Biochemical Basis of the Pharmacologic Action of Chondroitin Sulfates on the Osteoarticular System

Jean-Pierre Bali, Henri Cousse, and Eugène Neuzil

**Background:** Chondroitin sulfates (CS) are involved in articular metabolism and could be used as therapeutic agents in degenerative articular diseases.

**Objectives:** To review the published reports describing both the metabolism of glycosaminoglycans (GAG) and their involvement in osteoarticular pathophysiology.

**Methods:** MEDLINE search for relevant articles and review of cited references.

**Results:** 1) CS are formed of disaccharide units; sulfated galactosamine residues in position 4 or 6 are found in various ratios, depending on the age and the type of tissue. Binding to the core protein through N- and O-linkages leads to aggregates of monomers with high molecular weights. The proteoglycan aggregate exhibits viscoelastic and hydration properties and an ability to interact with the surrounding tissue through electric charges leading to protection of the cartilaginous tissues. 2) CS are synthesized both in chondrocytes and in bone cells by the action of specific glycosyl-transferases; their catabolism occurs in the matrix and involves numerous matrix (metalloproteinases) and lysosomal enzymes. 3) CS are inhibitors of extracellular proteases involved in the metabolism of connective tissues. In addition to their anti-inflammatory effects, CS in vitro stimulate proteoglycan production by chondrocytes; they also inhibit cartilage cytokine production and induce apoptosis of articular chondrocytes. CS increase the intrinsic viscosity of the synovial liquid. 4) In vivo in experimental arthritis, the number and severity of articular symptoms decreases after CS administration. In bones, CS accelerate the mineralization process and bone repair.

**Conclusions:** All these data suggest that CS play a role in articular and bone metabolism by controlling cartilaginous matrix integrity and bone mineralization.

**INDEX WORDS:** Chondroitin sulfates; proteoglycans; cartilage; bone; chondrocytes; articular diseases; mineralization.

The growing interest in the therapeutic use of glycosaminoglycans (GAG) parallels the recent advances in understanding their biological functions. In addition to the well-known anticoagu-
cally and are able to reduce consumption of nonsteroidal anti-inflammatory drugs (5-7).

In this article, the structure and biosynthesis of CS are reported, and their pharmacologic effects on the osteoarticular system are reviewed.

**STRUCTURE AND BIOCHEMISTRY OF THE CARTILAGE PROTEOGLYCAN AGGREGATE**

*The Proteoglycan Aggrecan and Chondrocytes*

Normal mature cartilage consists of chondrocytes embedded in an extracellular matrix. Chondrocytes are responsible for the biosynthesis, homeostasis, and catabolism of cartilage. Besides collagen fibers (types II, IX, and XI), which give the cartilage its tensile strength, the extracellular matrix contains a more specific component, a proteoglycan aggregate (“aggrecan”) (8) that results from the association of various GAG chains with 2 types of proteins. The entire complex is a large macromolecule of about $10^6$ daltons that shows extreme polydispersity in size and composition. The cartilage proteoglycan aggregate has a length of several microns, occupying a volume equivalent to that of a bacterium; when isolated from tissues, the macromolecule can be readily seen under the electron microscope.

*Biochemical Structure of CS*

The main disaccharide units of cartilage GAG are formed by the (1→3) linkage of D-glucuronic acid to N-acetylgalactosamine; the disaccharide units are associated themselves by β (1→4) galactosamine links. The galactosamine residues are sulfated either in position 4 (4-CS) or 6 (6-CS): the sulfate groups, together with the carboxyl groups of glucuronic acid, are ionized, thus conferring to the chain a strong global negative charge (Fig 1).

The sulfation pattern of chondroitin disaccharides from normal human articular cartilage varies with the age of the subject, the topography of the joint surface, and the zone of cartilage examined. The deeper layers of immature cartilage have 4 times more sulfated residues than the upper regions of the tissue. As the cartilage ages and gets thinner, the 6-CS predominate (9). In cancellous or compact bones, 4-CS is the usual disaccharide (10), as, for example, in the femoral neck of patients with a fracture or osteoarthritis (11). In cartilaginous tissue, about 100 CS chains, each containing 50 to 60 disaccharide units, are covalently attached to a long polypeptide backbone composed of more than 2,000 amino acid residues (the serine-rich core protein with a molecular weight of 250,000 to 300,000). This O-linkage occurs between a xylose or galactose residue (1 and 2 moles, respectively, per mole of proteoglycan) and a serine or threonine (approximately 1 CS chain for every 20 amino acid residues).

The other end of the core protein is not covalently linked to a long filament of hyaluronic acid through a link protein; the connection is achieved by means of the terminal part of the core protein, which forms a globular region (40,000 to 90,000 d) that surrounds a stretch of 5 disaccharide units along the length of the hyaluronic chain and the core protein (12,13). The total molecular weight of a proteoglycan monomer is 1.5 to 2.5 $10^6$ d. Approximately 100 core proteins are bound to the hyaluronic acid chain, at regular intervals of 300 Å. The general structure is shown in Figure 2.

The domain of the core protein located between the link protein and the CS region is occupied by about 50 keratan sulfate chains; the keratan sulfate disaccharide unit, represented by a galactosido-1,4-N-acetylglucosamine-6-sulfate, has only one negative charge; these disaccharide units are joined by a β (1→3) linkage.

*Physicochemical Properties of the Proteoglycan*

The properties of the proteoglycan aggregate can mainly be explained by the properties of the GAG chains, which account for 80% to 90% of the mass of the aggregate. The presence of a highly ordered array of negative charges explains the

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**Abbreviations**

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<tr>
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<td>CS</td>
<td>Chondroitin sulfates</td>
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<td>GAG</td>
<td>Glycosaminoglycans</td>
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<td>MMPs</td>
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<td>TGF-β</td>
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<td>TIMPs</td>
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<td>TNF-α</td>
<td>Tumor necrosis factor-α</td>
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<td>UDP</td>
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<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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attraction of a large number of water molecules by electrostatic forces; the small electric dipoles of water become organized in multiple interacting layers or shells surrounding the electric charges (14). The physiology of cartilage and its characteristic viscoelastic properties are linked to the fact that water is a prominent constituent of cartilage. When pressure is applied to cartilage, water is forced away from the ionized sulfate and carboxy groups; when the negative charges come into close proximity, the repulsive forces of the charges exert further compression, generating an osmotic swelling pressure. When the pressure is released, the water dipoles return to the charged domains (12). One other property of the proteoglycan aggregate is to regulate the function of cytokines and growth factors that bind to its core protein (15).

Biosynthesis of Proteoglycan

The biosynthesis of the proteoglycan aggregate was described in the 1970s and comprehensively reviewed by Bailey and Robbins (16) and subsequently by Dorfman (17). The synthetic pathways involve proteins, activated carbohydrate units (most of them as uridine diphosphate[UDP]-derivatives), glycosyltransferases, and sulfotransferases (18,19).

The core protein is synthesized on membrane-bound ribosomes and threaded into the lumen of the endoplasmic reticulum; the polysaccharide chains are assembled on the core protein in the Golgi complex. For the CS chains, a special trisaccharide link (xylose-galactose-galactose) is first attached to a serine residue of the polypeptide chain to serve as a primer for polysaccharide growth; then, one sugar residue is added by specific glycosyl transferases (20), as shown in Figure 3. Some serine residues only accept N-acetylgalactosamine to make keratan sulfate. Sulfation by 3'-phosphoadenosyl-5'-sulfate is the final step. More than 10,000 enzymatic steps are required for the synthesis of one proteoglycan aggregate.

Regulation of Proteoglycan Biosynthesis

Regulation of cartilage proteoglycan biosynthesis implies both inhibition by UDP-GlcNac, an aminotransferase inhibitor, and activation by UDP-xylose, an initiator of the polysaccharide chain. Moreover, each disaccharide unit formed activates the elongation of the polysaccharide chain.

There exists a close relationship between the 3 main tissues of mesodermal origin: cartilage, bone, and connective tissue, where collagen is synthesized. This is particularly evident when one considers the catabolism of the cartilage matrix, a
process occurring at every stage of life, in healthy and diseased subjects.

**Similarities Between Bone Formation and Angiogenesis**

Chondrocytes, the specific cartilage-forming cells, appear early in embryonic development, when capillaries, present at the center of the limb, recede. When the capillaries reappear in the proximity of cartilage, bone formation begins. This leads to progressive disappearance of both chondrocytes and cartilage matrix, which are replaced by osteoblasts and calcified tissue. Gerber et al (21) recently showed that vascular endothelial growth factor (VEGF), an angiogenic factor involved in the development of some malignant tumors, plays a significant role in the endochondral ossification process. In the young growing organism, cartilage is still present at the tips of the bones, forming growth plates from which the bones extend their length. The growth plates finally disappear, suggesting a probable link with the secretion of VEGF by hypertrophied degenerated chondrocytes. In adults, cartilage remains only in the joints where its role in articular physiology appears obvious. In healthy subjects, joint cartilage shows great stability: The turnover of its characteristic molecular components is slow.

The catabolism of cartilage also must be considered in pathologic cases. When a bone is fractured, undifferentiated cells invade the breakage and become chondrocytes: The cartilaginous matrix fill the gap and join the bone fragments together. This

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**Fig 2. Hypothetical structure of cartilage aggrecan.** The dimeric unit of glucuronic acid and N-acetyl-galactosamine is polymerized to form GAG side chains. The “tree” structure of this proteoglycan is typical. GAG are covalently linked to the core protein through a specific binding domain with a Ser-Gly sequence. A hydrophobic region, which is the site of linkage to the membrane glycosylphosphatidylinositol, is found in the protein core along with a highly conserved adhesion protein N-CAM, immunoglobulin (lg) and repetitive tandem proteoglycan (RTP) domain.

**Fig 3. Sequential events in the biosynthesis of cartilage proteoglycan.** The first step of biosynthesis is the attachment of a xylose unit to a serine residue through an O-linkage. Other enzymes are sequentially involved to elongate the polysidic side chain attached to the core protein.
obligatory step has a limited duration and finishes with the intervention of VEGF, formation of new capillaries, aggrecan destruction, and the appearance of new bone. The intense proteoglycan catabolism, leading to progressive destruction of joint cartilage (22) and resulting in joint space narrowing and articular inflammation, is one phenomenon involved in the pathogenesis of arthritis.

**CS Catabolism**

CS are catabolized within the matrix by the action of lysosomal enzymes secreted by cells of the connective tissue such as glycosidases (N-acetyl-glucosaminidase, galactosidase, glucuronidase) and chondroitinas that destroy the osidic bond between N-acetylg glucosamine and glucuronic acid.

There are 4 major enzymes secreted by chondrocytes that are involved in the degradation of joint cartilage: 1) Matrix metalloproteases (MMPs) are a family of at least 15 endopeptidases that function extracellularly at neutral pH; they are divided into 3 subfamilies (collagenases, gelatinases, and stromelysins) and are also known as ADAMTS (a desintegrin and metalloproteases). MMPs all possess a catalytic sequence in which 3 histidine residues are linked to a zinc atom to form the active site. Nine MMPs (MMP-1, -2, -3, -7, -8, -9, -10, -11, -13) and a membrane-bound MMP (MT1-MMP-14) specifically cleave the aggrecan core protein between amino acid residues Asn341 and Phe 342 (23,24). Tissue inhibitors of metalloproteases (TIMPs) are physiologic regulators of MMPs. 2) Fragments of aggrecan found in the synovial fluid of arthritic joints result from a specific cleavage between Glu373 and Ala 374 (25,26), catalyzed by an aggrecanase that has only recently been characterized. This enzyme contains in its catalytic domain a zinc-binding motif similar to that found in MMPs (27). Aggrecanase proteolysis probably occurs at several other sites within the aggrecan core protein. 3) Thiolproteases (cathepsins B and L). 4) Serine proteases. The end result is decreased viscoelastic properties of cartilage.

**PHARMACOLOGIC ACTIONS OF CS**

**General Pharmacodynamics**

No significant clinical harmful symptoms were found after oral administration of CS to animals. In rodents, unique dose experiments reached 2 g/kg; in rats, dogs, and cats a daily dose of 60 to 100 mg/kg given for more than 3 months was well tolerated. Administered orally at 1 g/kg/d to rats and rabbits, the drug had no observable effect on mutagenesis or on reproductive function (28).

In the digestive tract, using the isolated rabbit intestinal loop model, no change in the amplitude of intestinal contractions or in the tonicity of the intestine was noted in the presence of 1 to 3 mg/mL CS. At doses of 0.25 to 1 g/kg, no change occurred in the rate of intestinal transit in mice. With regard to blood, CS does not modify the coagulation time. On the cardiovascular system, CS at 25 to 100 mg/kg (perfusion rate 25 mg/min) has no effect on the electrocardiogram; 100 mg/kg induces a slight and transitory decrease of arterial pressure. Whatever the dose, CS causes an increased respiratory rate and amplitude (28). Regarding renal function, no change in the volume or the electrolyte concentration of urine was found after subcutaneous administration of CS at 100 mg/mL (28).

**Pharmacokinetics**

The first evidence of the presence of low–molecular-weight chondroitin-4 sulfate in blood after administration of CS in rats was reported in 1978 by Hata and Nagai (29). They found a half-life for the tritiated hexosamine of 10 to 12 hours after intraperitoneal administration.

Other studies using labelled (3H, 99mTc) and unlabelled CS administered to dogs and rabbits also have been published (30,31). After oral administration, a rapid increase in blood concentrations was found, followed by a plateau at the 14th (in rats) and 28th hour (in dogs). More than 30% of the unchanged compound was excreted in the urine and 30% in feces, showing good intestinal absorption. In addition, CS exhibited a selective tropism toward GAG-rich tissues, such as the eyes and joint cartilage, the lumbar disks, and the corresponding vertebral epiphysis. Molecular weight analysis of the radioactive material showed that, when using compounds with relative molecular mass corresponding to those of CS polysaccharides, oligosaccharides, and monosaccharides, at least 10% of the total radioactivity injected was found as high–molecular-weight proteoglycans. In humans, after administration of CS orally at 2 or
3 g, an increase in CS blood concentrations was observed 3 to 6 hours after absorption (30).

**Effects on Extracellular Proteases Involved in the Metabolism of Connective Tissues**

Various enzymes are required to degrade cartilage; they are secreted by leukocytes gathering at the inflammatory site (elastase) or by chondrocytes (cathepsin B, metalloproteases, etc). Leukocyte elastase destroys the proteoglycan barrier of the cartilage and solubilizes collagen by disorganizing its molecular network. In vitro studies have shown that CS inhibit this enzyme activity by formation of electrostatic bonds between the negatively charged sulfate residues and the positive charges at the catalytic site of the enzyme ($K_i = 3.4 \, \mu g/mL$). The inhibitory effect increases with the molecular weight of CS and the proportion of 6-isomers versus 4-isomers ($K_i = 1.8 \, \mu g/mL$) (32). This result was confirmed in vivo in rats on plasma elastase activity (57% inhibition of the activity after 600 mg/kg for 8 days) (33).

CS also are able to moderately inhibit in vitro chymotrypsin-like neutral proteases and elastase-like activities extracted from human granulocytes. The degree of inhibition of both activities is higher with the 6-isomer than with the 4-isomer, and this inhibition also occurs through ionic interactions (34).

Cathepsin B is a thiolprotease produced by chondrocytes and is involved directly or indirectly in the destruction of cartilage by the conversion of procollagenase to collagenase and, in a subsequent step, by the degradation of the molecular matrix. When added to cultures of rabbit articular chondrocytes in vitro at 1 to 100 $\mu g/mL$, 4-CS and 6-CS isomers reduce the release of cathepsin B in a transitory manner. A polysulfated derivative of CS with a sulfate/disaccharide ratio of 3.25 shows potent and persistent inhibitory effects, indicating that numerous sulfate residues are required to cause significant inhibition of cathepsin B production (35).

As indicated above, the major enzymes involved in the degradation of joint cartilage are secreted by chondrocytes: metalloproteases (collagenase I–MMP-1, stromelysin–MMP3), thiolproteases (cathepsin B and L), serine proteases, and their regulatory factors such as TIMPs. In arthritis, MMP production increases, leading to massive destruction of proteoglycans and collagen. In human ar- ticular chondrocytes cultured in clusters, CS significantly stimulated proteoglycan production in the clusters but decreased the collagenolytic activity in the culture medium (36). Added to 3-dimensional chondrocyte cultures at concentrations of 100 to 1000 $\mu g/mL$, CS did not modify MMP3 secretion but counteracted the stimulatory effect of interleukin-1$\beta$ (IL-1$\beta$) on this enzyme. In addition, an increase in TIMP1 and pro-MMP1 synthesis in the culture was observed (37). Other reports have shown that CS also are able to inhibit cyclic AMP–dependent protein kinase activity in vitro, possibly related to the activation of this enzyme by parathyroid hormone receptors (38).

**Anti-inflammatory Properties**

CS administered orally at 200 mg/kg showed anti-inflammatory properties in rats and rabbits in inflammatory models such as edema induction by subcutaneous implants of carragehenin or Evans blue diffusion from edematous fluids (31,33). Furthermore, CS also exhibit some scavenger properties in the Fenton reaction (where oxygenated free radicals are generated), independent of the position of the sulfate groups (4-CS or 6-CS) and the length of the carbohydrate chain. This effect appears to protect cartilage matrix against degradation by oxygenated free radicals (hyaluronic acid depolymerization and loss of intrinsic viscosity) (39).

The intramuscular administration of egg white to rats leads to an anaphylactic reaction linked to histamine release. CS both prevent and decrease edema formation at the injection site (33).

**In Vitro Regulation of Chondrocyte Function**

Numerous in vitro studies have shown that exogenous CS stimulates the production of proteoglycans. Added at 200 $\mu g/mL$ to monolayer-cultured chondrocytes, CS increase sulfate incorporation into CS proteoglycan, depending on the stage of the culture (maximum effect during the log phase) (40). Similarly, when added to monolayer cultures of synovial lining cells during the log phase, CS stimulated synthesis of hyaluronate (11%), which is a part of the proteoglycan molecule. When added during the stationary phase of growth, the increase in hyaluronate synthesis was greater (88%) (41). In rabbit knee synovial membranes, sulfated GAG also increases hyaluronic acid biosynthesis (42).
Collagen formation in chondrocytes is enhanced by transforming growth factor-β (TGF-β) and CS amplify this effect (36). However, in fetal rat calvariae, in contrast to heparin, CS do not modify collagen synthesis (43). A more recent study shows that CS prevent collagen II degradation induced by IL-1β (44).

At concentrations higher than 300 μg/mL, CS in vitro inhibit IL-1β, tumor necrosis factor-α (TNF-α), and IL-6 production by mononuclear cells from peripheral blood and by differentiated U-937 cells (43). Binding tests showed that CS do not bind to receptors for IL-1β (CHO cells), IL-1β, TGF-α (Balb/c 3T3), or IL-6 (U-266 cells) but interact with TNF-α receptors (U-937 cells), with a 50% inhibitory concentration (IC-50) of about 300 μg/mL (44). These data suggest that CS act on TNF-α metabolism (a cytokine involved in cartilage degradation) by limiting its synthesis and by blocking its receptor. Thus, although CS do not interact with the IL-1β receptor, they exert a double action on this cytokine: On one hand, they reduce its production, and on the other, they counteract the inhibitory effect of IL-1β on proteoglycan and collagen synthesis and antagonize prostaglandin E2 secretion generated by this cytokine.

In joint cartilage, more than 50% of chondrocytes show signs of apoptosis compared with 10% in normal cartilage. Nitric oxide production may be involved in this process, because in osteoarthritis, nitric oxide appears to be increased in articular chondrocytes stimulated by IL-1β. In 70% of the cases, preventive treatment with 100 μg/mL of 4-CS and 6-CS isomers reduces the number of apoptotic cells (45).

Effects on Synovial Fluid

In patients with hip osteoarthritis, CS levels in synovial fluid and the ratio of isomers vary with the severity of the disease, reflecting extracellular matrix catabolism in joint tissues (46,47). High-molecular-weight molecules of hyaluronic acid prevent the release of proteoglycans and fibronectin from the cartilaginous matrix of rabbit knee joints by forming a viscous barrier on the matrix through sugar-sugar or sugar-protein interactions. Moreover, in vitro addition of CS at 0.5 to 10 mg/mL increases the intrinsic viscosity of hyaluronic acid solutions (48) the same effect was observed after oral administration of CS in rabbits (42), and after proteoglycan depletion induced by bradykinin in rats (49). These data were confirmed in vivo by 42 days of oral administration of CS at 12 g/d in arthritic horses; this led to an increase in synovial fluid viscosity (50).

Efficacy and Tolerance In Vivo in Experimental Arthritis

In different animal models of arthritis, the efficacy of CS treatment on clinical symptoms was evaluated. In the C-57–black mouse, a strain that develops a hereditary gonarthrose, oral administration of CS at doses of 50 to 150 mg/kg for 4 months led to functional improvement. The number of articular lesions and their severity decreased (51). Similarly, administration of CS at 250 mg/d for 2 months to arthritic cats reduced the pain and functional symptoms by 70%: Lameness decreased by about 45%, the amplitude of bending was increased, and pain caused by stretching the limb was reduced. In this study, the efficacy of CS was similar to that of acetylsalicylic acid given at a dose of 10 mg/kg/d for 2 months (52). The same study was performed in arthritic dogs with the same results. Administration of CS at 25 mg/kg/d for 2 to 3 months had the same efficacy as acetylsalicylic acid at 20 mg/kg/d for the same period of time. Lameness was improved by about 44%, the amplitude of bending increased, and pain caused by stretching the limb was reduced (52). Horses frequently exhibit arthritis, and when administered at a dosage of 12 g/d for 90 days to 13 horses with clinical symptoms of arthritis, CS significantly improved the biomechanical parameters of the horses, leading to a significant decrease of lameness at rest and after effort, of pain after bending, and of infirmity. The global functional evaluation performed both by the owner and by the veterinarian improved. In addition, CS did not cause side effects in these horses (50).

PHARMACOLOGIC PROPERTIES IN BONE MINERALIZATION PROCESS

Proteoglycans represent the main macromolecular components of noncalcified tissues. They also are present in bones, where they are synthesized by osteoblasts. The 4-CS and 6-CS isomers, CS, dermatan sulfate, keratan sulfate, hyaluronic acid, and heparan sulfate are the primary GAG representatives, and their relative proportion varies with age and the animal species.
Effects on Calcium Homeostasis

The first study of the effects of CS on calcium metabolism was performed in 1969 by Blanquet (53), who studied 45Ca metabolism in aged osteoporotic women (66 to 87 years old). After oral administration of CS at 2 g/d for 15 days followed by 1.5 g/d for 120 days, a significant increase in the total calcium pool and better intestinal absorption of calcium were observed.

Effects on Bone Mineralization

Several studies have shown that GAG and collagen are produced during bone mineralization. Calcification and bone maturation are associated with a decrease in the proteoglycan contents of the organic matrix. CS is the predominant component: 25% to 50% of CS recently synthesized is lost (54). However, in contrast to the 6-CS isomer, the 4-CS isomer increases significantly in proliferative tissue in contact with the mineralization zone (55). As indicated above, GAG, together with TGF-β, up-regulates GAG biosynthesis in tissues such as neonatal calvariae that possess a rapid turnover (56). CS inhibit hydroxyapatite formation in solution (57). In cell systems, CS also prevent calcium accumulation in periosteal cell cultures and thus mineralization in the presence of α-glycerophosphate; in contrast, CS do not modify phosphate accumulation, suggesting the existence of differential mechanisms for calcium and phosphate accumulations (56). A similar observation arises from a study on the periodontal ligament of sheep (58).

Another report from Bouvier et al (59) on bone-derived cells cultured in a 3-dimensional reconstituted matrix showed, by immunocytochemical and ultrastructural means, that calcification only occurs in the collagen-CS sponge fibers. This suggests that CS, in association with collagen, promotes in vitro mineralization.

Studies performed on murine osteoblasts (60) show an alteration of proteoglycan synthesis with loss of hydrophobicity during the mineralization process. However, in the presence of 1,25-dihydroxy vitamin D, mineralization was not noted in the cultures and the levels of CS remained low during this period of treatment. Thus, CS may protect the calcium pool of bone by counteracting the effect of parathyroid hormone.

In contrast to heparin, which induces osteoporosis in experimental animals and humans (61,62), in vitro osteoclast activity, measured by the size of the bone resorption lacunae, although enhanced by heparin (100 μg/mL), was not altered by low concentrations of CS (25 to 100 μg/mL) (63). Similarly, heparin, but not CS, inhibited collagen synthesis in 21-day fetal rat calvarias (42). However, in organ culture studies, CS stimulated calcium release from bone, albeit at higher concentrations (64).

In Vivo Effects on the Rate of Bone Repair

The matrix, the nonmineral material of bone, is of critical importance in the dynamics of the remodeling process. An increase in 4-CS occurs simultaneously and enhances the development of cartilage mineralization. During osteogenesis, CS induced an increased capacity of the injured bone to regenerate. However, the clinical data are somewhat obsolete and lack pertinent statistical analysis.

DISCUSSION

CS isomers are synthesized in cells involved in the metabolism of bone and cartilage: namely, chondrocytes, synoviocytes, fibroblasts, and osteoblasts. Several clinical studies have shown their chondroprotective effects in osteoarthritis. However, the pharmacologic basis of such action has not been reviewed previously. The large proteoglycan molecule aggrecan found in articular cartilage contains many CS chains. The chondroprotective properties of this molecule are due, at least in part, to its physiochemical and mechanical properties mimicking the composition of the extracellular matrix. Changes in the composition and sulfation of the oligosaccharide chains are signs of disturbances in the metabolism of cartilage found in pathologic situations and aging.

In many experimental models CS participate in the control of cartilaginous matrix integrity by improving the anabolic activity of chondrocytes and by limiting excessive degradation of the cartilaginous matrix. By its anti-chemotactic and scavenger properties, CS also inhibited the development of inflammation. These experimental data were confirmed in patients with osteoarthritis using oral CS isomers, compounds of natural origin, at dosages varying from 1 to 3 g/d. CS improved clinical symptoms and led to fewer nonsteroidal anti-inflammatory drug prescrip-
tions. They may act as structure modulators by maintaining the interarticular space. No adverse side effects on vital functions were observed in these patients. Thus, CS may play an essential role in the control of cartilaginous matrix integrity and in the mineralization process (Fig 4).

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