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Review Article

Articular Cartilage- A Literature Review

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Abstract

Articular cartilage, a highly specialized and unique tissue, is capable of dispersing immense compression loads and almost eradicating friction in diarthrodial joints. This paper to investigates the structure, nutrition, and repair of cartilage to further understand the unique tissue. A breakthrough in cartilage repair and regeneration is discussed.

Keywords: Cartilage regeneration; Stem cells; Growth hormone.

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Introduction

Articular cartilage is hyaline cartilage of diarthrodial joints which, due to its unique viscoelastic properties, provides an almost frictionless surface for joint articulation and load transmission [1,2]. Articular cartilage facilitates the distribution of load over the articular surfaces of the joint, thus preserving weight bearing bones from damage and deterioration [3]. The earliest recorded comment on cartilage is attributed to Aristotle in the fourth century BCE who described it as "pliable and glutinous for the benefit of the surrounding flesh" [4].

Interestingly, current research has shown articular cartilage to be an avascular, aneural and alymphatic tissue. This, in addition to its harsh external environment where it is exposed to shear compression forces, and has restricted access to nutrition and oxygen, may contribute to its limited capacity for intrinsic healing and repair [1,5,6]. As such, preservation of articular cartilage and research into methods of regeneration and repair is most important for the health of synovial joints.

Structure and attributes of articular cartilage

Treatment and repair of articular cartilage is difficult due to its unique and elaborate structure. Articular cartilage is a hydrated soft tissue consisting largely of water. A large component is the extracellular matrix (ECM) which contains proteoglycans, a collagen

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network, and ions (mainly Na^+ and Cl^-). These components assist in water maintenance, which is critical to the preservation of the mechanical characteristics of articular cartilage [1,7]. In addition, water and proteoglycans equip cartilage with compressive strength, while collagen fibrils contribute to defence against tensile forces [8]. Joint inactivity has been linked to cartilage degradation, hence frequent joint motion and application of dynamic weight is important for conservation of healthy cartilage [1].

Chondrocytes

The resident cell of articular cartilage is the chondrocyte. Arising from mesenchymal stem cells, they are responsible for cartilage formation and functionality. Chondrocytes are critical in the repair, maintenance and synthesis of the extracellular matrix which facilitates nutrition diffusion within cartilage and biomechanical competence of the joint surface [1,8,9].

The regulation and maturation of chondrocytes involves several important growth factors including fibroblast growth factors (FGFs), the TGF-β family, and insulin-like growth factor (IGF)-1 [9]. Dependent on age and joint, chondrocytes can comprise less than 5% of total cartilage volume.

Unlike most mammalian cells contained in vascularized tissue that use oxidative phosphorylation for energy production in the mitochondria, chondrocytes consume oxygen to stimulate glycolysis [6]. It is widely recognised that chondrocytes receive this oxygen, limited as it might be, from the synovial fluid, a dialysate of blood [10]. In addition to oxygen, chondrocytes divert most of the glucose to the energetically and biosynthetically less efficient glycolytic pathway [11]. A 2020 study on glutamine metabolism in chondrocytes observed that chondrocytes are also somewhat reliant on exogenous fatty acids for energy production and metabolism [12].

Chondrocytes are isolated in small cavities called lacunae, which has given rise to the notion that cells are not in direct communication with each other, but rather communicate via diffusion of substances in the matrix. Mayan, et al. conducted a study which investigated chondrocyte communication and verified that human adult chondrocytes retain communication capacity through voltage-gated gap junctions which play a key role both communication and metabolic function [13]. In fact, Mayan et al. hypothesized that a three-dimensional cellular network mediated through GJs might contribute to the metabolic and physiological homeostasis required to maintain the health of cartilage tissue. Dramatic changes in cartilage metabolism have been linked to development of diseases such as osteoarthritis, which occur when there is an imbalance between the degradation and synthesis of chondrocytes.

Extracellular Matrix (ECM) and its macromolecules

While the major component of the ECM is water, collagen, and proteoglycans (PGs) are the also considerable constituents, with Type II collagen and aggrecan being the most common of each respective macromolecule [7]. Type II collagen contributes to the tensile properties of cartilage through water maintenance, while aggrecan gives cartilage its property of compression resistance. The

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high negative charged cells in the aggrecan macromolecule swell against the collagen network, drawing water in to resist compression [9,10,14]. Proteoglycans represent 10-15% of the wet weight of the ECM and are synthesized, maintained, and secreted by chondrocytes [1].

Whilst 90-95% of the collagen in the ECM is Type II, at least 5 different types have been identified in cartilage, each with their own function. Markedly, Type VI is instrumental in attachment of chondrocytes to the matrix, Type IX assists the binding of collagen fibres and type XI regulates fibre size. Because of the restriction and maintenance of water within the cartilage by collagen, the ECM is hydrated to a limited degree and thus is able to maintain a swelling pressure that plays a part in its mechanical qualities [10]. Smaller amounts of additional molecules can be found in the ECM including lipids, phospholipids, non-collagenous proteins, and glycoproteins [1].

Age is a determining factor on the composition of the matrix, as well as the organisation of chondrocytes and their response to external factors like cytokines. As age increases, hydration of the matrix decreases corresponding to a stiffer joint. This is likely to have repercussions for the subchondral bone, which may experience increased forces as a result of irreversible cartilage deformation [1].

Water

Water constitutes between 65 and 80% of the wet weight of cartilage and has two important functions; (1) Transportation of nutrients and waste products and (2) as touched on before, the minimal permeability of cartilage means water creates a 'cushioning' effect when a compressive force is applied, reducing the effects of compression on the ECM, chondrocytes, and subchondral bone [10].

Structural layers

Articular cartilage is made up of four distinct zones, the Superficial (tangential) zone, Middle (transitional) zone, Deep Zone and Calcified Zones in which cells vary in shape, size, and metabolic activity. Collagen and water content is highest in the superficial zone, reducing by around 15% each in the middle (transitional) and deep zones. Proteoglycan content follows the opposite trend. Such variability in the structural composition leads to nonuniform transport of nutrients [1,7]. The Superficial (tangential) Zone (STZ) acts to protect the deeper layers from shear stresses and constitutes approximately 10-20% articular cartilage thickness. This zone is in contact with Synovial Fluid and its integrity is vital for the protection the layers beneath. Here, collagen fibers are tightly packed and aligned parallel to the articular surface.

The Middle (transitional) zone provides an anatomic and functional bridge between the superficial and deep zones, representing 40-60% of total cartilage volume. This zone contains proteoglycans and thicker collagen fibrils arranged obliquely. Since collagen fibers of the Deep Zone provides are arranged perpendicular to the articular surface, this zone provides the greatest resistance to compressive forces. It represents around 30% of cartilage total volume. Finally, the tide mark distinguishes the Calcified Zone from the Deep Zone. The calcified cartilage anchors the collagen fibrils of the deep zone to the subchondral bone.

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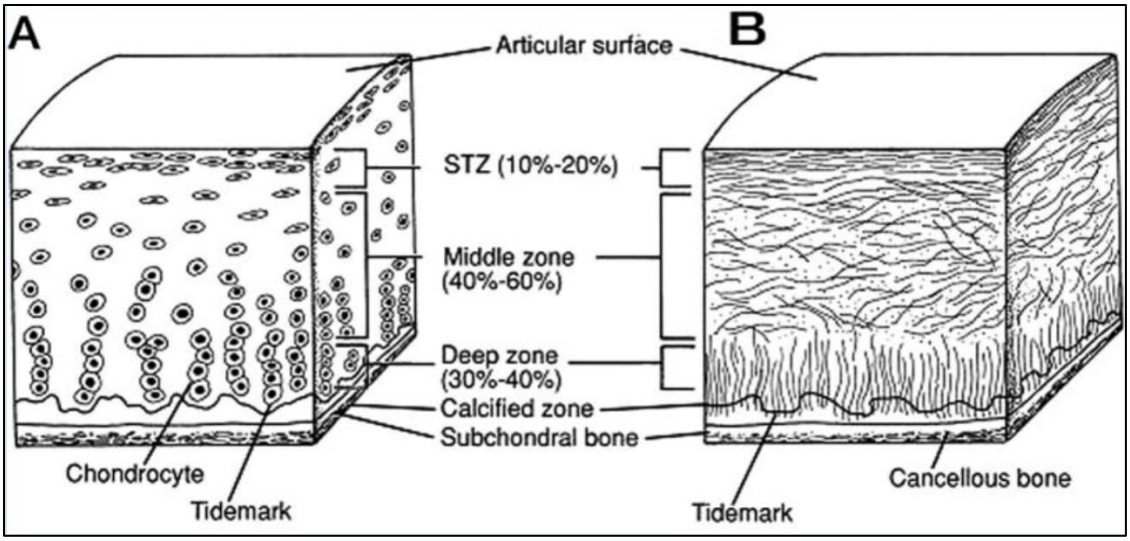

Figure 1: Diagram, cross-section of healthy cartilage structure: A: Organisation of zones; B: Collagen fiber alignment [15].

Synovial fluid

In a 2006 analysis, Brannan et al. described Synovial Fluid (SF) as a "highly viscous, straw-colored fluid believed to have two main functions: to assist in the mechanical function of the joint by lubrication of articular surfaces, and to aid in the nutrition of articular cartilage by acting as a transport medium for nutrients such as glucose" [16]. Indeed, by forming a viscous film over the joint surface, synovial fluid acts as a useful lubricant [3]. Being transudate of blood, SF shares numerous transporter proteins and immunoglobins with plasma, which alludes to the shared functions of the two fluids as a transport media for cellular products. As well as proteins derived from blood, SF contains components contributed by the surrounding articulating joint, such as synovium and cartilage [17]. Healthy SF will consist of no more than 200 white blood cells (WBC/mm^3) as well as large synovial cells, monocytes, macrophages, lymphocytes, neutrophils, glucose, and uric acid [16]. SF is present in all joint cavities and is continually being replenished by the synovial lining which actively secretes glysaminoglocan hyaluronan the glycoprotein lubricin [18]. A distinct characteristic of Synovial fluid is its viscosity which tends to increase as temperature decreases, which may be a contributing factor to joint stiffness felt during cold weather [16].

Factors affecting cartilage health and development

There are a multitude of factors which impact the health and development of cartilage, some of which include oxygen tension, load, and fluid flow. The homeostasis of these factors is imperative in maintaining cartilage health and promoting development.

Oxygen tension

It is known that, physiologically, oxygen diffusion occurs from the synovial fluid through cartilage tissue and reaches a tension around 10% in the superficial zone and 5% in the deep zone [5,6,19]. When developing tissue-engineered cartilage, studies have shown benefits of reduced oxygen tension, mimicking the in vivo environment. It can

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generally be said that low oxygen tension has an auspicious effect on chondrocyte production and metabolism. In tissue engineering, chondrocytes cultured under low oxygen tension (5%) maintain their phenotype and synthesize more cartilage-specific molecules compared with chondrocytes culture in nomoxic conditions (21%) [5].

Load and fluid flow

Diarthrodial joints are significant components of the musculoskeletal system and enable people to maintain posture, position their body, move, and manipulate objections around them. Joints often undergo forces several times body weight, so maintenance of and understanding their health is imperative in maintaining mobility and a healthy lifestyle [2]. Mechanical stresses exceeding normal pressures are thought to cause physical damage to cartilage. Injury can disrupt matrix components, and catalyse cartilage degeneration, leading to chondrocyte death and posttraumatic arthrosis. Primary cartilage injury, residual joint incongruity and ligamentous injury are all causes of posttraumatic arthrosis [10]. Repo and Finlay concluded that "impact loads sufficient to create femoral shaft fractures were near sufficient to cause chondrocyte death and mechanical disruption of the articular cartilage of the knee or hip" [20]. Whilst excessive, unexpected forces can damage cartilage, joints are designed to cope with the mechanical demands of everyday life. In fact, those who exercise regularly demonstrate more substantial bone and muscle mass compared to their inactive counterparts in which can tissue atrophy is often present [2]. As such, mechanical loading influences the development, maintenance, and aging of skeletal tissues, including articular cartilage. O'Connor [21] confirmed that cartilage thickness is in part determined by mechanical joint loading and movement. As a result of shear stress and compression, cell metabolism can be stimulated by an increase in fluid flow through the cartilage tissues [5]. This is covered in more detail below, see Nutrition.

It is now accepted that both mechanical loading and 'hypoxia' are two permanent stresses that dramatically impact articular cartilage [14].

Nutrition

The avascular nature of articular cartilage has been accepted for over 200 years; however, speculation and controversy have surrounded the problem of how this tissue obtains its nutrition [22]. Current research concludes that nutrition attained from synovial fluid is the dominant source for adult cartilage, in which joint movement and loading increases SF production and supply of nutrients throughout the entire joint [1,23].

Wang, et al. conducted a study [24] investigating nourishment of articular cartilage from both diffusion from subchondral bone and from synovial fluid. They concluded that while blocking of nutrition of both SF and bone marrow resulted in decreased mRNA levels of aggrecan and Type II collagen, SF-derived nutrition is the predominant source of nourishment since significantly higher cartilage degeneration occurred when the SF pathway was blocked.

Additionally, a study conducted by Strangeways in the early 20th century

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examined “free bodies” sometimes found in a joint cavity that were hypothesized to be due to “traumatic detachment of a portion of articular cartilage” [25]. Strangeways discovered that the process of cellular nutrition was still occurring even after separation. While it might have been concluded that it was the death of the cells of the fragment that provided the nutritive material, the fragments were shown to increase in size over time. Hence was hypothesized that articular cartilage may derive some, if not most of its nourishment from the synovial fluid.

Pumping

Considering joint inactivity has been proven to contribute cartilage degradation [26], it makes sense that the flow of synovial fluid in and out of cartilage tissue caused by cyclic loading is thought to assist in nutrient delivery. This is commonly called ‘pumping’ [23]. While there is no experimental evidence to support pumping influencing the movement of low molecular weight molecules, like oxygen or glucose, there is evidence that pumping can assist in the movement of high molecular weight substances like enzyme inhibitors, hormone carrier complexes or cytokines through the matrix.

Further, as mentioned previously, loading can impact synovial fluid formulation and help distribute it throughout the joint. Without movement and loading, SF may become stagnant and depleted of nutrients accumulating acidic waste products. As such, a lack of joint activity and subsequent fluid flow can result in nutrient deficiencies within the cartilage tissue [23].

A wider study of human articular cartilage by Maroudas, et al. investigated the permeability of articular cartilage and how pumping influences nutrition [27]. They found that, while adult calcified cartilage was found to be water impermeable, the joint of a ten-year-old was permeable to water, glucose, and methylene blue. Thus, it was concluded that mature cartilage relies only on the exchange of material through the articular surfaces, whereas immature cartilage can derive nutrients from the underlying bone as well as the joint cavity.

This is important when considering the permeability of adult cartilage and chondrocytes of the deepest layer. It was calculated from the permeability coefficient of glucose that the thickness of cartilage adequately supplied with nutrients is 3mm. Considering, under normal conditions, the thickness of cartilage does not exceed 3mm, joint movement producing agitation of the synovial fluid cells should provide a sufficient glucose supply.

However, without agitation, penetration can be as shallow as 1.5mm, hence, cartilage must derive some nutrition to the deeper layers by compression under load resulting expression and absorption of fluid. While pumping occurs, diffusion is decreased since compression reduces cartilage’s permeability to solutes.

Degeneration of cartilage and techniques for repair

Cartilage, particularly when damaged, is limited in its ability to regenerate [28]. Damage and degradation of cartilage may occur as a result of many stimuli including metabolic or genetic disorders, mechanical

stress, and trauma [5]. Injury to cartilage can lead to osteoarthritis (OA), in which patients present with swelling, pain and joint deformity, seriously limiting joint movement and quality of life [29]. Mehmet et al. characterises it as "cartilage loss, sclerosis and cyst formation in subchondral bone and marginal osteophyte formation" [8]. The synovial joint cartilage is maintained by a delicate equilibrium between synthesis and death of chondrocytes. Development of OA can occur because of a disruption in this balance, or in other words, an "unbalanced see-saw, favouring catabolic breakdown over anabolic synthesis" [30]. In addition, Toillon et al investigated the role of osteochondral angiogenesis in the progression of OA, which can result in vascular channels penetrating the articular cartilage resulting in further tissue damage [31].

Kim, et al. outline the non-surgical options for management of OA which include "weight loss, exercise, activity modification, assistive devices, non-steroidal anti-inflammatory drugs (NSAIDs) analgesics and intraarticular glucocorticoid and hyaluronic acid (HA) preparations" [3]. Such assistive devices might include orthotics and braces [32]. Common surgical methods for repair and/or management of OA include mosaic plasty, autologous chondrocyte implantation, matrix-induced autologous chondrocyte implantation, mesenchymal stem cell implantation and other cell-based therapies, lavage and arthroscopy, osteotomy, and grafts. Often, most of these techniques can relieve pain but fail to entail complete restoration and result in the formation of fibrocartilage. Composed of both type I and type II collagen, fibrocartilage is inferior in strength and resilience to the preferred hyaline cartilage which naturally exists in a healthy joint [5,28,33-35].

According to Jiang et al, "tissue-engineered cartilage is considered to be the most promising strategy for the complete restoration of hyaline cartilage," further, they indicate the critical role mesenchymal stem cells (MSC) may play in cartilage repair [29]. However, current techniques for MSC implantation have their limitations, including finding an ethical source of cell and appropriate scaffold materials. More research and clinical applications still need to be conducted to gain further understanding on the impact of tissue-engineered cartilage, especially MSC derived, on joint repair.

Human growth hormone as a mechanism for cartilage repair

It is established that Human Growth Hormone promotes cartilage generation by "triggering active chondrocyte growth at the postnatal epiphyseal growth plates of the long bone" [36]. This effect of HGH on cartilage has led to it being suggested for treatment of OA. Growth hormone is an important regulator of skeletal growth and bone mineral density. HGH could be used with the purpose of increasing cartilage metabolism and chondrocyte proliferation through systemic insulin-like growth factor 1 (IGF-1) production and direct stimulation of cartilage cell proliferation [3,37-40]. Dunn published a study in 2001 [41] presenting a new form of angiogenesis named 'morphoangiogenesis' (M-A) which produces stem cells in vivo in adults through intraarticular growth hormone (IAGH) injection.

Dunn explains morphoangiogenesis produces two structures, the first which resembles

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cartilage canals normally only observed in foetuses starts to develop 24 hours after injection, and the second resembles renal glomeruli and develops several weeks later. Amazingly, both structures contained thin-walled fenestrated capillaries and produced stem cells which contributed to generation of articular cartilage. Through experimentation on rabbit knees, Dunn discovered the presence of morphoangiogenesis and vascularity in all the IAGH-injected knees to be directly correlated to production of healthy articulophyseal cartilage (APC). The cartilage canals and glomeruloids produced by M-A contain stem cells, making them readily available in adults. As such, not only does growth hormone injection present remarkable repair capacity for cartilage, but it may be able to regenerate other tissues such as cardiac muscle, organs such as liver and promote benign vascular structures which obstruct the neovascularisation of cancers and starve tumours. To the author's knowledge, this is the only published research on morphoangiogenesis and its astonishing ability for repair and regeneration of cartilage.

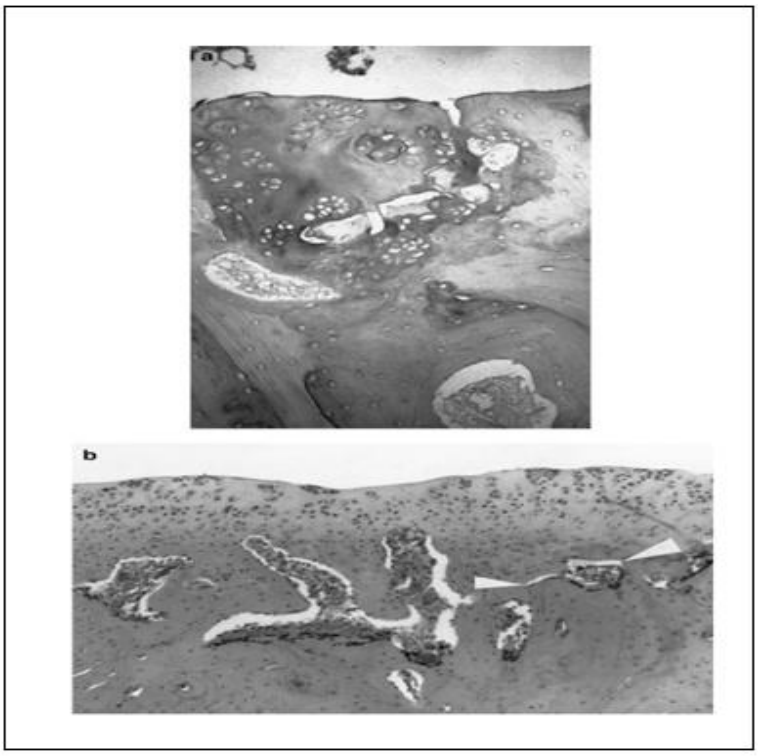

Figure 2: Dunn's research on the effects of IAGH on articular cartilage was fruitful. These images are of animals sacrificed at 47 days. (a) Control Knee: Morphoangiogenesis is absent, subchondral osteones and central arteries remain intact. Occasional submerged island of cartilage on the debrided surface which has no blood supply in contrast to M-A structures. (b) Morphoangiogenesis is present. Arrow indicates line of debridement. M-A created vascular structures composed of thin-walled fenestrated capillaries [41].

Conclusion

Articular cartilage has a unique ability to provide an almost frictionless surface for joint articulation and load transmission, making it imperative for joint health and mobility. It's avascular, aneural and alymphatic nature contribute to a limited ability for intrinsic healing and repair. Understanding the nature

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and structure of cartilage is essential for developing viable techniques for restoration. Whilst there are numerous methods for the treatment of damaged cartilage, many result in the formation of the inferior fibrocartilage, not the preferred hyaline cartilage. The exceptions to this include treatments involving mesenchymal stem cells, namely, the injection of intraarticular growth hormone which aids in the production of stem cells on vivo in adults, removing the need for stem cells from an external source. This treatment acts to 'reverse' the age of cartilage, changing its physical structure and returning its ability to receive nutrients from the underlying bone via thin-walled fenestrated capillaries, an attribute similar to that of immature cartilage. It is the author's opinion that this is a major step forward in cartilage repair that shows huge promise. As such, more research should be conducted to further determine the applications and effects of intraarticular growth hormone injection on the regeneration of cartilage.

Disclosure

Dr Gordon Slater is a medical director of Integrant Pty Ltd, an orthobiologics company.

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