Review Article

Articular Cartilage: Structure, Composition, Injuries and Repair

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Abstract

Articular cartilage has a unique structure that makes it very different from any other tissues in the body. It has such specific roles and functions such as weight bearing with low frictional coefficient that the main bulk of its structure is based on that alone, thus making it a vascular, and thereby greatly limiting its self regeneration capabilities. This article aims to review the structure of articular cartilage and structural changes during osteoarthritis, one of the most common cartilage degenerative diseases around, and as well as insights into some of the current treatment options available for cartilage degenerative diseases.

ABBREVIATIONS

ECM: Extra Cellular Matrix; PGS: Proteoglycans; GAGS: Glycosaminoglycans; COMP: Cartilage Oligomeric Matrix Protein; CMP: Cartilage Matrix Protein; MRI: Magnetic Resonance Imaging; ACI: Autologous Chondrocyte Implantation

INTRODUCTION

Structure and composition of articular cartilage

Articular cartilage has a unique structure that is designed to be durable, long lasting and expected to remain functional throughout our lifetime. Articular cartilage is avascular, aneural and alymphatic and thus has very poor regenerative potential once reaching maturity. Instead it depends mainly on the simple diffusion of oxygen and nutrients from surface synovial fluid and basal subchondral bone (bone marrow) for nourishment [1-3]. In addition, it is reported that synovial fluid derived nutrition is the dominant source of sustenance for chondrocytes in adult articular cartilage. Limitation to only bone marrow derived nutrition leads to vascular invasions into bone marrow and thus affecting quality of cartilage [4]. Articular cartilage serves as a shock absorber, as well as to protect joint surfaces by distributing weight loads. The principal function of articular cartilage is to allow smooth gliding movements between bones with low frictional coefficient.

Two major components can be found in the articular cartilage, the extracellular matrix (ECM) and chondrocytes which are distributed sporadically throughout the cartilage. The ECM is predominantly made up of type II collagen, negatively charged proteoglycans (PGs), water and some other minor components including some glycoproteins and non-collagenous proteins.

Type II collagens are responsible for the building of cartilaginous framework and contributing to tensile strength of articular cartilage with PGs contributing to hydrophilic behavior of articular cartilage. Together with hydrophilicity of PGs, collagen and the other components of articular cartilage aids to preserve water within the ECM, which contributes to the high tensile and mechanical resistance of articular cartilage. In addition, different layers of the cartilage has different composition components with chondrocytes expressing different cellular morphology in each layer [5]. Chondrocytes play an important role in the maintenance of articular cartilage homeostasis as they secrete matrix constituents and matrix-degrading enzymes as well as having surface receptors for various cytokines and growth factors.

Zonal structure of mature articular cartilage

Articular cartilage is a highly organized anisotropic tissue composed of 4 different zones, namely the superficial or tangential zone (10-20% of total cartilage volume), middle or transitional zone (40-60% of total cartilage volume), deep or radial zone (30-40% of total cartilage volume) and the calcified zone (see Figure 1). Each of these zones possesses unique structural, functional and mechanical properties and chondrocytes in different zone produce specific responses to different stimuli by secreting different proteins [6].

The superficial or tangential zone, also known as lamina splendens, constitutes 10 to 20% of the total cartilage thickness. In this zone; chondrocytes have a flat and elongated appearance and the collagen fibers (made predominantly of type II collagen), are densely packed and aligned horizontally at the very surface
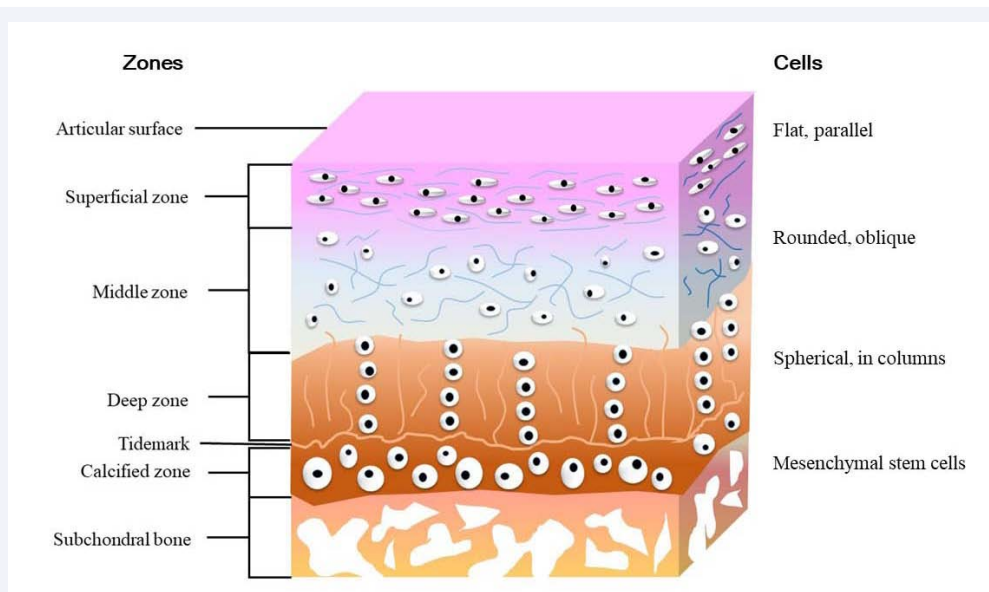
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Figure 1 Structure of mature articular cartilage zones.

of this cartilage. Type II collagen has been known to be able to create a highly cross linked network of collagen fibrils with interconnections. This superficial layer is adjacent to the synovial fluid and it contains the highest amount of collagen but lowest proteoglycan content in comparison to other deeper layers. It protects deeper layers from deformation and also contributes to most of the tensile properties of the cartilage which makes it capable of withstanding the harsh compressive forces placed during articulation [7,8].

Right underneath the superficial zone is the middle zone, or some may refer it as the intermediate zone. The middle zone made up about 40 to 60% of the total cartilage volume. It has higher proteoglycan content and contains thicker collagen fibrils. Chondrocytes in this zone appeared to be spherical and the collagen fibers have an oblique orientation. Their distributions are random and chondrocytes content in this zone is lower.

Deep zone, otherwise radial or basal zone, contributes 30-40% of the total cartilage thickness. Chondrocytes in this layer are spherical and arranged in columns. As this layer contains the highest level of proteoglycan content and the collagen fibrils in this layer are larger and oriented perpendicularly to the surface, this layer has been thought to provide the greatest resistance to compressive forces imposed by articulation [3,5].

Deep and calcified zones are separated by a thin basophilic line known as the tidemark. It distinguishes the mineralized layer from the un mineralized layer [2]. Collagen fibrils from the deep layer are anchored to the subchondral bone, attaching cartilage to the joint surfaces, holding them in place. There are very few cells in the calcified layer and chondrocytes are large in this layer.

Extracellular matrix of a mature articular cartilage

The ECM of a mature articular cartilageis made up of three major components: fibers (collagen and elastin), ground substance (proteoglycans, glycosaminoglycans, noncollagenous proteins) and intercellular fluid. Collagen and elastin are both insoluble

macromolecules. Articular cartilage has several types of collagen, and 90 to 95% of them are type II collagen. Type III collagen (approximately 10%), type IX collagen (1%), type XI collagen (3%) and type VI collagen (<1%) are the other types of collagen fibres present in the ECM. All these collagens are responsible for resistance to tensile loads and type VI collagen is thought to be crucial in the regulation of chondrocyte mechanotransduction. Elastin provides elasticity to the articular cartilage. It is able to be stretched to about 150% of its original length and yet has the elasticity to return to its original size. In contrast to the elastic fibers, collagens can only be stretched up to10% of its original length under tension [9,10]. However, elastin only makes up a small percentage of the ECM. Proteoglycan refers to a family of proteins that are densely glycosylated. It contains a core protein which has one or more highly anionic sulfated polysaccharides called glycosaminoglycans (GAGs) covalently attached to it. GAGs in proteoglycans have unique physicochemical features that gives proteoglycans its hydrophilic behaviour which attracts water molecules and allow water retention, thereby allowing the cartilage to resist compression forces[2,11].The largest proteoglycan and also one of the most abundant proteoglycans present in the cartilage is the aggrecans. Aggrecans interact with hyaluronan via link proteins (see Figure 2) forming large proteoglycan aggregates, enabling cartilage to resist compression forces with minimal deformation and they also contributes to water retention in articular cartilage. The ECM also contains a small amount of non-collagenous and non-proteoglycans proteins. Some of those that are better studied include cartilage oligomeric matrix protein (COMP) or thrombospondin-5, cartilage matrix protein (CMP) or matrilin-1, fibronectin and so on. These proteins have structural function in the matrix and are thought to participate in the cell-cell or cell-matrix interactions [12].

However, a recent study employs Raman spectroscopy to look into the compositional and structural properties of articular cartilage and it is reported that there is a much more
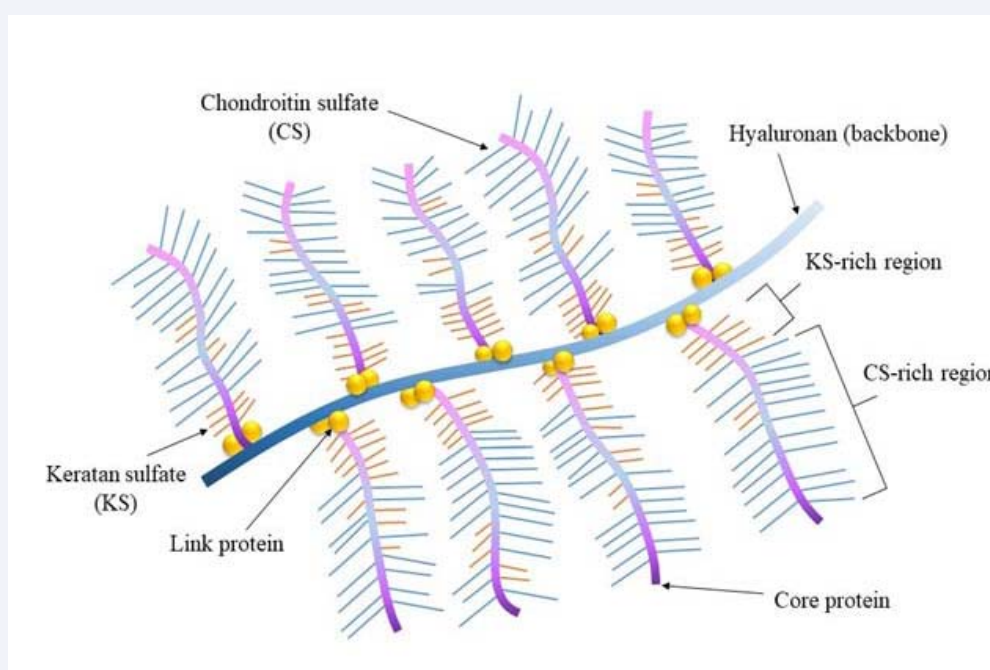
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Figure 2 Structure of an aggrecan-type complex proteoglycan.

complex zonal arrangement than previously proposed. Based on their analysis, there is at least six different and distinct depth-dependent zones that has different composition and structural contents [13].

Mechanism of articular cartilage injuries

Self-regeneration processes are only initiated when damage reaches subchondral bones. Therefore, with a higher rate of wear and tear as compared to repair, chronic and progressive degenerative joint diseases such as osteoarthritis and rheumatoid arthritis seems unpreventable [14,15]. In addition, direct blunt trauma, sudden impact loading or torsion stress can cause damage to the zone between calcified cartilage and subchondral bone without damaging the rest of the tissues [16]. Sudden and rapid applied excessive force would not allow for sufficient fluid to move through the matrix for shock absorption, therefore allowing the stress to be applied fully on the macromolecule network, thus causing micro tears and injuries to the matrix. Thankfully, with major advances to imaging technologies such as magnetic resonance imaging (MRI), we are able to obtain clear information and insights into structural organization of our cartilage, therefore allowing early detection [17]. However, micro injuries usually do not have any presentable clinical symptoms. Chondrocytes are presumed to be able to restore the matrix if the rate of damage is not faster than rate of repair, and that if there are enough viable chondrocytes [18]. Repetitive stress or trauma can cause fissure-like disruption to the matrix and in severe cases, even segmental loss of cartilage. Macromolecules synthesized by chondrocytes are insufficient to fill the gaps caused by injuries. Over a period of time, osteoarthritis will occur, causing chronic pain and disability to the patient. Osteoarthritis is the most common form of degenerative disease, affecting over 40 million people worldwide and affecting up to 70% of the population aged 65 years and above [15]. Animal model studies and analysis of human cartilage specimen has helped us to establish pathological changes in cartilage [19]. At the matrix level, there would be swelling due to fluid influx with disruption of matrix network leading to gradual fragmentation of matrix. On the chondrocyte level, there would be initial increase of anabolic and catabolic activities to repair matrix networks, thus leading to production of reactive oxygen species and other inflammatory cytokines and chemokines. After chronic exposure, chondrocytes would undergo apoptosis, form chondrocyte clusters and even become hypertrophied. At the calcified cartilage and osteochondral junction, both blood and lymphatic vessels would penetrate the cartilage with calcified cartilage invading into the articular cartilage level thus recreating a new tidemark. Lastly, there would be new bone formation at the osteochondral junction.

It is important for us to understand the evolution of osteoarthritis and its impact on our osteochondral unit. Under certain situations, only one part of the osteochondral would be affected. However, with prolonged exposure to stress, the different components would interact and thus leading to a breakdown of all the components in a cartilage. With this understanding, we would be able to target a certain Pathophysiology to prevent disease progression and to come up with better treatment options.

Articular cartilage repair

Current repair options depend on the severity of conditions. Patients with mild degenerative joint diseases are usually given the options of pharmacotherapy, physical therapies, lifestyle management suggestions and non are usually non-operative. Surgical approaches are usually not indicated for patients with mild to moderate joint diseases [20]. Non-operative options may not be a definitive treatment option for severe degenerative

Table 1: Treatment options for degenerative joint diseases.

Non-operative options (usually for mild to moderate degenerative joint diseases)

Treatment options	Advantages	Disadvantages	References
Exercise	Decrease clinical symptoms, improve joint functions, prevent disability	Poor form can cause further damage	[36,37]
Weight loss	Reduced pain, significant improvement in function and pain if weight is lost and maintained	None	[38,39]
Strength training	Decreased pressure on joints, improved stability, decreased pain, improved function, slower rate of degeneration	Poor form can cause further damage	[40-42]
Braces	Alleviate pain, improved function, provide more stability	Uncomfortable, poor fitting, actions limiting	[43]
Oral non-steroidal anti-inflammatory drugs (NSAIDs)	Pain relief	Increased risk of gastrointestinal, renal, cardiac and vascular side effects	[44]
Topical NSAIDs	Significant reduction in pain, minimal systemic absorption	Slight increase in skin irritation	[45]
Supplements	Slight pain reduction, slight protective effects for joints (only for glucosamine),	Effects might not be significant	[46,47]
Prolotherapy and biologics	Promotion of fibrocartilage and hyalinelike cartilage formation in animal studies, reduced pain, improved function	Fear of needles, lack of insurance coverage	[25,26]
Surgical options (usually for moderate to severe degenerative joint diseases)			
Non-cell reconstruction therapies			
Mosaicplasty	Promote regeneration of fibrocartilaginous cartilage	Limited donor site, availability of donors, limited high quality graft, variable outcomes	[14,48]
Microfracture		Formation of post-surgical fibrocartilaginous tissues lack mechanical properties, require very long post-surgical treatment, efficacy of treatment depends largely on age and initial extent of damage, variable outcomes	[21,22]
Autologous chondrocyte implantation	Usage of arthroscopy minimizes damage, autologous cells minimizes rejection and prevent implantations of external pathogens	Two surgeries required, require very long post-surgical treatment, variable outcomes	[24,33,49,50]
Matrix-induced autologous chondrocyte implantation	Superior in-vitro histological results	No superior functional outcomes when compared to autologous chondrocyte implantation or microfracture	[51,52]

joint diseases; it is found that non-operative options are able to provide definitive treatment for mild and moderate joint diseases patients. In addition, it is also reported that non-operative options, albeit not being able to reverse pathological and physiological injuries, are able to prevent further degeneration and can potentially alleviate discomfort and provide huge pain relief for patients. Surgical options can be further classified into cell based and non-cell reconstructive therapies. Non-cell reconstructive therapies include micro fracture and mosaicplasty are commonly the preferred treatment option for patients with moderate degenerative joint diseases. Micro fracture is a novel method to induce growth of new fibro cartilaginous tissue by inducing damage to the subchondral bone via arthroscopy to promote self-regeneration [21,22]. Mosaicplasty includes implantation of graft from another site which is exposed to lower weight-bearing. In short, auto or allograft of cartilage with part of the subchondral bone is retrieved and implanted into a "gap" created by removal of damaged cartilages [23].

Unpredictable outcomes of non-cell reconstructive therapies along with other shortcomings have led researchers to develop cell based therapies such as autologous chondrocyte implantation (ACI). It is a two stage surgical procedure, with the first arthroscopic stage retrieving a biopsy of healthy tissues from a low weight bearing area of the patient and the second stage involves chondrocytes retrieval from the tissue and implanted back to the damaged area [24,25]. Phototherapy and biologics are another injection method of no biologic and biologic substances such as dextrose or platelet rich plasma into the damaged tissue to stimulate repair [26,27]. But the mechanism for these methods is not totally understood. The golden treatment for severe degenerative joint diseases has been total joint replacement. However, these treatment therapies are only able to provide temporary relief of pain and none can reliably regenerate the full functions of cartilage, including its natural structure, integrity, tissue integration and mechanical properties [28-30]. A list of currently practiced treatment options can be found in Table 1.

CONCLUSION

Huge efforts are ongoing to improve these procedures and considerable progress has been made with regards to novel approaches to promote full regeneration of cartilage tissues. Gene transfer is one such novel technique to identify gene

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sequences that can promote cartilage repair [31]. In addition, there are a number of pre-seeded cartilage scaffolds in the market to supplement current treatment options [32]. This method is also termed as Matrix-induced ACI and it uses engineered 3D matrix to act as a scaffold for cell delivery and implantation while maintaining cell integrity [33,34]. With advancing bio printing technologies and improving biomaterials knowledge, current studies are aimed at creating scaffolds that can mimic the zone structure of native cartilages with appropriate mechanical properties [35-52].

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REFERENCES

1. Stoddart MJ, Grad S, Eglin D, Alini M. Cells and biomaterials in cartilage tissue engineering. Regen Med. 2009; 4: 81-98.

2. Carballo CB, Nakagawa Y, Sekiya I, Rodeo SA. Basic Science of Articular Cartilage. Clin Sports Med. 2017; 36: 413-425.

3. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. Sports Health. 2009; 1: 461-468.

4. Wang Y, Wei L, Zeng L, He D, Wei X. Nutrition and degeneration of articular cartilage. Knee Surg Sports Traumatol Arthrosc. 2013; 21: 1751-1762.

5. Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. Biomed Res Int. 2013; 2013: 1-10.

6. Ulrich-Vinther M, Maloney MD, Schwarz EM, Rosier R, O'Keefe RJ. Articular cartilage biology. J Am Acad Orthop Surg. 2003; 11: 421-430.

7. Decker RS, Koyama E, Pacifici M. Articular cartilage: structural and developmental intricacies and questions. Curr Osteoporos Rep. 2015; 13: 407-414.

8. Mow VC,Guo XE. Mechano-Electrochemical Properties of Articular Cartilage: Their inhomogeneities and anisotropies. Annu Rev Biomed Eng. 2002; 4: 175-209.

9. Zelenski NA, Leddy HA, Sanchez-Adams J, Zhang J, Bonaldo P, Liedtke W, et al. Collagen VI regulates pericellular matrix properties, chondrocyte swelling, and mechanotransduction in articular cartilage. Life Sci J. 2014; 11: 300-308.

10. Cameron R. Connective tissues: matrix composition and its relevance to physical therapy. Phys Ther. 1999; 79: 308-319.

11. Yanagishita M. Function of proteoglycans in the extracellular matrix. Acta Pathol Jpn. 1993; 43: 283-293.

12. Roughley PJ. Articular cartilage and changes in arthritis: noncollagenous proteins and proteoglycans in the extracellular matrix of cartilage. Arthritis Res. 2001; 3: 342-347.

13. Bergholt MS, St-Pierre JP, Offeddu GS, Parmar PA, Albro MB, Puetzer JL, et al. Raman spectroscopy reveals new insights into the zonal organization of native and tissue-engineered articular cartilage. ACS Cent Sci. 2016; 2: 885-895.

14. Santo VE, Gomes ME, Mano JF, Reis RL. Controlled release strategies for bone, cartilage, and osteochondral engineering-part II: challenges on the evolution from single to multiple bioactive factor delivery. Tissue Eng Part B Rev. 2013; 19: 327-352.

15. Vinatier C, Mrugala D, Jorgensen C, Guicheux J, Noël D. Cartilage engineering: a crucial combination of cells, biomaterials and biofactors. Trends Biotechnol. 2009; 27: 307-314.

16. Buckwalter JA. Articular cartilage: injuries and potential for healing. J Orthop Sports Phys Ther. 1998; 28: 192-202.

17. Eckstein F, Kwoh CK, Link TM. Imaging research results from the osteoarthritis initiative (OAI): a review and lessons learned 10 years after start of enrolment. Ann Rheum Dis. 2014; 73: 1289-1300.

18. Buckwalter JA, Mankin HJ. Articular cartilage repair and transplantation. Arthritis Rheum. 1998; 41: 1331-1342.

19. Goldring MB, Goldring SR. Osteoarthritis. J Cell Physiol. 2007; 213: 626-634.

20. Poddar SK, Widstrom L. Nonoperative Options for Management of Articular Cartilage Disease. Clin Sports Med. 2017; 36: 447-456.

21. Farr J, Cole B, Dhawan A, Kercher J, Sherman S. Clinical cartilage restoration: evolution and overview. Clin Orthop Relat Res. 2011; 469: 2696-2705.

22. Steadman JR, Rodkey WG, Briggs KK. Microfracture: Its History and Experience of the Developing Surgeon. Cartilage. 2010; 1: 78-86.

23. Vogt S, Imhoff AB. Injuries to the articular cartilage. Eur J Trauma. 2006; 32: 325-331.

24. Saris DB, Vanlauwe J, Victor J, Almqvist KF, Verdonk R, Bellemans J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med. 2009; 37: 10S-19S.

25. Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med. 2013; 11: 229-237.

26. Sit RW, Chung VCh, Reeves KD, Rabago D, Chan KK, Chan DC, et al. Hypertonic dextrose injections (prolotherapy) in the treatment of symptomatic knee osteoarthritis: A systematic review and meta-analysis. Sci Rep. 2016; 6: 25247.

27. Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grøntvedt T, Solheim E, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am. 2004; 86-A: 455-464.

28. Horas U, Pelinkovic D, Herr G, Aigner T, Schnettler R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. J Bone Joint Surg Am. 2003; 85-A: 185-192.

29. Tibesku CO, Szuwart T, Kleffner TO, Schlegel PM, Jahn UR, Van Aken H, et al. Hyaline cartilage degenerates after autologous osteochondral transplantation. J Orthop Res. 2004; 22: 1210-1214.

30. Hunziker EB. Articular cartilage repair: Basic science and clinical progress. A review of the current status and prospects. Osteoarthr Cartil. 2002; 10: 432-463.

31. Cucchiarini M, Madry H. Gene therapy for cartilage defects. J Gene Med. 2005; 7: 1495-509.

32. Huang BJ, Hu JC, Athanasiou KA. Cell-based tissue engineering strategies used in the clinical repair of articular cartilage. Biomaterials. 2016; 98: 1-22.

33. Demoor M, Ollitrault D, Gomez-Leduc T, Bouyoucef M, Hervieu M, Fabre H, et al. Cartilage tissue engineering: Molecular control of chondrocyte differentiation for proper cartilage matrix reconstruction. Biochim Biophys Acta - Gen Subj. 2014; 1840: 2414-2440.

34. Grigolo B, Lisignoli G, Piacentini A, Fiorini M, Gobbi P, Mazzotti G,et al. Evidence for redifferentiation of human chondrocytes

grown on a hyaluronan-based biomaterial (HYAff11): Molecular, immunohistochemical and ultrastructural analysis. Biomaterials. 2002; 23: 1187-1195.

35. Daly AC, Freeman FE, Gonzalez-Fernandez T, Critchley SE, Nulty J, Kelly DJ. 3D Bioprinting for cartilage and osteochondral tissue engineering. Adv Healthc Mater. 2017.

36. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U. S. bone and joint initiative. Semin Arthritis Rheum. 2014; 43: 701-712.

37. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis.Osteoarthr Cartil. 2014; 22: 363-388.

38. Anandacoomarasamy A, Leibman S, Smith G, Caterson I, Giuffre B, Fransen M, et al. Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. Ann Rheum Dis. 2012; 71: 26-32.

39. Vincent HK, Heywood K, Connelly J, Hurley RW. Obesity and weight loss in the treatment and prevention of osteoarthritis. PM R. 2012; 4: 59-67.

40. Nguyen C, Lefèvre-Colau MM, Poiraudeau S, Rannou F. Rehabilitation (exercise and strength training) and osteoarthritis: A critical narrative review. Ann Phys Rehabil Med. 2016; 59: 190-195.

41. Mobasheri A. Osteoarthritis year 2012 in review: biomarkers. Osteoarthritis Cartilage. 2012; 20: 1451-1464.

42. Svege I, Nordsletten L, Fernandes L, Risberg MA. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. Ann Rheum Dis. 2015; 74: 164-169.

43. Brouwer RW, Jakma TS, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev. 2005; 25: CD004020.

44. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. Lancet. 2013; 382: 769-779.

45. Derry S, Conaghan P, Da Silva JA, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2016; 4: CD007400.

46. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: A meta-analysis. Rheumatol Int. 2010; 30: 357-363.

47. Pelletier JP, Raynauld JP, Beaulieu AD, Bessette L, Morin F, de Brum-Fernandes AJ, et al. Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. Arthritis ResTher. 2016; 18: 256.

48. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br. 2003; 85: 223-230.

49. Saris DB, Vanlauwe J, Victor J, Haspl M, Bohnsack M, Fortems Y, et al. Characterized Chondrocyte Implantation Results in Better Structural Repair When Treating Symptomatic Cartilage Defects of the Knee in a Randomized Controlled Trial versus Microfracture. Am J Sports Med. 2008; 36: 235-246.

50. Behery OA, Harris JD, Karnes JM, Siston RA, Flanigan DC. Factors influencing the outcome of autologous chondrocyte implantation: a systematic review. J Knee Surg. 2013; 26: 203-211.

51. Aldrian S, Zak L, Wondrasch B, Albrecht C, Stelzeneder B, Binder H, et al. Clinical and radiological long-term outcomes after matrix-induced autologous chondrocyte transplantation. Am J Sports Med. 2014; 42: 2680-2688.

52. Marlovits S, Aldrian S, Wondrasch B, Zak L, Albrecht C, Welsch G, et al. Clinical and radiological outcomes 5 years after matrix-induced autologous chondrocyte implantation in patients with symptomatic, traumatic chondral defects. Am J Sports Med. 2012; 40: 2273-2280.