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Biomaterials for Cartilage Repair: A Review

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The quest for an ideal material that could mimic and replace damaged articular cartilage tissue, has been the focus of several past and current researches. Metals, ceramics and ultrahigh molecular weight polyethylene (UHMWPE) have shown some success in Total Joint Replacements (TJR). However, there is still a need to develop materials that would possess the physiological, engineering and tribological properties of natural cartilage tissue and form suitable scaffolds for tissue engineering of cartilage. This is to overcome the drawbacks of total joint replacements such as excessive surgery, stress shielding, harmful wear particles, and an abnormal recovery, among others. The review touches upon the properties and structure of natural cartilage tissue, the problem of arthritis and follows it up with studies on various polymeric materials that have been considered for cartilage replacement and tissue engineering. Outcomes of these studies will be helpful in optimizing structure-property relations and further converge to an ideal material for cartilage repair.

Key words: Articular cartilage, biomaterials, arthritis, total joint replacements

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INTRODUCTION

Cartilage structure: Articular cartilage, the tissue that lines all diarthrodial joints (freely moving joints), provides good wear resistance and works with small friction. It is composed of sparsely scattered chondrocytes in a dense extracellular matrix (ECM) composed primarily of type 2 collagen, proteoglycans and water. The ECM can be classified into four different zones based on structure and function namely (1) Superficial zone, (2) Middle zone, (3) Deep zone and (4) Calcified zone as shown in Fig. 1.

The superficial zone which is about 10-20% of the thickness of articular cartilage, gives a frictionless gliding surface and also provides shear resistance. This zone is collagen rich and has closely packed fibers (Mow *et al*., 1989). The chondrocytes have proteins and provide protection, frictionless movement, cushion effect etc. (Wong *et al*., 1996). Among the proteins involved in surface lubrication, Superficial Zone Protein (SZP), also known as lubricin, has been identified as a functionally important molecule. The presence of hyaluronic acid in the synovial fluid provides frictionless articulation, as it has very small coefficient of friction (Schumacher *et al*., 1994, 1999).

In the middle zone compressive modulus is higher as compared to superficial zone due to thick and obliquely aligned articular surface arrangement. The third type i.e., the deep zone comprises about 30% of the cartilage and has large diameter collagen fibrils lying normal to the articular surface. The above deep zone when partly calcified becomes the fourth zone of the cartilage. In cartilage, a typical large proteoglycan has 100 long chondroitin sulfate chains and 50 much shorter keratin sulfate chains. The sulfated glycosaminoglycan (GAG) chains account for approximately 90% of the molecular weight of the proteoglycan (Ateshian and Wang, 1997). The proteoglycans when hydrated have the ability of articular cartilage that can take compressive loads. The mesh of collagen makes the tissue more resistant under tension and shear forces (Maroudas *et al*., 1980).

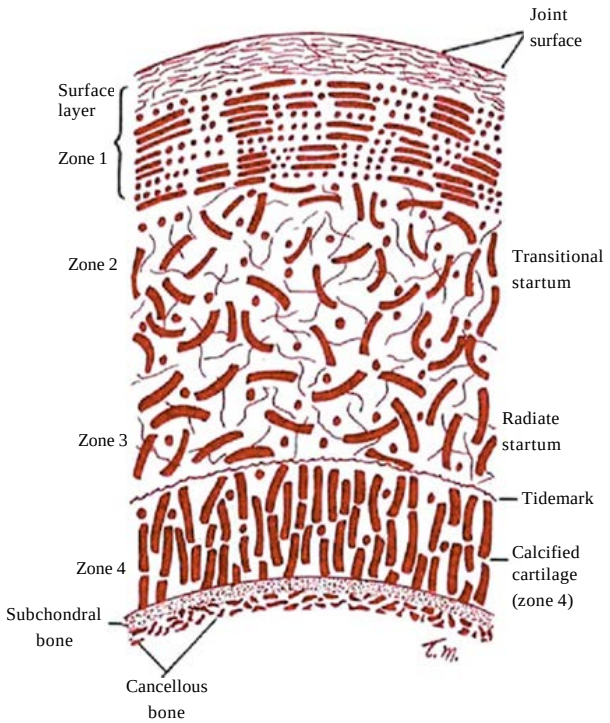

Fig. 1: Cross section of articular cartilage (Levangie and Norkin, 2005)

Cartilage damage and osteoarthritis: Cartilage degradation is caused by the imbalance of synthesis and catabolism due to function of damaged chondrocyte cells and over time this leads to osteoarthritis (OA). This disease is more common with people of older age. The studies show that 10, 50 and almost 100% of people over the age of 50, 65 and 75 years, respectively suffer from osteoarthritis (Felson, 1988; Peyron, 1988, 1991; Bland and Cooper, 1984).

The total annual societal cost for arthritis has been estimated at over 2% of the United States gross domestic product, making the understanding of the pathophysiology and the search for novel treatments of paramount importance in health care science (Felson *et al*., 2000).

Cartilage defects are generally classified into three types namely (1) Matrix disruption, (2) Partial thickness defects and (3) Full thickness defects. Blunt trauma, such as dashboard injuries in road accidents causes Matrix disruption and sometimes partial thickness defect. Full thickness defects occur from damage that goes through the entire cartilage thickness and enters into the subchondral bone.

As articular cartilage has limited potential for regeneration, so, once articular cartilage is damaged, osteoarthritis eventually develops and loss of joint function happens gradually. Many methods for treatment of cartilage tissue have been used with varying success rates in animal studies and clinical trials, including shaving (Bert, 1993), micro-fracture (Sledge, 2001) and transplantation of osteochondral grafts (Outerbridge *et al*., 1995), chondrocytes (Brittberg *et al*., 1996), biodegradable material (Kawamura *et al*., 1998) and artificial cartilage (Carranza-Bencano *et al*., 2000; Hasegawa *et al*, 1999). Tissue engineering and gene therapy have been tested too (Evans *et al*., 2000; Temenoff and Mikos, 2000). So far none of the treatment methods mentioned above has a predominant advantage.

Material properties of artificial cartilage: The prerequisites of a biomaterial to be used for an artificial articular cartilage include:

- Frictionless lubrication
- Provide sufficient cushion effect against shocks
- Excellent wear resistant
- Should be biocompatible
- Simple and firm attachment mechanism to the underlying bone

Based on above mentioned requisites, the biomaterials are designed to resist the high mechanical stresses within articulating joints. Thus, the objective of this review is to provide an overview of the emerging trends in articular cartilage substitute biomaterials. Following are the biomaterials involved in cartilage replacement/regeneration.

BIOMATERIALS FOR CARTILAGE REPAIR/REPLACEMENT

Hydrogels

Poly vinyl alcohol (PVA): The invention of PVA which is considered to be the first synthetic polymers tested as an artificial cartilage, gave start to the research for use of synthetic polymers as cartilage substitute. It is a non-degradable polymer and to design a non-degradable polymer for cartilage replacement many vital parameters need to be considered e.g., good lubricating properties, biocompatibility and mechanical properties like good wear resistance and fatigue life. There are many beneficial characteristics of PVA as an artificial cartilage. PVA is a hydrogel that contains same water content as that in natural cartilage. Moreover, it can be sterilized and molded into desired shapes. However, like other hydrogels, it does not posses enough mechanical stability as a cartilage replacement. Literature survey shows many attempts by researchers to change the process of synthesizing PVA to enhance hydrogel with better mechanical properties (Oka *et al*., 2000; Corkhill *et al*., 1990; Stammen *et al*., 2001; Gu *et al*., 1998). Salubria™ (Salumedica, Atlanta, GA) is produced by carrying out a series of freeze/thaw cycles with the PVA polymers and 0.9% saline solution. Any nondegradable material to be used as a cartilage replacement should have sufficient strength to withstand physiological loading consistently over millions of cycles (Stammen *et al*., 2001).

Oka *et al*. (2000) made an artificial articular cartilage using PVA. In their method, the polymer was dried in vacuum and it was rehydrated until it contained 20% water. However, inspite of above improvements, the authors noted that PVA would not be suitable for total joint replacement but may prove useful for smaller scale cartilage replacement/joint resurfacing.

In shoulder arthroplasty, the possible complications are mostly due to wear and loosening of glenoid components. Swieszkowski *et al.* (2006) developed a noble glenoid implant design by using artificial cartilage at the surface and modeled its material from the tests and hyperelasticity law. This implant is made up of poly (vinyl-alcohol) cryogel (PVA-c).

Wu *et al.* (2008a) developed a composite hydrogel made up of Hydroxyapatite (HA) and polyvinyl alcohol hydrogel (PVA-H). This composite hydrogel was used as artificial cartilage. It was seen that with increase in HA content and immersion time for the composite, the precipitation of apatite increased.

Thomas *et al.* (2009) developed a hydrogel with a combination of hydrophilic as well as hydrophobic structures. These materials exhibit many of the desired mechanical properties to be useful in cartilage replacement materials. Furthermore, the introduction of hydrophobic groups in the materials has been shown to have a positive effect on mechanical properties with a minimal effect on COF and contact angle. Thus, it is possible to produce hydrogels that exhibit signs of hydrodynamic lubrication which are stronger than the reference PVA hydrogels.

Bera (2009) developed an artificial articular cartilage. It consists of PVA/Si nanocomposite. This showed the improvement in the mechanical strength of PVA up to 35 MPa. The authors also prepared an adhesive from PVA/Si nano-composite containing 40% Tetra ethoxy silane (TEOS) for its attachment to under lying bones.

Polyacrylates: Polyacrylates, are another type of non-degradable polymer hydrogel. It is thermally copolymerized 2-hydroxyethyl methacrylate (pHEMA) with acrylic acid in different proportions (Malmonge and Arruda, 2000). In another study, Malmonge *et al.* (2000) tested the mechanical characteristics of newly formed cartilage tissue within a defect treated with a pHEMA implant. They carried out *in vivo* tests on wistar rats with cartilage defects and found the enhanced mechanical characteristics of the pHEMA implant.

In another study, Sawtell *et al.* (1995) developed a polymer named poly(ethyl methacrylate)/ tetrahydrofurfuryl methacrylate (PEMA/THFMA) to enhance the properties of neocartilage. The PEMA/THFMA is not bio-degradable, however its network supports for mechanical uniformity and implantation. It may also be employed in complete resurfacing with hyaline-like artificial cartilage, with

excellent collagen and proteoglycans distribution (Reissis *et al*., 1995). Recently, Wyre and Downes (2000) compared this polymer with Thermanox, a polyethylene terephthalate film. Their results showed that the seeding of chondrocyte on the Thermanox control occurs better than on PEMA/THFMA.

Poly (N-isopropylacrylamide): The poly (N-isopropylacrylamide) (pNIPAAm) for usage as an injectable hydrogel for cartilage tissue applications was investigated by Stile *et al.* (1999). This pNIPAAm (aqueous form) may be used for cartilage repair by injecting in situ, as it has a Lower Critical Solution Temperature (LCST). However, such a system demands future research.

Amidated polysaccharide hydrogel: Leone *et al.* (2008) obtained an amidic derivative of carboxymethyl cellulose-based hydrogel (CMCA) and it was characterized in terms of amidation degree. The rheological investigation by the authors showed that CMCA hydrogels exhibit a similar behavior like the rheological performance of human cartilage. The magnitude of the complex shear modulus [$|G^*| = (G'^2+G''^2)^{1/2}$] of the cartilage increases monotonically from 0.2-2.5 MPa, whereas within the same frequency range, the phase shift angle (δ) between solicitation and response varies between 9 and 22° [$\tan \delta = G''/G'$: energy dissipated during the sharing]. A comparable behavior was found when comparing these values with those of CMCA with δ assuming a mean value of 13° for CMCA. Also, the complex modulus value was as comparable with that of cartilage. The articular cartilage is a relatively high-compliant tissue having a shear modulus ranging from 0.2-0.4 MPa and decaying very quickly.

Strong gel for artificial cartilage: A group of researchers at the National Institute of Standards and Technology (NIST), Gaithersburg, USA developed a strong synthetic cartilage replacement in form of gel that won't break apart even when deformed more than 1,000%. It is made up of layers of gelatin and is also known as double-network hydrogels. Initial work on it was first reported by researchers at Hokkaido University in Japan in 2003. Most commonly used hydrogels having 80-90% water content in a polymer network easily break apart like a gelatin. NIST's researchers used neutron scattering techniques to explore the structure of the gel at molecular-level toughening mechanism that is found in this unique hydrogel (Wu *et al*., 2008b).

Silicon rubber: Silicone rubber (having silicon-oxygen linkages) is another polymer that may be used as artificial cartilage. Implants made up of Silicone rubber were used by Wang and Yu (2004) to replace by filling cartilage defects in the knee joint of rabbits, to find the long-term effect of silicone rubber implant on nearby articular cartilage. They found that the implants remain fit firmly into the defects for a period of about one year after surgery. The authors demonstrated that implantation of silicone rubber can be used to repair defected articular cartilage.

Polymeric composite material: Ribeiro *et al.* (2007a) developed and tested a nano-composite material containing polytrimethylene carbonate and hydroxyapatite. It consists of multiwalled carbon nanotubes (MWNT) to mimic real cartilage and HAP for reinforcement as well as for enabling bone ingrowth. The experimental results showed close value of the coefficient of friction of the nanocomposite material with natural articular cartilage.

Some other biomaterials used for cartilage replacement: Ribeiro *et al.* (2006a) performed tribological test on boronized chromium looking to their good industrial applications and uses in joint arthroplasty. The authors found that the friction coefficient of the boronized chromium in simulated body fluid conditions was in the same range as that for natural bone joints. Ribeiro *et al.* (2006b) studied tribological properties of the boride coatings on niobium in both dry and simulated body fluid conditions. The authors found that the friction coefficient for the boronized niobium reduced remarkably under simulated fluid conditions when compared with dry conditions. Ribeiro *et al.* (2007b) investigated the wear characteristics of boronized tantalum under dry and simulated body fluid conditions and found that it cause tribological reactions and result in increased friction relating with amorphous debris under simulated body conditions. Ribeiro *et al.* (2012) carried out Nano-indentation and pin-on-flat tribological tests on polyamide (PI)-carbon nanotube (CNT) for its mechanical and tribological properties by changing the CNT concentration in a PI matrix.

CONCLUSION

This review covers more recent studies on potential materials for articular cartilage repair. The results indicate certain advantages in each case. The use of these materials for the intended purpose is still limited. Further trials and success thereafter would lead to marketability and a possible shift from the current total joint replacement technique.

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