Advanced Glycation Endproducts and Osteoarthritis

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Non-enzymatic glycation of proteins, such as collagen, results in the formation of advanced glycation endproducts (AGE). Advanced glycation endproducts result in pathologic stiffening of cartilage and extracellular matrix and accumulate with age. Pentosidine, an AGE, is present in serum, synovial fluid, and articular cartilage from patients with osteoarthritis (OA). However, AGE levels are not always increased, and may be decreased locally, in association with osteoarthritic pathology. The finding of pentosidine in articular cartilage of individuals with OA may not be specific for that disease, independent of chronologic age. Advanced glycation endproduct modification of normal articular cartilage increases its stiffness, increases chondrocyte-mediated proteoglycan degradation, reduces its susceptibility to matrix metalloproteinase–mediated degradation, and decreases proteoglycan synthesis by chondrocytes. These observations parallel findings in osteoarthritic cartilage, which suggests that AGE modification could contribute to the pathogenesis of OA. However, a causative link between AGEs and OA has not yet been established.

Introduction

Osteoarthritis (OA) is characterized by the softening, ulceration, and disintegration of articular cartilage, as well as by the formation of outgrowths of bone and cartilage at the joint margins. The development of OA strongly correlates with chronologic age [1] and also with obesity in weight-bearing joints [2]. The molecular basis for predisposition to and development of OA, however, has only recently begun to be elucidated. Various pathologic processes observed in articular cartilage contribute to the development of OA, including increased water content, loss of compressibility, decreased proteoglycan concentration, and increased synthesis and activity of matrix-degrading enzymes. The discovery of advanced glycation endproducts (AGE) and their receptors in articular tissue provides insight into the chemical and physical changes to cartilage, bone, and synovium that contribute to joint damage in OA.

Advanced Glycation Endproducts

Crosslinking of collagen contributes to the structural integrity of cartilage. Crosslinking increases during growth and remodeling of cartilage and may be altered in disease states. Crosslinks form by enzymatic and by non-enzymatic processes. Enzymatic modification of collagen results in the formation of irreducible, intra- and intermolecular crosslinks, such as pyridinoline and deoxypyridinoline. These enzymatic cross links contribute to collagen stability, are degraded during normal collagen remodeling, and do not accumulate with chronologic age [3]. In contrast, non-enzymatic modification of collagen results in the formation of AGE. Advanced glycation endproducts result in pathologic stiffening of cartilage and extracellular matrix, and accumulate with age [4••].

Advanced glycation endproducts are a heterogeneous group of compounds that have several characteristic properties—they are yellow-brown in color, fluoresce with emission at 440 nm on excitation at 370 nm, and covalently crosslink macromolecules [5]. Advanced glycation endproduct–modified proteins exhibit enhanced binding to collagen and trap non-glycosylated serum proteins, such as immunoglobulin, albumin, and low-density lipoproteins. Advanced glycation endproduct–modified proteins are less susceptible to degradation by proteases than are unmodified proteins [6]. Advanced glycation endproducts generate reactive oxygen intermediates [7]. These properties of AGE-modified proteins are presumed to contribute to the development of atherosclerosis and various complications of diabetes mellitus, including nephropathy, neuropathy, retinopathy, and cataracts [8].

Post-translational modification of proteins, as well as of lipids and nucleic acids, with AGE results from non-enzymatic glycation by the Maillard reaction between reducing sugars, such as glucose, and free amino groups. Other carbohydrates, such as threose, ribose, triose phosphate, fructose, and methylglyoxal, also serve as substrates for Maillard reactions in vivo and react with free amino groups to form AGE identical to those formed from glucose. Thus, AGE are not direct products of a single Maillard reaction with glucose, but instead are derived from a series of reactions (hence, the term *advanced*) [9].

In the first step of the Maillard reaction, an alpha-amino group of the N-terminal amino acid or the epsilon-amino group of lysine reacts with the carbonyl group of a reducing sugar to form a Schiff base (Fig. 1) [10]. This step

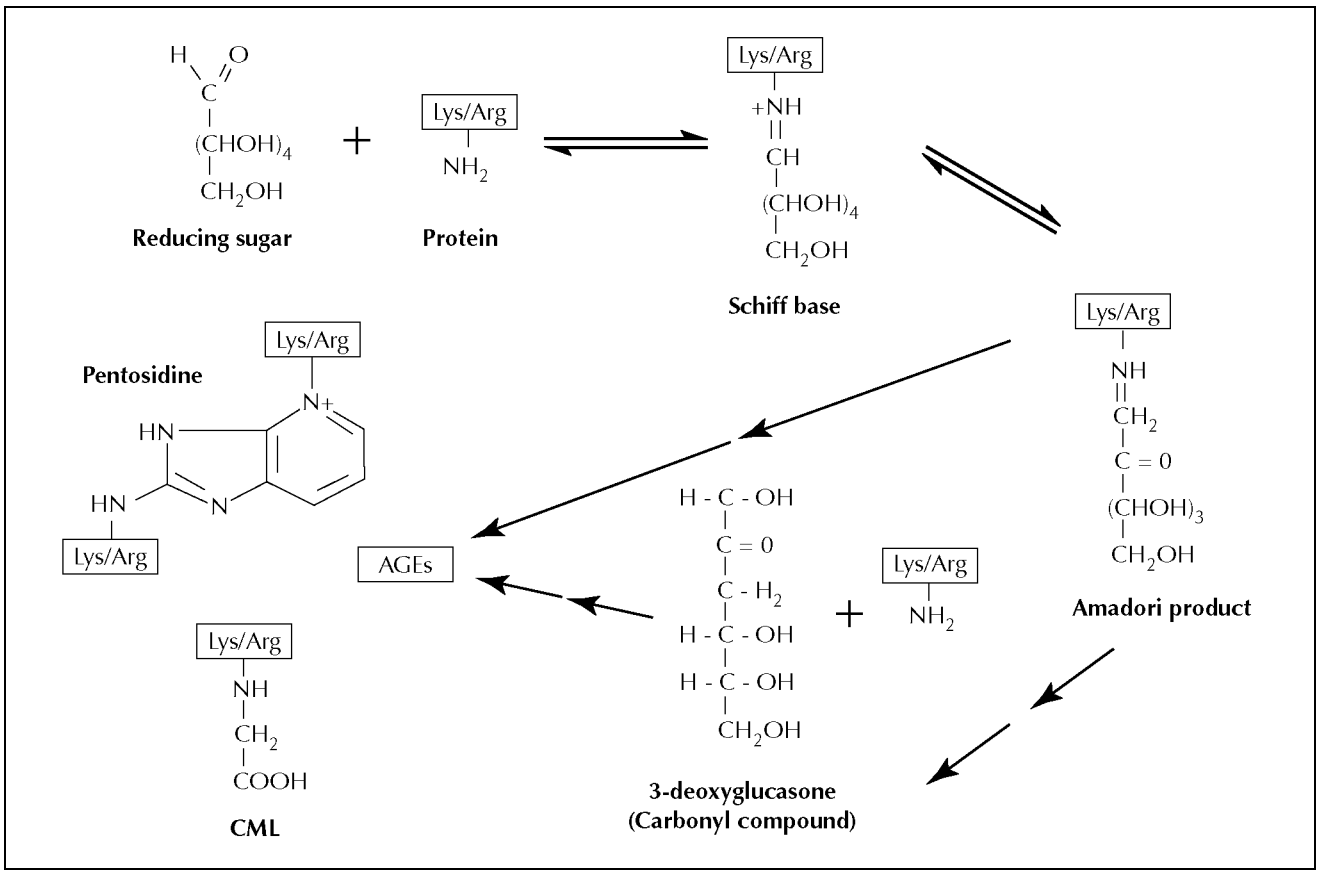

Figure 1. Formation of advanced glycation endproducts. Lys—lysine; Arg—argenine; CML—Nε-(carboxyethyl)lysine.

is reversible and reaches equilibrium over several hours. The Schiff base then undergoes intramolecular rearrangement to form the more stable Amadori product, reaching equilibrium over 28 days. This second step is also reversible, but favors Amadori product formation. The Amadori products subsequently undergo a series of irreversible chemical reactions, including dehydration and rearrangement, to form highly reactive carbonyl compounds, such as 3-deoxyglucosone. Over weeks to years, these carbonyl compounds undergo condensation with additional reactive amino groups to form AGEs.

Some AGEs, such as pentosidine, crosslines, and vesperlysines, are derived completely from carbohydrate substrate [11]. Other AGEs, such as Nε-(carboxymethyl)lysine (CML), Nε-(carboxyethyl)lysine (CEL), 1,3-bis(5-amino-5-carboxypentyl)imidazolium, and methyl glyoxal lysine dimer, can be created entirely or in part from carbohydrate or lipid substrate. Thus, glycation or lipoxidation may be involved in the formation of the same AGEs. The overlap of these synthetic pathways creates difficulties in taxonomy, because identical structures may appropriately be called AGEs, advanced lipoxidation end products (ALEs), or AGEs/ALEs.

Glucose concentration and protein half-life, among other variables, determine the extent of Amadori product and, consequently, of AGE formation [12]. Thus, AGE and their precursors accumulate in diabetes mellitus because of increased substrate production and in aging because of accumulation over time. Advanced glycation endproduct formation in skin collagen is increased by two- to fivefold in type I diabetes patients, and correlates directly with levels of Amadori products, such as hemoglobin A_{1c} [13]. Renal disease is also associated with AGE accumulation, because clearance of AGE-modified proteins is reduced in the setting of impaired renal function [14].

Chronologic aging is also associated with AGE accumulation. Advanced glycation endproducts irreversibly bound to long-lived proteins, such as collagen [5], increase linearly in proportion to age. Although all proteins with lysine and argenine residues are susceptible to AGE modification, the extremely slow rate of collagen turnover (approximately 100 years) makes collagen the primary site of articular AGE accumulation [15]. Advanced glycation endproducts deposit as adducts on individual collagen fibers and as crosslinks between adjacent fibers (Table 1) [16]. Glycation changes the tertiary structure and distribution of charges on type I collagen fibrils [17]. Advanced glycation endproduct formation on type II collagen (the predominant collagen in articular cartilage) and on types I and III collagen is increased, compared with that on type IV collagen (a collagen found in basement membranes), when each is incubated in vitro for 30 days with glucose under identical conditions [18]. Thus, AGE-modified collagen may be more

Table 1. Advanced glycation endproducts

Adducts
Nϵ-(carboxyethyl)lysine
Nϵ-(carboxymethyl)lysine
Crosslinks
Crosslines
1,3-bis(5-amino-5-carboxypentyl)imidazolium
Deoxyglucasone-lysine dimer
Methyl glyoxal lysine dimer
Pentosidine
Vesperlysines
N^6-{[2(5-amino-5-carboxypentyl)amino]-2-oxyethyl}lysine
N^6-glycoloyllysine
Unknown
Pyralline
Argpyrimidine
Fluerolink
Imidazolone
Argentine

abundant in osteoarticular tissue than in visceral basement membranes of older patients. The accumulation of AGE-modified proteins with age corresponds with the observation that OA is more prevalent among older patients [1].

Advanced Glycation Endproducts in Osteoarthritis

Advanced glycation endproducts in serum and synovial fluid from individuals with osteoarthritis

The AGE pentosidine is present in plasma, serum, urine, and synovial fluid of patients with OA [19,20,21•]. Plasma pentosidine levels do not reflect blood glucose levels, because they are similar among normoglycemic patients with OA, hyperglycemic patients with diabetes mellitus, and healthy individuals [19]. Synovial fluid pentosidine levels correlate with plasma levels of this AGE. However, serum and synovial fluid pentosidine levels in patients with OA are lower than those in patients with rheumatoid arthritis (RA) [19,21•]. Levels of synovial fluid pentosidine do not correlate significantly with age in patients with OA or RA [20].

Pentosidine levels have not been correlated with measures of disease activity in OA. However, in subjects with RA, the increased serum pentosidine level correlated significantly with elevated acute phase reactants—erythrocyte sedimentation rate, C-reactive protein, and leukocyte and platelet counts [19].

Advanced glycation endproducts in cartilage from individuals with osteoarthritis

Normal human articular cartilage is modified with AGEs after incubation with reducing sugars. In vitro incubation with L-ribose of articular cartilage, obtained postmortem from individuals without joint disorders or at surgery for bone tumors not involving the joint space, resulted in AGE modification [22]. The cartilage acquired a yellowish color and pentosidine levels increased 50-fold. Similarly, in vitro incubation of postmortem samples of normal human articular cartilage with the ascorbic acid degradation product L-threose also increased AGE formation [4••]. Characteristic AGE fluorescence and modification of argenine, lysine, and hydroxylysine increased; susceptibility to collagenase digestion decreased in a dose-dependent manner. After incubation with 200 mM L-threose, levels of CML and CEL increased by 2.7- and 7.2-fold, respectively, whereas that of pentosidine increased by only 1.2-fold. These three AGEs, however, accounted for only 1.1% of the lysine modifications, which indicates that AGE other than CML, CEL, and pentosidine are largely responsible for non-enzymatic glycation of articular cartilage. Nonetheless, most studies of AGEs in OA cartilage have measured only pentosidine levels as a marker for AGE formation rather than total AGE content.

Advanced glycation endproducts are also present in osteoarthritic cartilage. Pentosidine was detected by high-performance liquid chromatography in hydrolysates of cartilage obtained from 17 patients with OA who underwent total hip or knee arthroplasty surgery [3]. However, mean pentosidine levels in cartilage of patients with OA were significantly lower compared with those in 18 patients with RA. Whereas levels of the enzymatically derived crosslink pyridinoline were constant, levels of the AGE pentosidine increased with patient age.

Levels of pentosidine, but not pyridinoline and deoxypyridinoline, also correlated with patient age in menisci retrieved from the knees of 21 patients with OA, 17 of whom underwent total joint replacement and four of whom underwent arthroscopic debridement and meniscectomy [23]. However, pentosidine levels in hydrolysates of cartilage removed from seven patients with OA were not significantly higher than levels in seven age-matched individuals without OA who underwent arthroscopic partial meniscectomy after trauma. This suggests that pentosidine levels in cartilage do not correlate with the presence or absence of OA.

Pentosidine levels do not necessarily differ between osteoarthritic and normal areas in articular cartilage. To control for the presence of newly synthesized collagen, in a study of the enzymatically-formed crosslinks lysylpyrodinoline and hydoxylysylpyrodinoline, pentosidine levels were measured by high-performance liquid chromatography in hydrolysates of articular cartilage [24]. Articular cartilage was obtained postmortem from the knees of six donors without a history of joint disorders. A sample of cartilage was obtained from an area with macroscopic evidence of fibrillation of the articular surface, which represented the "pre-clinical stage" of OA, and a sample of normal-appearing cartilage was removed from a similar site on the contralateral knee. Pentosidine was present in fibrillated and normal cartilage from these individuals, who ranged in age from 49 to 92 years. Pentosidine levels were comparable and varied by 10% (at most) between fibrillated and normal samples

from the same individuals. In contrast, levels of hydoxylysylpyrodinoline, but not of lysylpyrodinoline, were significantly higher in the upper half of fibrillated cartilage samples than in normal cartilage samples. These data also suggest a lack of correlation between cartilage pentosidine content and OA. However, because pentosidine accounts for only a small proportion of the AGE in articular cartilage, it does not necessarily reflect total AGE content.

Total AGE content is best measured by observing the characteristic fluorescence of AGE in tissue. Articular cartilage from 25 patients undergoing total hip or knee arthroplasty for OA and from six patients without OA undergoing total hip arthroplasty after femoral neck fracture demonstrated strong background fluorescence characteristic of AGE modification [25•]. This background fluorescence was lost in areas of highly fibrillated cartilage, predominantly in the pericellular matrix surrounding deeply embedded chondrocytes and, more diffusely, in cartilage covering osteophytes. These areas of presumably decreased AGE deposition are postulated to be because of chondrocyte-mediated destruction and turnover of AGE-modified cartilage in OA, followed by the deposition of new, non–AGE-modified, cartilage matrix. Although this study demonstrates background fluorescence characteristic of AGE modification of collagen matrix in OA cartilage, the degree of AGE modification appears to correlate more with the duration of time that the collagen had been present in the articular cartilage than with the presence or absence of OA.

Pentosidine is present in serum, synovial fluid, and articular cartilage from patients with OA. However, AGE levels are not always increased, and may be decreased locally, in association with osteoarthritic pathology. Thus, pentosidine may not be representative of all AGE in osteoarthritic cartilage and AGE other than pentosidine may be present in articular tissues from patients with OA, possibly contributing to its pathogenesis.

Association between advanced glycation endproducts and chronologic aging

Advanced glycation endproducts accumulate with chronologic aging in articular cartilage from individuals with no symptomatic or diagnosed joint disease. There is a strong linear correlation between background fluorescence characteristic of AGE modification and donor age in samples of articular cartilage taken from macroscopically normal areas [25•]. Pentosidine levels increase linearly with age in human articular cartilage from individuals without joint disorders [26••]—pentosidine levels are 50-fold higher in cartilage from subjects aged 80 to 95 years compared with those aged 20 years [22]. In collagen extracted from rabbit knee joint articular cartilage, pentosidine levels are sixfold higher in 12-month-old animals than in 3-month-old animals; in contrast, levels of pyridinoline crosslinks are similar in rabbits of both ages [27]. Fluorescence characteristic of AGE modification also increases with age in skin collagen [28]. Levels of Nε-(carboxymethyl)lysine increased fivefold between ages 20 and 80 in skin samples from individuals without diabetes. Pentosidine levels in skin collagen also increase significantly with chronologic age. Thus, the observations of pentosidine in articular cartilage of individuals with OA may not be specific for that disease, independent of chronologic age.

Studies of Advanced Glycation Endproduct Modification of Normal Cartilage

Several studies have demonstrated that AGE modification of normal articular cartilage in vitro results in physical and biochemical changes that may contribute to the development of OA. These studies correlate increased AGE levels with increased tensile strength, altered degradative properties, and decreased synthetic function.

Incubation of articular cartilage from individuals without joint disorders with threose or ribose increases cartilage stiffness [4••,22]. Stiffness of a cartilage sample was measured as the relative decrease in deformation of the cartilage plug with mechanical compression by a fixed force applied perpendicular to the orientation of the collagen fibrils. This was expressed as instantaneous deformation (ID), which is the percentage change in diameter of the surface of the cartilage plug perpendicular to the collagen fibrils. Incubation of cartilage with 0.6-M ribose [22] or with 200 mM threose [4••] resulted in a decrease in articular cartilage ID by 25% and 40%, respectively. This decrease in cartilage ID was dose-dependent in the presence of increasing concentrations of threose. The ID of articular cartilage correlated inversely with levels of pentosidine [4••,22], CML, and CEL [4••] in collagen. Incubation of articular cartilage with 200 mM threose in the presence of 20 mM argenine or 20 mM lysine, which are amino acids that compete with cartilage proteins for carbohydrate and prevent the formation of AGE crosslinks, inhibited the decrease in cartilage ID by 50% and 68%, respectively [4••].

Thus, in vitro, carbohydrates increase the stiffness of articular cartilage by forming AGE that crosslink collagen in vitro. This correlates with the observed increased stiffness of articular cartilage [29] and the increased prevalence of OA [1] with chronologic age. The increased stiffness of cartilage caused by collagen crosslinking is postulated to decrease the body's ability to absorb mechanical stress, most notably in weight-bearing joints, and may contribute to the development of OA.

Chondrocyte degradative function correlates directly with AGE levels. Chondrocyte-mediated glycosaminoglycan (GAG) release in a 4-day culture, reflecting cartilage degradation, decreased with chronologic age in samples of normal human articular cartilage obtained post mortem from the femoral condyles of 30 individuals ranging in age from 19 to 82 years [30••]. This GAG release was because of chondrocyte-mediated cartilage degradation, because it was fourfold greater than spontaneous GAG release from age-matched devitalized cartilage explants. Normal humeral head human

articular cartilage samples, after incubation with varying concentrations of glucose, ribose, or threose to enhance AGE modification with diverse AGE, exhibited reduced chondrocyte-mediated GAG release in a 4-day culture. This reduction correlated linearly with cartilage AGE levels, as determined by characteristic AGE fluorescence and modification of argenine, lysine, and hydroxylysine.

Advanced glycation endproduct modification decreases the susceptibility of articular cartilage to proteolysis by matrix metalloproteinase (MMP) in synovial fluid. To assess this, GAG release was measured after samples of normal human articular cartilage, which were obtained postmortem from the femoral condyles of 30 individuals ranging in age from 33 to 83 years, were incubated for 4 days with pooled synovial fluid from patients with RA [31••]. Matrix metalloproteinase–mediated GAG release decreased with chronologic age. This decrease correlated strongly with cartilage pentosidine levels. Normal humeral head human articular cartilage samples, after incubation with up to 250-mM ribose to enhance AGE modification in vitro, also exhibited reduced GAG release after incubation with pooled RA synovial fluid for 4 days. This reduction also correlated linearly with cartilage AGE levels. Incubation of bovine nasal cartilage for 4 days with knee joint synovial fluid from each of two patients with OA also induced GAG release, but less occurred with pooled RA synovial fluid. Glycation of the bovine nasal cartilage with 1 M D-ribose and 50 mM L-threose reduced the amount of GAG release in response to OA or RA synovial fluid. Thus, MMP in synovial fluid from patients with OA may degrade articular cartilage, and AGE modification of articular cartilage reduces its susceptibility to this degradation.

Chondrocyte synthetic function also correlates directly with AGE levels. Ex vivo proteoglycan synthesis by human articular cartilage, obtained postmortem from 129 individuals without joint disorders, decreased with increasing chronologic age [26••]. This decrease correlated linearly with the cartilage pentosidine content. Incubation of cartilage from the same individuals with up to 50-mM ribose for 12 days in vitro decreased the rate of proteoglycan synthesis by chondrocytes, as measured by sulfate incorporation into GAG. The decreased rate of proteoglycan synthesis was not because of direct toxicity of the ribose, because it was sustained after cartilage was washed on day 4 of culture to remove ribose. Sulfate incorporation into GAG, which reflects proteoglycan synthesis by chondrocytes, correlated inversely with levels of the AGE pentosidine. In a separate study, macroscopically normal human articular cartilage, obtained postmortem from the humeral heads of three individuals without joint disorders, was incubated with varying concentrations of glucose (3 to 30 mM), ribose (3 to 30 mM), or threose (3 to 10 mM) to enhance modification with diverse AGE [30••]. The decrease in ex vivo proteoglycan synthesis by these AGE-modified articular cartilage samples in 4-day culture correlated linearly with fluorescence characteristic of AGE modification, which reflected the total AGE content of cartilage rather than just that of a single AGE. These data suggest that AGE formation in articular cartilage decreases proteoglycan synthesis by chondrocytes.

Thus, AGE modification of normal articular cartilage increases its stiffness, increases chondrocyte-mediated proteoglycan degradation, reduces its susceptibility to MMP-mediated degradation, and decreases proteoglycan synthesis by chondrocytes. These observations parallel findings in osteoarthritic cartilage, suggesting that AGE modification could contribute to the pathogenesis of OA.

Advanced Glycation Endproduct Receptors

The decrease in chondrocyte GAG synthesis in the presence of AGE-modified cartilage implies the presence of AGE receptors that transduce signal. Surface AGE-binding receptors are found on neutrophils, monocytes, lymphocytes, endothelial cells, vascular smooth muscle cells, and neuronal cells [32–34].

Galectin-3 (AGE-R3) binds AGE-modified proteins and forms an AGE receptor complex in association with AGE-R1 (OST-48/p60) and AGE-R2 (80K-H/p90) [35]. Galectin-3 is expressed on monocyte-macrophage-derived type A synovial lining cells in synovium from patients with chronic renal failure and beta$_2$-microglobulin amyloidosis [36]. It has also been detected in articular tissue from individuals with OA, in synovium on a few cells in the lining layer [37], and, in cartilage in the cytoplasm and nucleus of adult chondrocytes [38]. Although galectin-3 lacks a transmembrane anchor sequence, signal transduction may occur when AGE-modified proteins bind to this AGE receptor complex [39]. Galectin-3 expression, as well as that of the other components of the AGE receptor complex, is upregulated by exposure to AGE-modified proteins [40,41]. Thus, one could speculate that AGE in articular cartilage and synovium may induce galectin-3 expression in OA. The specific role of this AGE receptor complex in the pathogenesis of OA, however, is unknown.

The receptor for AGE (RAGE) is present on the surface of fibroblast-like type B synoviocytes in synovial tissue from individuals without joint disorders [42]. Receptor for AGE is a 35,000 dalton cell-surface receptor encoded in the histocompatibility class III region of chromosome 6. On mononuclear phagocytes and endothelial cells, a 30,000 dalton lactoferrin-like polypeptide (LFL) binds noncovalently to the extracellular domain of RAGE, forming a RAGE/LFL complex that also binds AGE [43]. Binding of AGE-modified proteins to the RAGE/LFL complex on macrophages results in monocyte chemotaxis [43], increased expression of the cytokine transcription factor nuclear factor-kappa B [44], and increased secretion of proinflammatory cytokines, such as interleukin-1, tumor necrosis factor-alpha (TNFα) [45], and interleukin-6 [46]. However, RAGE has not yet been identified in articular tissue from individuals with OA.

Macrophage scavenger receptors induce endocytosis and digestion of the AGE, CML, and mediate macrophage binding to type IV collagen [47,48]. These receptors have not been described in articular tissue.

Inhibitors of Advanced Glycation Endproduct Formation and Crosslink Breakers

If AGEs are involved in the pathogenesis of OA, therapy may be directed toward interfering with AGE formation or accumulation. Compounds have been developed that inhibit AGE formation, break AGE crosslinks, and inhibit binding of AGE to AGE receptors. The nucleophilic hydrazine-derivative aminoguanidine hydrochloride is the best-studied inhibitor of AGE formation. In a phase III clinical trial of type I diabetes patients, aminoguanidine lowered LDL levels and reduced rates of progression of retinopathy [49] and nephropathy [50]. It is the only AGE inhibitor that has been studied in tissue from individuals with OA. Aminoguanidine decreased lipopolysaccharide-stimulated interleukin-1-beta and nitric oxide release from cultures of human synovial tissue and articular cartilage, obtained during total hip or knee arthroplasty surgery from patients with OA [51]. Aminoguanidine treatment also prevents AGE crosslink formation [52]. However, this has not yet been demonstrated in articular tissue.

Although there is no direct evidence that antioxidants antagonize AGE-mediated events in articular tissue, the risk of radiographic progression of knee OA is reduced in patients who report higher levels of vitamin C, vitamin E, and beta-carotene intake [53]. In vitro, the antioxidant N-acetylcysteine inhibits macrophage TNFα release induced by binding of AGE-modified $beta_2$-microglobulin to RAGE [54]. Thus, it is possible that antioxidant dietary supplements may exert similar effects in OA by inhibiting the release of proinflammatory cytokines in synovial tissue.

The thiazolium derivatives, N-phenacylthiazolium bromide [55] and Three-phenacyl-4,5-dimethylthiazolium chloride [56], catalytically break existing AGE crosslinks between proteins. N-phenacylthiazolium bromide cleaves the crosslinks that form when AGE-modified bovine serum albumin reacts with unmodified native collagen and reduces AGE-mediated crosslinking in collagen isolated from tail tendons of diabetic rats, thereby increasing the collagen's susceptibility to cyanogen bromide digestion [55]. Three-phenacyl-4,5-dimethylthiazolium chloride has been studied in rats with streptozotocin-induced diabetes, older dogs, and rhesus monkeys, as well as humans with vascular disease. Treatment of diabetic rats with 3-phenacyl-4,5-dimethylthiazolium chloride for 1 to 3 weeks reversed the diabetes-induced increase of large artery stiffness [56]. Three-phenacyl-4,5-dimethylthiazolium chloride decreased age-related left ventricular stiffness and improved cardiac function in aged dogs [57]. Three-phenacyl-4,5-dimethylthiazolium chloride also reduced arterial stiffness and improved left ventricular function in older nondiabetic rhesus monkeys [58]. In a placebo-controlled trial in 93 patients aged 50 years and older with vascular stiffening, 3-phenacyl-4,5-dimethylthiazolium chloride improved total arterial compliance [59]. Although it is interesting to speculate whether these crosslink breakers may reverse changes observed in AGE-modified cartilage, neither has yet been studied in articular tissue.

Conclusions

Advanced glycation endproducts are present in serum, synovial fluid, and articular cartilage of patients with OA, although it is not clear that this differs significantly from the AGE deposition that occurs with aging. Ex vivo studies demonstrate that AGE modification of normal articular cartilage decreases its deformability and increases its stiffness, reduces its susceptibility to MMP-mediated degradation, increases chondrocyte-mediated proteoglycan degradation, and decreases chondrocyte proteoglycan synthesis. These properties of AGEs may contribute to the pathogenesis of OA. However, a causative link between AGEs and OA has not yet been established. Certainly, many factors other than AGE formation contribute to the development of OA.

Obesity is associated with diabetes mellitus and OA. Because systemic hyperglycemia in pre-diabetic and diabetic individuals predisposes to AGE formation [60], AGE may accelerate the development of OA in diabetes patients. Further study of the prevalence of OA in diabetic and obese individuals will help to clarify the potential role of AGE in the pathogenesis of OA.

Although AGE receptors are present in articular tissue from individuals with OA, no studies have examined the effects of AGE binding to AGE receptors in these tissues. Advanced glycation endproduct-receptor interactions could stimulate the production of proinflammatory cytokines and reactive oxygen species, which have been invoked in the pathogenesis of OA. Also, AGE inhibitors and crosslink breakers may provide additional therapeutic options for OA, the course of which is difficult to modify with existing therapies.

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