Holmdahl DE, Ingelmark BE (1948) Der Bau des Gelenkknorpels unter verschiedenen funktionellen Verhältnissen. Experimentelle Untersuchung an wachsenden Kaninchen. Acta Anat (Basel) 6:120–126
32. Krause W-D (1969) Mikroskopische Untersuchungen am Gelenkknorpel extrem funktionell belasteter Mäuse-Ein Beitrag zur Aetiopathogenese degenerativer Gelenkveränderungen. Thesis. University of Cologne, Cologne, Germany
33. Videman T, Eronen I, Candolin T (1979) Effects of motion load changes on tendon tissues and articular cartilage. A biochemical and scanning electron microscopic study on rabbits. Scand J Work Environ Health 5 (Suppl):56–67
34. Vasan N (1983) Effects of physical stress on the synthesis and degradation of cartilage matrix. Connect Tissue Res 12:49–58
35. Kiviranta I, Tammi M, Arokoski J, Jurvelin JS, Säämänen A-M, Parkkinen JJ, Lammi MJ, Hyttinen MM, Helminen HJ (1997) Effects of mechanical loading and immobilization on the articular cartilage. Bailliere's Clin Orthop 2:109–122
36. Kiviranta I, Tammi M, Jurvelin J, Säämänen A-M, Helminen HJ (1988) Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. J Orthop Res 6:188–195
37. Säämänen A-M, Tammi M, Kiviranta I, Jurvelin J, Helminen HJ (1989) Levels of chondroitin-6-sulfate and nonaggregating proteoglycans at articular cartilage contact sites in the knees of young dogs subjected to moderate running exercise. Arthritis Rheum 32:1282–1292
38. Jurvelin J, Kiviranta I, Tammi M, Helminen HJ (1986) Effect of physical exercise on indentation stiffness of articular cartilage in the canine knee. Int J Sports Med 7:106–110
39. Kiviranta I, Tammi M, Jurvelin J, Arokoski J, Säämänen A-M, Helminen HJ (1992) Articular cartilage thickness and glycosaminoglycan distribution in the canine knee joint after strenuous (20 km/day) running exercise. Clin Orthop 283:302–308
40. Arokoski J, Kiviranta I, Jurvelin J, Tammi M, Helminen HJ (1993) Long-distance running causes site-dependent decrease of the cartilage glycosaminoglycan content in the knee joint of beagle dogs. Arthritis Rheum 36:1451–1459
41. Säämänen A-M, Kiviranta I, Jurvelin J, Helminen HJ, Tammi M (1994) Proteoglycan and collagen alterations in canine knee articular cartilage following 20 km daily running exercise for 15 weeks. Connect Tissue Res 30:191–201
42. Visser NA, de Koning MH, Lammi MJ, Häkkinen T, Tammi M, van Kampen GPJ (1998) Increase of decorin content in articular cartilage following running. Connect Tissue Res 37:295–302
43. Jurvelin J, Kiviranta I, Säämänen A-M, Tammi M, Helminen HJ (1990) Indentation stiffness of young canine knee articular cartilage—influence of strenuous joint loading. J Biomech 23:1239–1246
44. Arokoski J, Jurvelin J, Kiviranta I, Tammi M, Helminen HJ (1994) Softening of the lateral condylar articular cartilage in the canine knee joint after long distance (up to 40 km/day) running training lasting one year. Int J Sports Med 15:254–260
45. Arokoski J, Hyttinen MM, Lapveteläinen T, Takács P, Kosztáczky B, Módis L, Kovanen V, Helminen HJ (1996) Decreased birefringence of the superficial zone collagen network in the canine knee (stifle) articular cartilage after long distance running training, detected by quantitative polarized light microscopy. Ann Rheum Dis 55:253–264
46. Oettmeier R, Arokoski J, Roth AJ, Abendroth K, Jurvelin J, Tammi M, Kiviranta I, Helminen HJ (1992) Subchondral bone and articular cartilage responses to long distance running training (40 km per day) in the beagle knee joint. Eur J Exp Musculoskel Res 1:145–154
47. Puranen J, Ala-Ketola L, Peltokallio P, Saarela J (1975) Running and primary osteoarthritis of the hip. Br Med J 276:424–425
48. Sohn RS, Micheli LJ (1985) The effect of running on the pathogenesis of osteoarthritis of the hips and knees. Clin Orthop 198:106–109
49. Lane NE, Bloch DA, Jones HH, Marshall WH Jr, Wood PD, Fries JF (1986) Long-distance running, bone density, and osteoarthritis. JAMA 255:1147–1151
50. Panush RS, Schmidt C, Caldwell JR, Edwards NL, Longley Yonker R, Webster E, Nauman J, Stork J, Petterson H (1986) Is running associated with degenerative joint disease? JAMA 255:1152–1154
51. Konradsen L, Berg Hansen E-M, Søndergaard L (1990) Long distance running and osteoarthrosis. Am J Sports Med 18:379–381
52. Lane NE, Michel B, Björkengren A (1993) The risk of osteoarthritis with running and aging: a 5-year longitudinal study. J Rheumatol 20:461–468
53. Marti B, Knobloch M, Tschopp A, Jucker A, Howald H (1989) Is excessive running predictive of degenerative hip disease? Controlled study of former elite athletes. Br Med J 299:91–93
54. McDermott M, Freyne P (1983) Osteoarthrosis in runners with knee pain. Br J Sports Med 17:84–87
55. Adams ID (1976) Osteoarthrosis and sport. Clin Rheum Dis 2:523–541
56. Andersson S, Nilsson B, Hessel T, Saraste M, Noren A, Stevens-Andersson A, Rydholm D (1989) Degenerative joint disease in ballet dancers. Clin Orthop 238:233–236
57. Vingård E, Alfredsson L, Goldie I, Hogstedt C (1991) Occupation and osteoarthrosis of the hip and knee: a register-based cohort study. Int J Epidemiol 20:1025–1031
58. Kujala UM, Kaprio J, Sarna S (1994) Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes. Br Med J 308:231–234
59. Kujala UM, Kettunen J, Paananen H, Aalto T, Battié MC, Impivaara O, Videman T, Sarna S (1995) Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. Arthritis Rheum 38:539–546
60. Lane NE (1995) Exercise: a cause of osteoarthritis. J Rheumatol 43 (Suppl):3–6
61. Hannan MT, Felson DT, Anderson JJ, Naimark A (1993) Habitual physical activity is not associated with knee osteoarthritis: the Framingham study. J Rheumatol 20:704–709
62. Walker JM (1986) Exercise and its influence on aging in rat knee joints. J Orthop Sports Phys Ther 8:310–319
63. Lapveteläinen T, Nevalainen T, Parkkinen J, Arokoski J, Király K, Hyttinen M, Halonen P, Helminen HJ (1995) Lifelong moderate running training increases the incidence and severity of osteoarthritis in the knee joint of C57BL mice. Anat Rec 242:159–165
64. Newton PM, Mow VC, Gardner TR, Buckwalter JA, Albright JP (1997) The effect of lifelong exercise on canine articular cartilage. Am J Sports Med 25:282–287
65. Tammi M, Paukkonen K, Kiviranta I, Jurvelin J, Säämänen A-M, Helminen HJ (1987) Joint loading-induced alterations in articular cartilage. In: Helminen HJ, Kiviranta I, Säämänen A-M, Tammi M, Paukkonen K, Jurvelin J (eds) Joint Loading. Biology and Health of Articular Structures. Bristol, Wright, pp 64–88

66. Palmoski MJ, Colyer RA, Brandt KD (1980) Joint motion in the absence of normal loading dogs not maintain normal articular cartilage. Arthritis Rheum 23:325–334
67. Salter RB, Field P (1960) The effects of continuous compression on living articular cartilage. J Bone Joint Surg [Am] 42:31–49
68. Kiviranta I, Jurvelin J, Tammi M, Säämänen A-M, Helminen HJ (1987) Weight-bearing controls glycosaminoglycan concentration and articular cartilage thickness in the knee joint of young beagle dogs. Arthritis Rheum 30:801–809
69. Jortikka MO, Inkinen RI, Tammi MI, Parkkinen JJ, Haapala J, Kiviranta I, Helminen HJ, Lammi MJ (1997) Immobilization causes longlasting matrix changes both in the immobilized and contralateral joint cartilage. Ann Rheum Dis 56:255–261
70. Haapala J, Arokoski JPA, Hyttinen MM, Lammi M, Tammi M, Kovanen V, Helminen HJ, Kiviranta I (1999) Remobilization does not fully restore immobilization induced articular cartilage atrophy. Clin Orthop 362:218–229
71. Jurvelin J, Kiviranta I, Tammi M, Helminen HJ (1986) Softening of canine articular cartilage after immobilization of the knee joint. Clin Orthop 201:246–252
72. Palmoski M, Perricone E, Brandt KD (1979) Development and reversal of a proteoglycan aggregation defect in normal canine knee cartilage after immobilization. Arthritis Rheum 22:508–517
73. Behrens F, Kraft EL, Oegema TR (1989) Biochemical changes in articular cartilage after joint immobilization by casting or external fixation. J Orthop Res 7:335–343
74. Kiviranta I, Tammi M, Jurvelin J, Arokoski J, Säämänen A-M, Helminen HJ (1994) Articular cartilage thickness and glycosaminoglycan distribution in the young canine knee joint after remobilization of the immobilized limb. J Orthop Res 12:161–167
75. Jurvelin J, Kiviranta I, Säämänen A-M, Tammi M, Helminen HJ (1989) Partial restoration of immobilization induced softening of canine articular cartilage after remobilization of the knee (stifle) joint. J Orthop Res 7:352–358
76. Haapala J, Arokoski JPA, Pirttimäki J, Lyyra T, Jurvelin JS, Tammi M, Helminen HJ, Kiviranta I (2000) Incomplete restoration of immobilization induced softening of young beagle knee articular cartilage after 50-weeks remobilization. Int J Sports Med 21:76–81
77. Palmoski MJ, Brandt KD (1981) Running inhibits the reversal of atrophic changes in canine knee cartilage after removal of a leg cast. Arthritis Rheum 24:1329–1337
78. Ghosh P, Sutherland J, Bellenger C, Read R, Darvodelsky A (1990) The influence of weight-bearing exercise on articular cartilage of meniscectomized joints. An experimental study in sheep. Clin Orthop 252:101–113
79. Armstrong SJ, Read RA, Ghosh P, Wilson DM (1993) Moderate exercise exacerbates the osteoarthritic lesions produced in cartilage by meniscectomy: a morphological study. Osteoarthritis Cartilage 1:89–96
80. Kaab MJ, Ito K, Clark JM, Notzli HP (1998) Deformation of articular cartilage collagen structure under static and cyclic loading. J Orthop Res 16:743–751
81. Kiraly K, Hyttinen MM, Parkkinen JJ, Arokoski JPA, Lapveteläinen T, Törrönen K, Kiviranta I, Helminen HJ (1998) Articular cartilage collagen birefringence is altered concurrent with changes in proteoglycan synthesis during dynamic in vitro loading. Anat Rec 251:28–36
82. Torzilli PA, Grigiene R (1998) Continuous cyclic load reduces proteoglycan release from articular cartilage. Osteoarthritis Cartilage 6:260–268
83. McCormack T, Mansour JM (1998) Reduction in tensile strength of cartilage precedes surface damage under repeated compressive loading in vitro. J Biomech 31:55–61
84. Palmoski MJ, Brandt KD (1984) Effects of static and cyclic compressive loading on articular cartilage plugs in vitro. Arthritis Rheum 27:675–681
85. Larsson T, Aspden RM, Heinegård D (1991) Effects of mechanical load on cartilage matrix biosynthesis in vitro. Matrix 11:388–394
86. Sah RL-Y, Kim Y-J, Doong J-YH, Grodzinsky AJ, Plaas AHK, Sandy JD (1989) Biosynthetic response of cartilage explants to dynamic compression. J Orthop Res 7:619–636
87. Korver THV, van der Stadt RJ, Kiljan E, van Kampen GPJ, Vanderkorst JK (1992) Effects of loading on the synthesis of proteoglycans in different layers of anatomically intact articular cartilage in vitro. J Rheumatol 19:905–912
88. Parkkinen JJ, Lammi MJ, Helminen HJ, Tammi M (1992) Local stimulation of proteoglycan synthesis in articular cartilage explants by dynamic compression in vitro. J Orthop Res 10:610–620
89. Parkkinen JJ, Ikonen J, Lammi MJ, Laakkonen J, Tammi M, Helminen HJ (1993) Effects of cyclic hydrostatic pressure on proteoglycan synthesis in cultured chondrocytes and articular cartilage. Arch Biochem Biophys 300:458–465
90. Aydelotte MB, Greenhill RR, Kuettner KE (1988) Differences between sub-populations of cultured bovine articular chondrocytes. II. Proteoglycan metabolism. Connect Tissue Res 18: 223–234
91. Parkkinen JJ, Paukkonen J, Pesonen E, Lammi MJ, Markkanen S, Helminen HJ, Tammi M (1990) Quantitation of autoradiographic grains in different zones of articular cartilage with image analyzer. Histochemistry 93:241–245
92. Hering TM (1999) Regulation of chondrocyte gene expression. Front Biosci 15:D743–D761
93. Winter GM, Poole CA, Ilic MZ, Ross JM, Robinson HC, Handley CJ (1998) Identification of distinct metabolic pools of aggrecan and their relationship to type VI collagen in the chondrons of mature bovine articular cartilage explants. Connect Tissue Res 37:277–293
94. Hascall VC, Sanfy JD, Handley CJ (1999) Regulation of proteoglycan metabolism in articular cartilage. In: Archer CW, Caterson B, Benjamin M, Ralphs JR (eds) Biology of the Synovial Joint. Harwood, Amsterdam, pp 101–120
95. Quinn TM, Grodzinsky AJ, Buschmann MD, Kim YJ, Hunziker EB (1998) Mechanical compression alters proteoglycan deposition and matrix deformation around individual cells in cartilage explants. J Cell Sci 111:573–583
96. Quinn TM, Grodzinsky AJ, Hunziker EB, Sandy JD (1998) Effects of injurious compression on matrix turnover around individual cells in calf articular cartilage explants. J Orthop Res 16:490–499
97. Bolton MC, Dudhia J, Bayliss MT (1999) Age-related changes in the synthesis of link protein and aggrecan in human articular cartilage: implications for aggregate stability. Biochem J 337:77–82
98. Maroudas A (1980) Physical chemistry of articular cartilage and the intervertebral disc. In: Sokoloff L (ed) The Joints and Synovial Fluid, vol II. Academic, New York, pp 239–291
99. Lark MW, Gordy JT, Weidner JR, Ayala J, Kimura JH, Williams HR, Mumford RA, Flannery CR, Carlson SS, Iwata M, Sandy JD (1995) Cell-mediated catabolism of aggrecan. Evidence that cleavage at the "aggrecanase" site (Glu373-Ala374) is a primary event in proteolysis of the interglobular domain. J Biol Chem 270:2550–2556
100. Lark MW, Bayne EK, Flanagan J, Harper CF, Hoerner LA, Hutchinson NI, Singer II, Donatelli SA, Weidner JR, Williams HR, Mumford RA, Lohmander LS (1997) Aggrecan degradation in human cartilage. Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints. J Clin Invest 100:93–106
101. Tortorella MD, Burn TC, Abbaszade I, Hollis JM, Liu R, Rosenfeld SA, Copeland RA, Decicco CP, Wynn R, Rockwell A, Yang F, Duke JL, Solomon K, George H, Bruckner R, Nagase H, Itoh Y, Ellis DM, Ross H, Wiswall BH, Murphy K, Hillman MC Jr, Hollis GF, Arner EC (1999) Purification and

cloning of aggrecanase-1: a member of the ADAMTS family of proteins. Science 284:1664–1666
102. Abbaszade I, Liu RQ, Yang F, Rosenfeld SA, Ross OH, Link JR, Ellis DM, Tortorella MD, Pratta MA, Hollis JM, Wynn R, Duke JL, George HJ, Hillman MC Jr, Murphy K, Wiswall BH, Copeland RA, Decicco CP, Bruckner R, Nagase H, Itoh Y, Newton RC, Magolda RL, Trzaskos JM, Hollis GF, Arner EC, Burn TC (1999) Cloning and characterization of ADAMTS11, an aggrecanase from the ADAMTS family. J Biol Chem 274: 23443–23450
103. van Meurs JB, van Lent PL, Holthuysen AE, Singer II, Bayne EK, van den Berg WB (1999) Kinetics of aggrecanase- and metalloproteinase-induced neoepitopes in various stages of cartilage destruction in murine arthritis. Arthritis Rheum 42:1128–1139
104. Sztrolovics R, White RJ, Poole AR, Mort JS, Roughley PJ (1999) Resistance of small leucine-rich repeat proteoglycans to proteolytic degradation during interleukin-1-stimulated cartilage catabolism. Biochem J 339:571–577
105. Nelson F, Dahlberg L, Laverty S, Reiner A, Pidoux I, Ionescu M, Fraser GL, Brooks E, Tanzer M, Rosenberg LC, Dieppe P, Poole AR (1998) Evidence for altered synthesis of type II collagen in patients with osteoarthritis. Clin Invest 102:2115–2125
106. Aigner TY, Vornehm SI, Zeiler G, Dudhia J, von der Mark K, Bayliss MT (1997) Suppression of cartilage matrix gene expression in upper zone chondrocytes of osteoarthritic cartilage. Arthritis Rheum 40:562–569
107. Aigner T, Bertling W, Stöss H, Weseloh H, von der Mark K (1993) Independent expression of fibril-forming collagens I, II, and III in chondrocytes of human osteoarthritic cartilage. J Clin Invest 91:829–837
108. Bank RA, Bayliss MT, Lafeber FPJG, Maroudas A, Tekoppele JM (1998) Ageing and zonal variation in post-translational modification of collagen in normal human articular cartilage. The age related increase in non-enzymatic glycation affects biomechanical properties of cartilage. Biochem J 330:345–351
109. Maroudas A (1980) Metabolism in cartilaginous tissues. a quantitative approach. In: Maroudas A, Holborow EJ (eds) Studies in Joint Disease, vol 1. Pitman, Tunbridge Wells, pp 59–86
110. Hollander AP, Pidoux I, Reiner A, Rorabeck C, Bourne R, Poole AR (1995) Damage to type II collagen in ageing and osteoarthritis starts at the articular surface, originates around chondrocytes, and extends into the cartilage with progressive degeneration. J Clin Invest 96:2859–2869
111. Stoop R, van der Kraan PM, Buma P, Hollander AP, Billinghurst RC, Poole AR, van den Berg W (1999) Type II collagen degradation in spontaneous osteoarthritis in C57Bl/6 and BALB/c mice. Arthritis Rheum 42:2381–2389
112. Billinghurst RC, Dahlberg L, Ionescu M, Reiner A, Bourne R, Rorabeck C, Mitchell P, Hambor J, Diekmann O, Tschesche H, Chen J, van Wart H, Poole AR (1997) Enhanced cleavage of type II collagen by collagenases in osteoarthritic articular cartilage. J Clin Invest 99:1534–1545
113. Lewis EJ, Bishop J, Bottomley KM, Bradshaw D, Brewster M, Broadhurst MJ, Brown PA, Budd JM, Elliott L, Greenham AK, Johnson WH, Nixon JS, Rose F, Sutton B, Wilson K (1997) Ro 32–3555, an orally active collagenase inhibitor, prevents cartilage breakdown in vitro and in vivo. Br J Pharmacol 121:540–546
114. Beekman B, Verzijl N, Bank RA, von der Mark K, TeKoppele JM (1997) Synthesis of collagen by bovine chondrocytes cultured in alginate; posttranslational modifications and cell-matrix interaction. Exp Cell Res 237:135–141
115. Bendele AM, Hulman JF (1988) Spontaneous cartilage degeneration in guinea pigs. Arthritis Rheum 31:561–565
116. Wolff J (1892) Das Gesetz der Transformation der Knochen. Hirschwald, Berlin
117. Tobias JH (1999) Bone biology and the management of osteoporosis. Rheumatol Eur 28:93–98
118. Genant HK, Cooper C, Poor G, Reid I, Ehrlich G, Kanis J, Nordin BEC, Barrett-Connor E, Black D, Bonjour J-P, Dawson-Hughes B, Delmas PD, Dequeker J, Ragi Eis S, Gennari C, Johnell O, Johnston CC Jr, Lau EMC, Liberman UA, Lindsay R, Martin TJ, Masri B, Mautalen CA, Meunier PJ, Miller PD, Mithal A, Morii H, Papapoulos S, Woolf A, Yu W, Khaltaev N (1999) Interim report and recommendations of the World Health Organization task force for osteoporosis. Osteoporosis Int 10:259–264
119. Puustjärvi K, Nieminen J, Räsänen T, Hyttinen M, Helminen H, Kröger H, Huuskonen J, Alhava E, Kovanen V (1999) Does higher organization of collagen fibrils add to bone mechanical strength in loss of mineral density after one-year running time? J Bone Miner Res 14:321–329
120. Takano Y, Turner CH, Owan I, Martin RB, Lau ST, Forwood MR, Burr DB (1999) Elastic anisotropy and collagen orientation of osteonal bone are dependent on the mechanical strain distribution. J Orthop Res 17:59–66
121. Murray PDF, Selby D (1930) Intrinsic and extrinsic factors in the primary development of the skeleton. Wilhelm Roux' Arch Entwicklungsmech Org 122:629–662
122. Fell HB, Canti RG (1934) Experiments on the development in vitro of the avian knee joint. Proc R Soc Lond Ser B 116:316–351
123. Drachman DB, Sokoloff L (1966) The role of movement in embryonic joint development. Dev Biol 14:401–420
124. Moffett BC Jr (1965) The morphogenesis of joints. In: DeHaan RL, Ursprung H (eds) Organogenesis. Holt, Rinehart & Winston, New York, pp 301–313
125. Johnson LC (1959) Kinetics of osteoarthritis. Lab Invest 8:1223–1238
126. Archer CW, Francis-West P (1999) Development of joints and articular cartilage. In: Archer CW, Caterson B, Benjamin M, Ralphs JR (eds) Biology of the Synovial Joint. Harwood, Amsterdam, pp 11–22
127. Poole AR, Nelson F, Hollander A, Reiner A, Pidoux I, Ionescu M (1995) Collagen II turnover in joint diseases. Acta Orthop Scand 66 (suppl 266):88–91
128. Muir H (1995) The chondrocyte, architect of cartilage. BioEssays 17:1039–1048
129. Otterness IG, Eskra JD, Bliven ML, Shay AK, Pelletier JP, Milici AJ (1998) Exercise protects against articular cartilage degeneration in the hamster. Arthritis Rheum 41:2068–2076