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TRANSPORT PROPERTIES OF CARTILAGINOUS TISSUES

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Abstract

Cartilaginous tissues, such as articular cartilage and intervertebral disc, are avascular tissues which rely on transport for cellular nutrition. Comprehensive knowledge of transport properties in such tissues is therefore necessary in the understanding of nutritional supply to cells. Furthermore, poor cellular nutrition in cartilaginous tissues is believed to be a primary source of tissue degeneration, which may result in osteoarthritis (OA) or disc degeneration. In this mini-review, we present an overview of the current status of the study of transport properties and behavior in cartilaginous tissues. The mechanisms of transport in these tissues, as well as experimental approaches to measuring transport properties and results obtained are discussed. The current status of bioreactors used in cartilage tissue engineering is also presented.

INTRODUCTION

Cartilaginous tissues, such as articular cartilage and intervertebral disc (IVD), are avascular tissues which function in load support and distribution. Due to the lack of blood vessels in these tissues, transport of fluid and solutes through the extracellular matrix (ECM) plays an integral role in providing necessary nutrients, such as oxygen and glucose, to cells for maintenance of viability. Likewise, transport is necessary for removal of waste products, such as lactic acid, from the tissue. Transport may occur by diffusive processes or by fluid flow (i.e., convection) through the ECM, and is highly dependent upon tissue structure and composition as well as tissue loading conditions.

Knowledge of transport properties in cartilaginous tissues is fundamental in the understanding of cellular nutrition in these tissues. Poor nutritional supply to articular cartilage and intervertebral disc tissue, as well as inadequate removal of waste products, are believed to be a principal cause in the onset and progression of tissue degeneration, leading to osteoarthritis (OA) and disc degeneration, respectively [1–7]. If cells are not able to receive proper nutrition to maintain viability, matrix degradation and synthesis can no longer be properly regulated. Changes in tissue composition and structure, which occur as a result of degeneration, affect the ability of the tissue to act in its primary role of load support [8].

Osteoarthritis, or degenerative joint disease, is the most prevalent joint disorder in the United States. With approximately 58% of individuals over 70 years of age experiencing symptoms, OA is the most common cause of disability in the elderly [9,10]. OA carries an annual cost of nearly \$65 billion in the United States [10]. Likewise, low back pain, a symptom related to degeneration of the IVD, is also a major socio-economic concern in the U.S., with annual prevalence ranging from 15 to 45% and 70% of all persons experiencing symptoms at some point in their lifetime. Low back pain is the number one cause of disability in workers under the age of 45, and is second only to upper respiratory infections as the most common reason

for seeing a physician [11–15]. The total annual cost of low back pain, including both direct and indirect costs, is estimated at between \$100 billion and \$200 billion, with two-thirds of this being attributed to indirect costs including loss of productivity and wages [16]. Clearly, the degeneration of cartilaginous tissues, such as articular cartilage and IVD, represents a significant health and economic concern in the United States.

In recent years, tissue-engineering approaches to the treatment of cartilage and disc degeneration have gained strong interest in the medical research community. The development of tissue-engineered cartilaginous tissues for the replacement of degenerated tissue would represent an enormous step toward a viable treatment for OA and disc degeneration. In order to develop such engineered tissues, it is necessary to consider the *in vivo* tissue environment and properties. Because transport plays such an integral role in cellular nutrition and tissue health, comprehensive knowledge of tissue transport properties is necessary for developing engineered tissues with properties similar to native cartilage. Furthermore, understanding the importance of nutrient transport is also essential for developing bioreactors capable of producing functional tissue.

In this review, we present the current knowledge regarding biotransport processes in cartilaginous tissues. Experimental methods and results are discussed. A brief review of the current status of bioreactors in cartilage tissue engineering is also presented.

COMPOSITION AND STRUCTURE

Articular cartilage is characterized as a charged, hydrated, soft tissue made up of an extracellular matrix (ECM) composed of a fibrous network, interstitial water, and ions (primarily Na^+ and Cl^- ions) (Fig. 1). Water is the major component of the tissue, accounting for 65–80% of the wet weight. Collagen, predominantly Type II, and proteoglycans (PG) make up the fibrous matrix, and account for 15–22% and 4–7% wet weight of the tissue, respectively. The cellular component of the tissue, composed of chondrocytes, is sparse, accounting for less than 10% of the tissue wet weight in normal adult articular cartilage [8].

Collagen is the major constituent making up the organic component of the tissue. The collagen fibers have a high degree of structural organization, consisting of a fine network which acts to entrap large PG aggregates in the extrafibrillar space. The PGs are macromolecules composed of a protein core with covalently-bonded glycosaminoglycan (GAG) chains. This composite forms a fiber-reinforced solid matrix, which conveys anisotropic and inhomogeneous mechanical and transport properties to the tissue.

Interstitial water is believed to exist in two compartments within cartilage: intrafibrillar (within the collagen fibers) and extrafibrillar [17,18]. Moreover, it is believed that the extrafibrillar water is able to move freely throughout the tissue under pressure (hydraulic and osmotic) gradients and mechanical consolidation of the matrix [19–24]. The pore size of articular cartilage has been estimated from hydraulic permeability experiments to range from 2 to 6 nm [22,25]. Pore size can also be estimated from the square root of the Darcy permeability [26].

The charged nature of the ECM derives from the proteoglycan component of the tissue [8,22, 27–29]. The GAG chains contain charged groups (SO_3^- and COO^-) which are considered as “fixed” to the extracellular matrix; thus, these charges are known as fixed negative charges and are measured in terms of fixed charge densities. The fixed charges attract oppositely charged ions, primarily Na^+ , dissolved in the interstitial water, allowing for maintenance of overall electroneutrality. Electrostatic interactions between immobile, fixed charges on the ECM and mobile free ions in the interstitial fluid induce tissue swelling effects [22,30–32].

Articular cartilage has been shown to be arranged in four distinct horizontal layers or zones: superficial tangential zone (STZ), middle (transitional) zone, deep zone, and calcified zone. The cells in the different layers vary in size, shape and metabolic activity [8,33]. The cartilage composition varies with depth from the articular surface. The collagen content is highest in the STZ, and decreases by approximately 15% in the middle and deep zones. Conversely, the proteoglycan content follows the opposite trend, being the lowest at the surface and increasing by approximately 15% in the middle and deep zones. Water content varies in the same manner as collagen content [8]. This variation in composition by layer results in inhomogeneous transport properties in articular cartilage.

Degeneration of articular cartilage is marked by a decrease in proteoglycan content and an increase in water content [22] [34,35]. A decrease in PG content and increase in water content leads to many changes in the tissue, including an associated decrease in tissue fixed charge density and increased tissue permeability which cause reduced swelling pressure within the tissue [8,34]. As a result, the tissue is no longer able to properly support compressive loads, causing further damage to the tissue ECM [8].

The intervertebral discs in the spine are also considered charged hydrated soft tissues. The major component of the IVD is water, making up 60–90% of the wet weight. It also has significant amounts of collagen (15–70% dry weight), proteoglycan (10–50% dry weight) and other matrix proteins (15–45% dry weight) [36–42]. The IVD is composed of three distinct regions: the nucleus pulposus (NP), annulus fibrosus (AF) and cartilaginous endplate (CEP). The NP, composed of randomly oriented collagen fibrils enmeshed in a proteoglycan gel. The AF surrounds the NP on its periphery and is composed of a series of concentric lamellae consisting of collagen fibers. The fibers run parallel to each other within each lamellae, but opposite those in adjacent lamellae, at an angle approximately $\pm 30^\circ$ to the horizontal axis [43,44]. The CEP surrounds the NP and inner one third of the AF inferiorly and superiorly. It consists of a thin layer of hyaline cartilage.

The different components of the disc have distinct biochemical composition and structure. The greatest quantities of water and PG can be found in the NP and inner AF regions, whereas the outer AF has the greatest collagen content. The outer AF is primarily type I collagen whereas the inner AF is predominantly type II. The ratio of type I to type II decreases from outer to inner AF. The CEP collagen composition is almost exclusively type II, similar to that of hyaline cartilage.

Disc degeneration is characterized as a degradation or deterioration of the structure of the disc tissue, which results in loss of mechanical function of the disc and eventually of the spine as a whole. As the disc degenerates, changes in disc morphology, biochemistry, function and material properties take place. Perhaps the most noteworthy biochemical change occurring in degenerated disc is the loss of proteoglycan content [45]. The loss of PG causes a decrease in osmotic pressure and tissue hydration [46]; the latter phenomenon is opposite to that which occurs in articular cartilage. These changes lead to a loss of the load support capability of IVD [47]. Changes in collagen content also take place, although they are not nearly as evident as those for proteoglycan [48].

MECHANISMS OF TRANSPORT IN CARTILAGINOUS TISSUES

The transport of fluid and solutes within porous tissue is primarily governed by transport properties including solute diffusivities and hydraulic permeability [32,49]. Transport through the extracellular matrix of cartilaginous tissues is integral for cellular nutrition as well as tissue growth. Due to the avascular nature of cartilaginous tissue, such as articular cartilage and intervertebral disc, nutrients required to maintain cell viability must be supplied by blood vessels located at the tissue margins; likewise, waste products must be transported out of the

tissue. Transport of such nutrients and waste products may occur by diffusion or by convection (i.e., due to fluid flow); it is generally believed that diffusion is the main mechanism of transport for small solutes through cartilaginous tissues [50–52], while convection plays an important role in transport of larger solutes [50,51,53–57].

Diffusion is defined as the movement of matter driven by a concentration gradient. A mathematical model for one-dimensional diffusion in fluids was first proposed by Adolf Fick and is known as Fick's law:

$$J = -D \frac{\partial C}{\partial x} \quad (1)$$

where J is the diffusive flux, defined as the quantity (i.e., moles) passing through per unit area per unit time, D is the diffusion coefficient (units: m^2/s), C is the concentration of solute in the solution, and x is the distance along the path of solute transport [58,59]. Convection, on the other hand, is a transport process resulting from the bulk motion of fluids.

In order to estimate the relative importance of convective and diffusive effects on transport in cartilaginous tissues, we may use the Peclet (Pe) number. The Peclet number is defined as:

$$Pe = UL/D, \quad (2)$$

where U is the characteristic fluid velocity, L is the diffusion distance, and D is the diffusivity of solute [60]. If the value of the Pe number is much greater than 1, convection is more significant; conversely, if the value of the Pe number is much less than 1, then diffusion is more significant. However, if the Pe number is on the order of 1, both convection and diffusion must be considered [60]. It has been found that the rate of solute transport in cartilaginous tissues is dependent upon loading conditions, solute diffusivities within the tissue, and other material properties, including modulus and hydraulic permeability.

Hydraulic permeability is an important material property of hydrated soft tissues. It is a measure of the ease with which fluid can flow through the tissue matrix. The hydraulic permeability, k , of a tissue is defined as (known as Darcy's law):

$$k = \left(\frac{Q}{A} \right) / \left(\frac{\Delta p}{h} \right) = \left(\frac{Q}{\Delta p} \right) \left(\frac{h}{A} \right) \quad (3)$$

where Q is the volumetric flow rate, defined as the volume passing through a given surface area per unit time and measured in m^3/s , Δp is the pressure difference across the sample, A is the permeation area of the sample, and h is the thickness of the sample. Since permeability governs the rate of fluid transport processes in cartilaginous tissues, it therefore significantly affects cellular nutrition. Hydraulic permeability (measured in most experiments reported in the literature) is related to tissue water content, fixed charge density, ion diffusivities, and the frictional coefficient between water and the solid matrix within the tissue [21,22,26,34,61]. These properties are, in turn, functions of tissue structure and composition.

SUMMARY OF EXPERIMENTAL FINDINGS

Solute Diffusivities

Due to the avascular nature of cartilaginous tissues, diffusion of solutes through the tissue extracellular matrix plays an integral role in cellular nutrition. The rate of diffusion depends

on several properties of both the solute and the matrix, including solute size and charge, as well as pore size of the matrix. Pore size is directly related to tissue hydration and structure [62,63]. Diffusion coefficients have been measured by a variety of methods. The most common of these include direct measurement based on Fick's law (equation 1) (e.g., [64–69]). More recently, imaging techniques such as magnetic resonance imaging (MRI) [70–72], nuclear magnetic resonance (NMR) [63,73,74], and fluorescence recovery after photobleaching (FRAP) [75,76] have been employed to determine solute diffusivities in cartilaginous tissues. The electrical conductivity method has also been used to determine diffusion coefficients of ions in IVD [77]. The diffusion coefficient, D , of several solutes in both human and animal cartilaginous tissues have been reported in the literature [62–69,73–76,78–86]. A summary of these results can be found in Table 1.

In general, it has been found that solute diffusivity is inversely proportional to solute size; that is, the diffusion coefficient of a solute in a particular tissue decreases as solute size increases [22,66,74,76,81,84,85]. It has also been shown that solute diffusivities increase with increasing tissue water content. An increase in tissue water content corresponds to an increase in the pore size of the tissue. Furthermore, the diffusion coefficients of solutes in cartilaginous tissues are generally smaller than those in aqueous solutions [50,51,54,63,66,69,75–77,83,84]. For small solutes, the value of diffusion coefficients in cartilage and IVD is approximately 35–60% of the value in aqueous solution [62,63,77,87,88]. Several investigators have also shown that diffusion in both articular cartilage and IVD is anisotropic (i.e., direction-dependent) due to the organization and structure of the collagen fibers [69,70,75,88–90]. Additionally, diffusion in these tissues is also inhomogeneous (i.e., varies by region), likely due to regional variation in tissue water content [70,76,88,90].

Solute Partitioning

The partition coefficient is defined as the solute concentration in a porous media relative to the concentration of solute in the surrounding fluid at equilibrium. Knowledge of partition coefficient values is important as they are one of the governing factors in determining solute concentration within the tissue. Numerous studies have been done on the partition coefficients for both small (glucose, urea, proline, sucrose, and ions) and large (myoglobin, serum albumin, IGG, IGF, and dextran) solutes in cartilage by many investigators [67,79,80,82,84,91–93]. In general, the partition coefficient decreases with increasing molecular size of solute in cartilage [82,84]. It has also been shown that the partition coefficient is dependent upon several tissue properties, including water content and fixed charge density (FCD) [79,82,92].

Hydraulic Permeability

Hydraulic permeability is an important property of cartilage as water is the major component of the tissue. It is an important factor for governing the rate of fluid transport in tissue. Values for hydraulic permeability may be measured directly or indirectly. Direct measurement is carried out via a permeation experiment (based on Darcy's law, i.e., equation 3), in which a constant pressure gradient (or flow rate) is applied across a tissue and the resulting flow rate (or pressure difference) is measured (e.g., [40,68,94,95]). Direct measurement is often difficult due to extremely low value of fluid flow rates in permeation testing; as a result, indirect methods are often employed for determining the hydraulic permeability of cartilaginous tissues, based on creep or stress-relaxation tests and the biphasic theory developed by Mow et al [24]. The hydraulic permeability of articular cartilage and IVD tissue in humans and animals has been reported in the literature [23,24,40,68,94–108]. A summary of results can be found in Table 2.

Hydraulic permeability has been shown to be dependent upon tissue water content (i.e., pore size) as well as tissue fixed charge density [21,22,34,40,50,61,101]. Several studies have also

shown that the hydraulic permeability of articular cartilage is inhomogeneous, depending on the region or zone of the cartilage [23,50,101]. This regional variation has been attributed to changes in collagen fiber organization and fixed charge density with cartilage depth. Hydraulic permeability in both articular cartilage and intervertebral disc has also been shown to be anisotropic [40,97,107].

EFFECT OF LOADING ON TRANSPORT

Loading plays an important role in the transport of fluid and solutes through cartilaginous tissues. Loading may occur either mechanically, in which the tissue is physically deformed by the application of a mechanical stress, or electrochemically, whereby an electrical current is applied across the tissue to induce electro-osmotic fluid flow. The effect of loading on transport properties in cartilaginous tissues is dependent upon the loading type and configuration. For instance, mechanical loading of tissue significantly affects the transport of fluids and solutes through the tissue; however, this effect is dependent upon the type of loading (i.e., dynamic vs. static loading).

Several studies have shown the effects of static compressive loading on the transport of solutes within cartilaginous tissues. Mechanical loading gives rise to a decrease in tissue water content, due to fluid exudation resulting from compression. It has been experimentally shown by various investigators that static compression of cartilaginous tissues results in decreased transport properties, likely due to related change in water content. The effect of compression on the diffusion of several molecules in cartilage has been investigated, including water [63], various sized dextran molecules [84,85], leucine [92], inulin [92], Na⁺ ions [73,92], Li⁺ ions [63] and SO₄²⁻ ions [92]. Moreover, the effect of static mechanical loading has also been demonstrated in IVD tissue; strain-dependent diffusivities of glucose [69] and water [70,71] in IVD have been investigated. These studies demonstrated a decrease in diffusivity with increasing compression in cartilaginous tissues. This decrease with increasing compressive strain is likely due to the changes in water content; diffusion of solutes in IVD tissues has been shown to be highly dependent upon tissue porosity. Therefore, a decrease in tissue water content would likely be accompanied by a decrease in solute diffusivity.

Furthermore, numerous studies have investigated the partition coefficient of solutes in cartilage under mechanical loading conditions. Quinn et al. (2001) found that static compression resulted in a decrease in partition coefficient of several solutes in cartilage, with strongest effects seen in relatively large molecular weight dextran molecules [85]. Nimer et al. found that partitioning based on tissue water of Na⁺ ions increased with increasing load, whereas that of SO₄⁻ decreased with increasing load in cartilage under static loading conditions [92]. The same study also showed that the partition coefficient of inulin decreased with increasing load.

Several studies have also reported on that the strain-dependent behavior of hydraulic permeability in cartilaginous tissues [21,25,26,94,97,107,109–113]. Mansour and Mow (1976) first reported on the dependence of hydraulic permeability in articular cartilage on mechanical compression, showing that permeability decreased as tissue compressive strain increased [94]. More recently, numerous investigators have shown this trend of decreasing hydraulic permeability with increasing compression in articular cartilage using a variety of techniques [25,26,97,107,109,110]. Additionally, it has been shown that compression of cartilage results in an anisotropic behavior of hydraulic permeability [97,107]. It has been suggested that this appearance of anisotropy with increasing compression may be the result of changes in glycosaminoglycan positions and orientations during compression of the tissue ECM [114].

The investigation of the effects of dynamic loading on the transport of fluids and solutes through cartilaginous tissues is important as it relates to *in vivo* loading of joints during movement. Dynamic loading of cartilage leads to convective flow within the tissue. Therefore, it is

expected that cyclical loading would result in enhanced transport of large solutes in cartilaginous tissues. Indeed, it has been shown experimentally that the diffusion of large solutes is enhanced by dynamic (cyclical) loading conditions, which is likely due to increase in convective flow within the tissue [52,56,83,85,115,116]. On the other hand, for smaller solutes, dynamic loading has not been shown to result in enhanced transport properties [52, 56,117].

Loading of cartilaginous tissues may also occur via the application of an electrical current across the tissue. When current is applied across the cartilage, an electro-osmotic fluid flow is induced in the tissue. This method has been used in order to enhance fluid flow in the cartilage ECM without the application of a mechanical load. It has been shown experimentally that the induced electro-osmotic fluid flow results in enhanced convective transport of solutes in articular cartilage [54,118]. Furthermore, the enhancement in solute transport was shown to increase with increasing solute size; nonetheless, it was shown that the effect of fluid flow is important even for small solutes [118].

BIOREACTOR SYSTEMS FOR CARTILAGE TISSUE ENGINEERING

The primary objective of tissue engineering is to aid the body in generating a material that closely mimics the native tissue. The growth and development of cartilaginous tissue depends on the environment that surrounds it, both *in vivo* and *in vitro*. Chondrocytes must be cultured such that the proper concentration of nutrients and oxygen are provided while wastes are removed. Mass transfer is a principal concern because oxygen and nutrients must be provided in sufficient amount for tissues to grow to a usable size. Furthermore, tissue-engineering processes involving articular cartilage are distinct from those of other tissues because chondrocytes depend on mechanical stimuli for differentiation [119,120]. Chondrocytes must experience external loading during their development for them to secrete the correct cartilaginous proteins and organize into the correct morphology. Many studies have been undertaken to understand which forces are most beneficial to the chondrocyte-culturing process [121–124]. From these results, special bioreactors and processes have been designed to take advantage of mechanical stimuli. The most common bioreactors use hydrostatic pressure, shear, or direct compression to stimulate chondrocytes.

Comprehensive reviews of articular cartilage bioreactors and bioprocesses can be found in the review papers by Darling and Athanasiou [125] and by Abousleiman and Sikavitsas [126]. To date, several different types of bioreactors have been used in tissue engineering applications. The most common type of mechanically stirred bioreactor with high shearing stress is the spinner flask [127]. The turbulent mixing of nutrients in the spinner flask allows for enhanced biochemical compositions [127]. Although it might not be optimal for producing cartilage, it still used successfully on scaffold-seeding application [128]. The rotating wall vessel (RWV), developed at NASA [129], provides the hydrodynamic environment that is conducive to cartilage growth, as well as allow for optimized nutrient transport [126,130,131]. For three-dimensional scaffolds, a flow system that forces medium through the scaffold gives the most thickness-independent results. This type of system is called a direct perfusion bioreactor [132–134]. The major benefits of this system are the continuous influx of fresh medium through the construct, which enhances the mass transport, and the convenient adjustment of nutrient level during tissue growth. Currently, the rotating-wall bioreactor with the perfusion system is very successful for cell culturing [135–138]. It can easily adjust the level of shear associated with the fluid flow because of its unique design. The improvement of this bioreactor was made by the hydrodynamic focusing bioreactor (HFB) to localize the nutrient flow and keep a more stable culturing environment [133]. More recently, researchers began combining different forces in single bioreactor to elicit a better response from the cells. For instance, Frank and associates [139] built a device that can physically compress and shear a scaffold.

Overall, a successful bioreactor for cartilage tissue engineering should take advantage of the mechanical stimuli in conjunction with good mass transfer properties to create an environment suitable for long-term cartilage growth. Providing good mass transport is a key element in developing a bioreactor environment that allows for long-term tissue growth. Hence, comprehensive understanding of transport phenomena is therefore fundamental in the development of engineered tissues in a bioreactor environment.

SUMMARY

This review has focused on the basic understandings of and current status of research into transport properties in cartilaginous tissues. Because cartilaginous tissues, such as articular cartilage and IVD, are avascular, transport of fluids and solutes through the extracellular matrix plays an important role in cellular nutrition. Poor nutritional supply is believed to be a primary cause of tissue degeneration, leading to osteoarthritis (in the case of articular cartilage degeneration) or low back pain (in the case of degeneration of the intervertebral discs). Therefore, knowledge of transport properties in cartilaginous tissues is important for elucidating the mechanisms and etiology of tissue degeneration. Furthermore, understanding of transport phenomena is also crucial in the development of strategies for the restoration of tissue function and/or retardation of degeneration by way of tissue engineering. In order to develop a successful bioreactor capable of producing viable cartilaginous tissue, good mass transport of nutrients and waste products to and from cells is imperative. For that reason, sufficient insight into transport properties is crucial to successful tissue engineering of functional cartilaginous tissues.

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Figure 1.
Schematic diagram of the charged extracellular matrix of cartilaginous tissues

Table 1

Summary of experimental results for diffusion coefficients, D , for various solutes in cartilaginous tissues obtained in the literature. Values are for zero compression unless otherwise noted.

Solute	Tissue	D ($\times 10^{-10}$ m ² /sec)	Reference
Na ⁺	Human adult cartilage	4.3 – 4.9	[68]
Cl ⁻	Human adult cartilage	6.6 – 7.9	[68]
K ⁺	Human adult cartilage	7.4	[68]
SO ₄ ⁻	Human adult cartilage	6.8	[68]
H ₂ O	Bovine cartilage	13.8	[63]
NaCl	Bovine cartilage	7.56	[63]
CF ₃ CO ₂	Bovine cartilage	5.92	[63]
Glucose	Adult bovine and equine articular cartilage	4.83	[65]
	Human adult cartilage	1.4 – 2.3	[68]
	Mature bovine cartilage	3.94 – 4.64	[78]
	Bovine cartilage	3.13	[63]
	Immature bovine cartilage	6.08	[67]
	Mature bovine cartilage	0.138 – 17.0	[66]
	Bovine coccygeal annulus fibrosus (IVD)	1.15	[69]
	Human lumbar annulus fibrosus (IVD)	2.5	[62]
	Human cartilage endplate	2.43	[62]
	Human articular cartilage	2.1 – 2.3	[81]
Sucrose	Human articular cartilage	1.3	[81]
Inulin	Adult bovine and equine articular cartilage	1.66	[65]
	Mature bovine cartilage	0.925 – 1.478	[78]
	Mature bovine cartilage	0.040 – 8.17	[66]
	Human articular cartilage	0.25	[81]
I-IGF-I	Adult bovine cartilage	0.21	[80]
	Calf articular cartilage	0.063	[83]
Hemoglobin	Human articular cartilage	0.115 – 0.16	[81]
Urea	Human articular cartilage	5.9 – 6.15	[81]
Serum albumin	Human articular cartilage	0.2	[82]
Gd-DTPA	Calf articular cartilage	1.4	[74]
Gd-lysozyme	Calf articular cartilage	0.25	[74]
Gd-trypsinogen	Calf articular cartilage	0.05	[74]
Gd-ovalbumin	Calf articular cartilage	0.04	[74]
Tetramethylammonium (TMA)	Bovine nasal cartilage	3.2 – 5.2	[73]
Tetraethylammonium (TEA)	Bovine nasal cartilage	2.0 – 3.0	[73]
Tetramethylrhodamine (TMR)	Bovine articular cartilage	0.15 – 0.7 [†]	[84]
	Bovine articular cartilage	0.38 – 0.52 [†]	[85]
Fluorescein (332Da)	Bovine coccygeal annulus fibrosus (IVD)	1.03	[75]
Fluorophore (500 Da)	Bovine articular cartilage	0.03 – 0.3 [†]	[86]
Dextran (3K)	Porcine articular cartilage	0.65 – 1.15	[76]

Solute	Tissue	$D (\times 10^{-10} \text{ m}^2/\text{sec})$	Reference
Dextran (10K)	Bovine articular cartilage	$0.3 - 0.65^{\dagger}$	[84]
	Bovine articular cartilage	$0.25 - 0.3^{\dagger}$	[85]
	Immature bovine cartilage	5.09	[67]
	Mature bovine cartilage	0.170 - 5.68	[66]
	Bovine articular cartilage	$0.01 - 0.1^{\dagger}$	[84]
	Bovine articular cartilage	$0.02 - 0.2^{\dagger}$	[86]
	Human articular cartilage	0.06 - 0.147	[81]
Dextran (20K)	Adult bovine and equine articular cartilage	1.58	[65]
Dextran (40K)	Mature bovine cartilage	0.113 - 3.30	[66]
	Human articular cartilage	0.0103 - 0.028	[81]
	Porcine articular cartilage	0.18 - 0.78	[76]
	Bovine articular cartilage	$0.01 - 0.4^{\dagger}$	[84]
Dextran (70K)	Bovine articular cartilage	$0.12 - 0.19^{\dagger}$	[85]
	Human ankle cartilage	0.346	[79]
	Human knee cartilage	0.354	[79]
	Mature bovine cartilage	0.397 - 0.773	[78]
	Porcine articular cartilage	0.1 - 0.6	[76]
Dextran (77K)	Mature bovine cartilage	0.045 - 3.68	[66]
Dextran (500K)	Porcine articular cartilage	0.04 - 0.11	[76]

[†] diffusion under compressive strain

Table 2

Summary of experimental results for hydraulic permeability, k , for various solutes in cartilaginous tissues obtained in the literature.

Tissue	k ($\times 10^{-15} \text{ m}^4/\text{N}\cdot\text{sec}$)	Reference
Bovine shoulder cartilage	0.43 – 0.765	[23]
Human articular cartilage	0.135 – 0.535	[68]
Human articular cartilage	0.14 – 0.38	[108]
Bovine articular cartilage	0.292 – 3.30	[94]
Human (young) cartilage	1.18	[96]
Human articular cartilage	0.47 – 2.17	[96]
Human knee cartilage	25.5 (normal)	[97]
	12.3 (tangential)	
Human medial collateral ligament	0.04 – 0.86 (apparent) [†]	[95]
	0.429 – 1.414 (intrinsic) [†]	[95]
Human shoulder cartilage	13.5 (glenoid)	[106]
	11.4 (humeral head)	
Bovine articular cartilage	7.60	[24]
Bovine (18–24 mos.) cartilage	0.43 – 1.42	[96]
Bovine (calf) cartilage	3.50	[99]
Bovine articular cartilage	2.72	[100]
Bovine articular cartilage	1.41	[40]
Bovine (fetal) cartilage	0.65	[98]
Bovine (calf) cartilage	0.25	[98]
Bovine (adult) cartilage	1.20	[98]
Bovine articular cartilage	0.04 – 15	[107]
Human annulus fibrosus (IVD)	0.25	[105]
Canine annulus fibrosus (IVD)	0.102 – 0.281	[103]
Human annulus fibrosus (IVD)	1.92 (axial)*	[40]
	1.53 (radial)*	
	1.15 (circumferential)*	
Human annulus fibrosus (IVD)	0.13	[104]
Porcine annulus fibrosus (IVD)	4.5	[102]
Bovine nucleus pulposus (IVD)	0.67	[101]
Bovine annulus fibrosus (IVD)	0.23	[101]

[†] permeation under 10 – 30% compressive strain and an applied pressure of 0 – 400 psi.

* permeation under 29% compressive strain and an applied pressure of 10 psi.