# Introduction

Magnetic resonance imaging (MRI) has emerged as a useful tool for clinicians and scientists to assess the health of cartilage and other soft tissues. Conventional MRI provides sufficient tissue contrast to detect morphological changes in cartilage where radiography cannot. However, changes in cartilage physiology prior to morphological changes cannot be visualized or measured with conventional MRI ***(Zhang et al., 2013).***

The recent advances in MR sequences together with the implementation of higher resolution MRI due to high field MR systems as well as sophisticated coil technology have overcome existing limitations and led to promising in vivo approaches in morphological and biochemical MRI of cartilage ***(Potter et al., 2012)***.

Since the introduction of MRI evaluation of joints, there has been a quest for MRI sequences that optimize articular cartilage evaluation. Over time, increased signal to noise ratio (SNR), contrast to noise ratio (CNR) and acquisition speeds have become available, along with coil and scanner improvements. Despite this, there is currently no single specific sequence that allows for one stop shopping

evaluation of this complex tissue. It is generally accepted that a combination of sequences is necessary for comprehensive morphologic and quantitative evaluation. Essential requirements for evaluation of hyaline cartilage include high in plane and through plane resolution and optimal SNR and CNR, thereby avoiding partial volume artifacts and allowing differentiation from surrounding fluid and tissues. To this end, utilization of high field strength scanners and dedicated coilsis strongly advised ***(Crema et al., 2011).***

Significant advances have been made in characterizing, quantifying, and standardizing the specific morphological as well as biochemical changes in patients with cartilage pathologies. Besides the exact evaluation of the cartilage defect, respectively, the cartilage degeneration, also the specific therapeutical approaches, can be assessed in best possible fashion noninvasively ***(Potter et al., 2012)***.

As structural cartilage damage is preceded by biochemical alterations such as proteoglycan loss, or changes in the collagen matrix, there is a substantial interest in detecting such changes in the course of cartilage disease/injury or after cartilage repair ***(Welsch et al., 2013)***.

Recently, quantitative MRI techniques such as T2, T2*, dGEMRIC (delayed gadolinium enhanced MRI of cartilage), sodium imaging ((23)Na), chemical exchange saturation transfer (CEST), diffusion weighted imaging (DWI) and T1rho mapping have been shown to be sensitive to biochemical changes in cartilage. Advanced magnetic resonance (MR) sequences for cartilage evaluation are focused on the assessment of articular cartilage biochemical composition, more specifically to the collagen and glycosaminoglycan content. Hyaline cartilage is in fact a macromolecular network that supports mechanical loads. Three quarters of its weight is composed of water and the rest is a molecular mesh composed of collagen and proteoglycans. Collagen accounts for one fifth of its volume, with aggrecanas the most abundant proteoglycan. Proteoglycans have glycosaminoglycans (GAGs) attached as side chains that are negatively charged. The preservation of proteoglycanis directly assessed by the distribution pattern of associated positively charged sodium (Na+). Similarly, regions lacking proteoglycan cause negatively charged gadolinium based contrast (Gd DTPA2–) agents to accumulate (***Crema et al., 2011).***

# Aim of the work

The aim of this work is to emphasize the role of new advances of magnetic resonance imaging in diagnosis of cartilage disease.

# Chapter (1)
# Overview of cartilage architecture & biochemistry

## Cartilage components

### Cartilage Composition and Importance

Matrix is the intercellular substance of cartilage consisting of fibers and ground substance. Depending on the composition of the matrix, cartilage in human body is classified into elastic, fibrocartilage, fibro elastic and hyaline cartilage. Gliding surfaces of synovial joint are covered with a specialized type of hyaline cartilage, called 'articular cartilage'. Hyaline cartilage provides a low friction gliding surface, with increased compressive strength and is known to be wear resistant under normal circumstances ***(Buckwalter and Mankin, 2011).***

Hyaline articular cartilage is largely a cellular as chondrocytes constitute only 4% of its wet weight. The main components of hyaline cartilage are water (65–85%), the extracellular matrix consisting of type II collagen (15–20%), and proteoglycans (PGs) (3–10%) ***(Oeiet al., 2014).***

## Functions of Hyaline articular cartilage

Functions of Hyaline articular cartilage are listed by ***Bhosale and Richardson, 2010*** as providing a low friction gliding surface, acting as a shock absorber and minimizing peak pressures on the subchondral bone.

## Functions of the matrix

They were listed by ***Bhosale and Richardson, 2010*** as follows:

- Protects the chondrocytes from mechanical loading, thus helping to maintain their phenotype.
- Storage of some cytokines and growth factors, required for chondrocytes.
- Determines the type, concentration and rate of diffusion of the nutrients to chondrocytes.
- Acts as a signal transducer for the cells.

They added that matrix deformation produces mechanical, electrical and chemical signals, affecting the functions of chondrocytes. Thus, matrix also plays a role in recording a loading history of the articular cartilage**.**

## Cartilage components

Articular cartilage is a biphasic tissue consisting of a solid phase, primarily collagen type II (approximately 15% of wet weight) and proteoglycans (PG) (approximately 8% of wet weight), and a liquid phase, water (approximately 80%). Other components of the tissue include the cartilage cells, chondrocytes, and the extracellular matrix ***(Koff and Potter, 2012).***

## Water

Sixty five to eighty per cent of net weight of the cartilage is formed by water, with 80% being in the superficial zone and 65% in the deep zones. It allows load dependent deformation of the cartilage. It provides nutrition and medium for lubrication, creating a low friction gliding surface ***(Bhosale and Richardson, 2010).***

## Collagens

Articular cartilage contains multiple genetically distinct collagen types specifically types II, VI, IX, X, and XI. Types II, IX, and XI form the cross banded fibrils seen with electron microscopy. The organization of these fibrils into a tight meshwork that extends throughout the tissue provides the tensile stiffness and strength of articular cartilage and

contributes to the cohesiveness of the tissue by mechanically entrapping the large proteoglycans ***(Buckwalter and Mankin, 2011).***

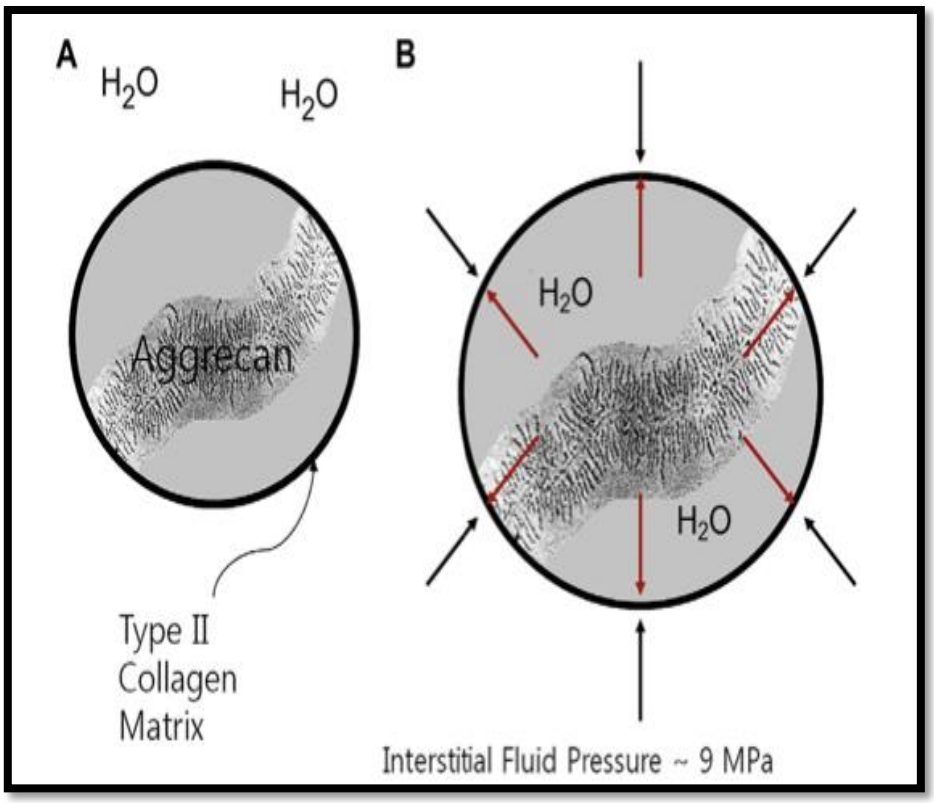


**Figure (1):** (A) Negative ions attract positive counter ions and water molecules. (B) This swelling of the proteoglycans is constrained by the surrounding collagen meshwork.

## Proteoglycans

These protein polysaccharide molecules form 10–20% wet weight and provide a compressive strength to the articular cartilage. There are two major classes of

proteoglycans (PG) found in articular cartilage, large aggregating proteoglycan monomers and small proteoglycans. They are produced inside the chondrocytes and secreted in the matrix ***(Bhosale and Richardson, 2010).***

PGs mainly consist of glycosaminoglycans (GAGs) that are negatively charged due to ionized sulfate and carboxyl groups. These strong negative electrostatic charges, collectively responsible for the so called fixed charge density, are important contributors to the structure and biomechanical properties of articular cartilage. They allow GAG molecules to be fixed to the extracellular matrix and attract positive ions that attract water molecules, resulting in a swelling pressure of cartilage. This tendency to expand is counteracted by the surrounding collagen mesh work and this balance between swelling pressure and collagen tension contributes to the tremendous tensile and compressive strength of hyaline cartilage under normal physiologic conditions***(Oei et al.,2014).***

## Chondrocytes

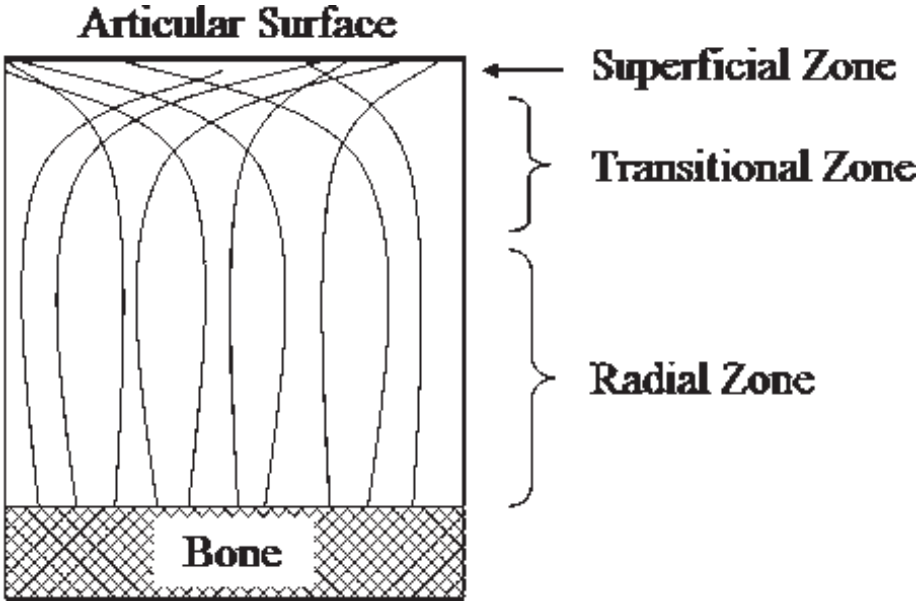


**Figure (2):** The arrangement of type II collagen fibrils in the extracellular matrix defines zones within cartilage. Near the bone–cartilage interface, collagen fibers in the radial zone are aligned perpendicular to the cortical surface. Random fiber orientation defines the transitional zone, and fibers at the surface are oriented parallel to the articular surface.

These highly specialized cells, forming only 1–5% of volume, are sparsely spread within the matrix. Chondrocytes synthesize all the matrix components and regulate matrix metabolism ***(Bhosale and Richardson, 2010).***

## Articular cartilage zones

Based upon differences in collagen fiber orientation and biochemical composition, the articular cartilage can be

divided according to ***Hesper et al.,2014***into the following four zones:

1. The superficial or tangential zone (10–20 % of cartilage thickness; collagen fibers running parallel to the articular surface).
2. The transitional or intermediate zone (~ 60 % of cartilage thickness; random collagen fiber orientation with collagen fibers bending to form arcades).
3. The radial or deep zone (~ 30 % of cartilage thickness; collagen fibers running perpendicular to the subchondral bone providing anchorage to the underlying calcified matrix).
4. The calcified zone (cartilage–bone interface).

**Superficial Zone**

The superficial zone, which is the most cellular zone, has a high collagen and water content, whereas the content of proteoglycan is low***(Hesper et al., 2014).***

It is the thinnest zone of articular cartilage, with specialized mechanical and possibly biological properties. This zone typically consists of two layers. A sheet of fine fibrils with little polysaccharide and no cells covers the joint

surface. This portion corresponds lamina splendens, which can be stripped from the articular surface in some regions. Deep to this acellular sheet of chondrocytes arrange themselves so that their major axes are parallel to the articular surface. The chondrocytes synthesize a matrix that has a high concentration of collagen and a low concentration of proteoglycan relative to the other cartilage zones; Concentrations of fibronectin and water are also highest in this zone (***Buckwalter and Mankin, 2011).***

The dense matrix of collagen fibrils lying parallel to the joint surface in the superficial zone helps to determine the mechanical properties of the tissue and affect the movement of molecules in and out of the cartilage. These fibrils give this zone greater tensile stiffness and strength than the deeper zones, and they may resist shear forces generated during use of the joint (***Buckwalter and Mankin, 2011).***

**II .Transitional Zone**

The transitional zone has higher proteoglycan content and a lower collagen and water content than the superficial zone ***(Hesper et al., 2014).***

As the name of this zone implies, the morphology and the matrix composition of the transitional zone are

intermediate between the superficial zone and the middle (radial) zone. The transitional zone usually has several times the volume of the superficial zone. Cells in the transitional zone assume a spheroidal shape and synthesize a matrix that has larger diameter collagen fibrils, a higher concentration of proteoglycan, and lower concentrations of water and collagen than does the matrix of the superficial zone ***(Buckwalter and Mankin, 2011).***

**III .Middle (Radial) Zone**

The radial zone has a high proteoglycan content (proteoglycan content is highest in the upper sector of the radial zone) while the collagen and water content is low ***(Hesper et al., 2014).*** The chondrocytes in the middle zone are spheroidal in shape and tend to align themselves in columns perpendicular to the joint surface. This zone contains the largest diameter collagen fibrils, the highest concentration of proteoglycans, and the lowest concentration of water ***(Buckwalter and Mankin, 2011).***

**IV . Calcified Cartilage Zone**

A thin zone of calcified cartilage separates the radial zone (uncalcified cartilage) from the subchondral bone. The cells of the zone of calcified cartilage have a smaller volume

than the cells of the radial zone. In some regions, these cells appear to be surrounded completely by calcified cartilage that is, they are buried in individual "calcific sepulchers" suggesting that the cells have an extremely low level of metabolic activity. However, recent work suggests that they may have a role in the development and progression of osteoarthritis***(Buckwalter and Mankin 2011).***

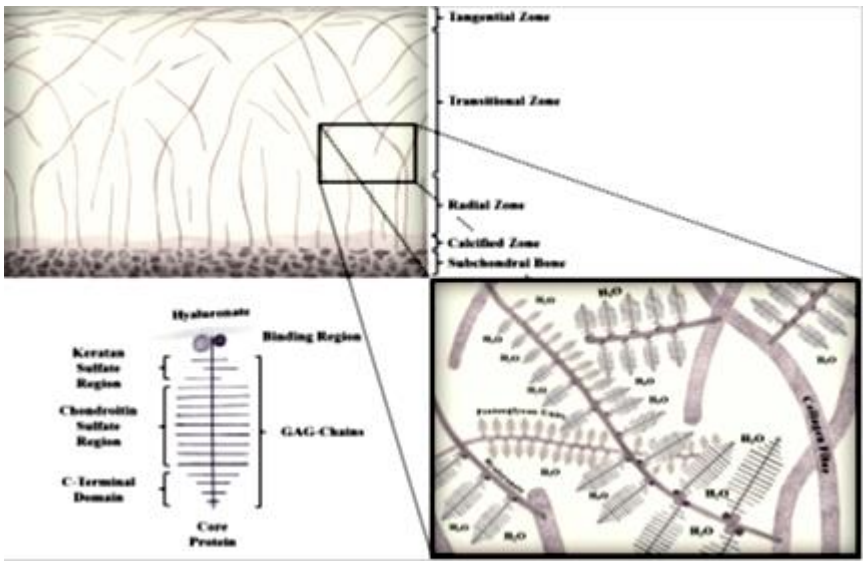


**Figure (3): illustrates:** Schematic drawing illustrating the zonal anatomy, the structure and composition of articular cartilage. The extracellular components form an interconnected lattice structure in which proteoglycan aggregates of hyaluronic acid and side units of glycosaminoglycan (GAG) chains with hydrophilic chondroitin and keratin sulfate regions bind collagen fibers and link them together. Both the high density of negatively charged GAG side chains, which attract positive ions and their surrounding fluid, and the tensile strength of the collagen network to resist this osmotic swelling, contributes to the mechanical stiffness of articular cartilage ***(Hesper et al., 2014).***

# Chapter (2)
# Variable MRI techniques used in evaluation of cartilage

Magnetic resonance imaging (MRI) is the gold standard method for non invasive assessment of joint cartilage, providing information on the structure, morphology and molecular composition of this tissue ***(Ronga et al., 2014).***

Cartilage imaging has grown rapidly due to the increase demand for non invasive cartilage evaluation required by the rapid development of new pharmacologic and surgical cartilage regenerative therapies. Imaging has become established as a decisive element in the treatment algorithm to select the appropriate therapeutic intervention, and is also relied on for the assessment of new treatment methods for articular cartilage disease. Multiple imaging modalities have been used, namely radiography, ultrasound, computed tomography (CT), MRI, and optical coherence tomography ***(Recht et al., 2007)***.

Conventional radiography help in indirect measure of articular cartilage through assessment of joint space but it is unable to detect early chondral damage. Arthrography associated with either x ray or CT is utilized in assessment of