ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 3, Issue – 1, January - February - 2020, Page No. : 49 - 56

Meniscal changes with relation to Age- An Article Review

[1]Dr Ayesha Bahar Hashmi, [2]Dr Aisha Syed, [3]Dr Muhammad Umar Farooq

[1]MBBS, Nawaz Sharif Medical College,Gujrat.

[2]MBBS, Punjab Medical College,Faisalabad.

[3]MBBS, Ameer ud Din Medical College,Lahore.

Corresponding Author: Dr Ayesha Bahar Hashmi, MBBS,Nawaz Sharif Medical College, Gujrat.

Type of Publication: Review Article

Conflicts of Interest: Nil

Introduction

Aging is an inevitable process, and is associated with functional impairment of various organs and tissues, including the musculoskeletal system in the form of osteoarthritis (OA), osteoporosis, and sarcopenia, age-related deterioration of joints, bones, and muscles, respectively. Equally, degeneration is often used as almost the same meaning as aging. However, aging can be considered separately from degeneration because degeneration can even occur in the young. In fact, although it has already been noted that degeneration is difficult to separate from aging [1,2], it has become acceptable to distinguish aging from degeneration in the case of articular cartilage and intervertebral discs. Degeneration is defined as the structural and functional failure of the tissue, while aging is defined as a result of time-dependent accumulation of molecular and cellular damage. Knee meniscus also changes with aging, but little is known about meniscal changes with aging, not with degeneration. Cellular aging (also referred to as cellular senescence) and tissue aging have recently gained much attention, and aging research has begun to focus on basic biological processes. It is of critical importance to understand how molecular and cellular changes occur in the aged meniscus. Clinically, meniscal dysfunction is mostly caused by tear based on degeneration, such as a horizontal tear or a posterior root tear [3]. Knee OA causes a major problem in the most fundamental daily activities, such as walking and running. Thus, preventing its pathogenesis and progression is vital for maintaining knee functions in old age. Not all knee OA is caused by the aging process, as meniscal injury can induce knee OA even in the young. However, the age-related changes might greatly contribute to its pathogenesis as in the cartilage. This review aimed to update the current knowledge associated with the aged meniscus. This might lead to methods to slow the progression of meniscal degeneration or to the development of a novel strategy for treatment.

Normal meniscus: structure and composition

The knee joint contains two crescent-shaped menisci between the femoral condyles and the tibial plateau. They are peripherally thick and taper centrally to a thin margin. The medial meniscus covers 50–60% of the medial tibial plateau, and the lateral meniscus covers 70–80% of the lateral plateau [4]. Both menisci have anterior and posterior tibial attachments. Although the fetal meniscus is fully vascularized, there is a gradual decrease in vascularity during development. By the age of 10 years, only the peripheral 10–30% of the meniscus is vascularized, and the remaining inner region is avascular. Three regions of the meniscus are classified: the outer

red–red zone, the middle red–white zone, and the inner white–white zone. The meniscus is mainly composed of water (72%) with the remainder being extracellular matrix (ECM) and cells. The dry weight is composed of 70% collagen, followed by 17% proteoglycans, two percent Deoxyribonucleic acid (DNA), one percent adhesion glycoproteins, and eight percent non-collagenous proteins, including one percent elastin. Type I accounts for the majority of the collagen, with variable amounts of types II, III, V, and VI. Type I collagen fibers are predominantly oriented circumferentially; this fiber arrangement serves to transfer vertical compressive load into hoop stresses. Radially oriented collagen 'tie' fibers are also present and woven between the circumferential fibers to create a fibrillary network. The amount of proteoglycans in the meniscus is one-eighth that present in the articular cartilage, and regional variation has also been observed. Proteoglycans are the major component of ECM. The main types of glycosaminoglycans (GAGs) are chondroitin-6-sulfate (40–60%), dermatan sulfate (20–30%), chondroitin-4-sulfate (10–20%), and keratin sulfate (15%) [5]. Adhesive glycoproteins that bind with other matrix or cells are present within the meniscus; these include type VI collagen, fibronectin, and thrombospondin. Three types of meniscal cells are classified according to their shape and localization. The outer zone cells have a fusiform shape and are described as fibroblasts, while the inner zone cells have more rounded shape and are described as chondrocytic cells. A third cell population has a flattened and fusiform appearance, and localizes in the superficial zone, and is a progenitor population. Although the inner chondrocytic cells are similar to articular chondrocytes, meniscal chondrocytic cells produce type I collagen. Thus, these inner cells are called fibrochondrocytes and are derived from another origin. These material compositions of the meniscus are closely related to its unique functions, such as joint stabilization, load transmission, shock absorption, and lubrication. The decline in the quality of each property with molecular or cellular damage may be the cause of aging of the meniscus.

Changes with advancing age

Macroscopic appearance

Macroscopically, the aged meniscus appears more opaque, with dark yellowish color, compared to the healthy young meniscus, which has a translucent, smooth, and glistening surface. Aged hyaline cartilage and aged vertebral disc nucleus are also described as yellowish or brownish in color with aging, and these color changes are considered to be caused by non-enzymatic glycation [6]. This chemical reaction between amino acids and reducing sugars is called the Maillard reaction, and is often described as the pathogenic mechanism in diabetic complication. In addition, surface roughening without severe fibrillation is common in the aged meniscus. This might occur with gradual loss of fibronectin. Additionally, the meniscus becomes harder and loses its elasticity. Unless torn, the meniscus is not deformed and looks visually almost normal, except for its color.

Microscopic appearance

Few articles have evaluated the histology of the natural aged meniscus, whereas most articles discuss the OA meniscus or torn meniscus. Among such histological evaluation studies, microscopic comparison was performed between the aged and young meniscus. Hematoxylin and eosin (H&E) staining showed decreases in cell density and evidence of mucoid degeneration in aged menisci. Increased Safranin-O staining intensity occurred in the central part of the avascular area. Increased Safranin-O staining with meniscal aging could represent a shift from a fibroblastic to chondrocytic phenotype during early degeneration. The earliest

microscopic changes were observed mainly along the inner rim [7]. With increasing age, greater width and variation in fibrillar diameter were found, and the collagen fibers were generally more condensed and thicker than in younger individuals. Additionally, a reduction in the density of the cell population from the outer zone to the inner rim of the meniscus was also described. In summary, with advancing age, cell density decreases, ECM exhibits more intense Safranin-O staining, and the fibrillar diameter increases and varies. These changes in meniscal cells, collagens, and proteoglycans are described in detail later. Blood supply of the human meniscus (from 22 weeks of gestation to 80 years of age) was investigated immunohistochemically to evaluate the age-related changes [8]. At birth, nearly the whole meniscus is vascularized. In the second year of life, an avascular area develops inside the inner circumference. In the second decade, blood vessels are present in the peripheral third. After 50 years of age, only the peripheral quarter of the meniscus near the capsule is vascularized. The dense connective tissue of the insertion is vascularized, but not the fibrocartilage of the insertion. Blood supply to degenerative menisci (obtained from subjects of 40–80 years of age) was also studied, although all the samples had massive degenerative changes based on the criteria established by Noble. Consequently, no change in the blood supply was shown compared with that of a normal meniscus. This implies that vascular supply may not change due to degeneration alone, but also due to aging.

Joint fluid and cytokines

Synovial fluid functions as a biological lubricant and pool of biochemical nutrients and regulatory cytokines. The avascular (white–white) zone of the meniscus is nourished through joint fluid, which is also reported to change with aging. Human synovial fluid (obtained from 23- to 91-year-old donors) without OA was analyzed for the concentration of protein and hyaluronan [9]. It was noted that the concentration of protein was not related to age, whereas that of hyaluronan had a strong relationship with age, decreasing about 10% per decade. This suggests that age-related deterioration of synovial fluid lubricant quality may increase the frictional force, and such repeated stress finally leads to the development of meniscal deterioration. Biochemical mediators found in synovial fluid that affect the cellular functions of tissues within the knee joint include interleukins, chemokines, growth factors, and matrix metalloproteinases. Interleukin-7 (IL-7) levels in synovial fluid are strongly correlated with age. Among many factors affecting the progression of OA, IL-7 was demonstrated as the most significant in the early phase. No other reports have considered cytokines in natural aging, while all previous reports mentioned cytokines in the OA meniscus or torn meniscus. Synovial fluids collected from knee injuries or OA knees were characterized by elevated levels of the pro-inflammatory cytokine Interleukin-1 (IL-1); this cytokine may also increase to a certain degree in the knee with natural aging. Thus, it may mediate increases in matrix metalloproteinase (MMP) activity and result in inhibition of integrative repair of the meniscus and meniscal destruction [10]. In addition, expression of other cytokines or Nuclear factor-kappa B (NF-κB) may also increase and finally trigger an inflammatory cascade. More studies are needed to evaluate these inflammatory changes in natural aging. Additionally, cytokines in the meniscal tissue itself also change with aging. Older menisci without significant OA changes secreted more IL-7 than healthy young menisci, while older OA menisci secreted more IL-7 and granulocyte-macrophage colony-stimulating factor than did healthy older menisci [11]. This result is consistent with the age-related increase of IL-7 levels in synovial fluid. Additionally, in older cartilage, senescence of

chondrocytes has been shown to elevate IL-7 expression rates. IL-7 secretion might be correlated with senescence-associated secretory phenotype (SASP), in which senescent cells secrete pro-inflammatory factors and cause chronic inflammation [12]. According to these results, upregulation of IL-7 causes inflammation-driven joint destruction. However, as mentioned above, additional studies are required to evaluate the inflammatory effect on aged meniscus.

Cells

Recent studies suggest that age-related changes in meniscal tissue may be related to cellular senescence, which has in fact been demonstrated in articular chondrocytes and ligament tissue. Cellular senescence was first described as the irreversible growth arrest of normal cells after prolonged proliferation in cell culture [13]. Two types of cellular senescence are recognized. Replicative senescence is the result of shortened telomeres, which have reached maximum cell division capability. Somatic cells demonstrate this type of senescence. On the other hand, induced premature senescence is the result of variable oxidative stress or oncogene activation, which is independent of telomere length. This type of senescence is thought to have a critical role in tumor suppression, which stops the accumulation of DNA damage. Both types can be seen in the meniscal cells. Meniscal cells have the potential for cell division, similar to articular chondrocytes. Surgically excised meniscal cells can grow in primary culture, and cell proliferation has been observed. Although telomere shortening of meniscal cells has not been reported, human somatic cells that can grow in culture are usually considered to reach replicative cellular senescence, similar to chondrocytes. Other stresses, including long-term compression stress or microtrauma, could also be a cause of premature senescence for meniscal cells. Senescent cells show a variety of changes in subcellular events, affecting the cell cycle, histone modification, heterochromatin appearance, and nuclear transport [14]. An increase in cell size is also characteristically seen in senescent cells, and has been observed in aged menisci. These changes could cause an imbalance in matrix synthesis and degradation, and might eventually result in disruption of tissue homeostasis. Cellular senescence has been investigated in the articular chondrocyte and intervertebral disc, but not in the meniscus. Recently, meniscal stem/progenitor cells have been identified. CD34-positive cells in the superficial zone may contribute to the homeostasis of meniscal tissue [15]. These cells may enhance tissue regeneration in the meniscus, and are currently the subject of research in tissue engineering. However, cellular senescence in stem cells, known as stem cell aging, is also a current area of study [16]. Although aged stem cells were not mentioned in reviews of chondrocyte or intervertebral disc aging, muscle stem cells have already been examined. It was shown that muscle stem cells from aged mice have intrinsic regeneration defects. Thus, even though meniscal stem cells have the capacity to regenerate, aged stem cells might be limited in their ability to regenerate tissue. Further studies are required before these cells can be practically used in any clinical application.

Collagens

There are a few studies on changes in meniscal collagen content with natural aging, although there are more reports that only compare the normal with the OA meniscus. The collagen content of the human meniscus does not change significantly with age [17]. Similarly, plots of collagen tissue concentration versus patient age showed no correlation. However, since those samples were from resected or torn menisci, the results might not be reflective of natural aged meniscus. However, other reports showed that the level of collagen content increases with natural

aging [18]. Collagen concentration increased from birth to 30 years and remained constant until 80 years of age. Additionally, the inner (white–white), middle (red–white), and outer (red–red) three zones demonstrated different rates of collagen increase with age [19]. Furthermore, since collagen has a low turnover rate, fibers accumulate in an age-related manner. To summarize these results, collagen content may increase and accumulate to increase the fibril diameter. Regarding collagen distribution, an ovine model study in two-day-old to 10-year-old pedigree merino sheep showed that the localization pattern changes with aging of collagen types I, II, and IV [20]. Type II collagen was strongly localized to the tip of the inner zone of the meniscus in newborns, but became more dispersed in older specimens. Type I collagen, however, was uniformly localized throughout the whole meniscus at all ages. Type IV collagen was strongly associated with blood vessels in newborn specimens, but was virtually undetectable after the subjects had reached adulthood. Cross-linked molecules of collagen play an important role in physiological and pathological changes. Formation of these advanced glycation end-products (AGEs) is an uncontrolled and irreversible process that results from post-translational non-enzymatic glycation [21]. Thus, long-lived proteins such as collagens are susceptible to AGE accumulation. These cross-linked products are continuously stored, leading to accumulation of increasing amounts of AGEs throughout life . The composition of different types of AGEs varies in each tissue, and the change with aging is poorly understood. However, age-related changes in collagen cross-links in human menisci are reported [22]. Pyridinoline and deoxypyridinoline, which are necessary to maintain the structure of the collagen fibril network, were found to be constant from maturation to old age. In contrast, pentosidine, which is most commonly measured as a marker of overall glycation, was significantly and exponentially increased with age. Therefore, pentosidine is called a senescent cross-link. Accumulation of AGEs is shown to increase tissue stiffness, decrease ECM turnover, and affect many cellular processes [23]. In fact, it has been reported that glycation does increase tendon stiffnes, resulting in a decrease in failure strain. Thus, the increase in AGEs renders tissue increasingly vulnerable and more prone to mechanical damage, which occurs in articular cartilage or cortical bone. Proteoglycans and other ECM components

The total proteoglycan content of the meniscus appears to increase with age up to maturity, and thereafter remains relatively constant, with the reverse observed in articular cartilage. As regards messenger Ribonucleic acid (mRNA) expression, decorin and aggrecan increased with age in the meniscus, but did not change in the articular cartilage [24]. An increase in expression will provide an immediately available source of mRNA that can be translated into protein during adverse loading, thus preventing tissue damage. On the other hand, perlecan, which plays important roles in ECM organization and stabilization, as well as cellular attachment and migration, steadily declined in the meniscus with the onset of age. These results suggest that agerelated changes in proteoglycans depend on variety, as shown in human skin and sclera , ultimately disrupting tissue homeostasis. Interestingly, at all ages, the meniscus was much more resistant to chemical degradation than other age-matched cartilage. It is suggested that the structure of proteoglycans removed from chondroitin sulfate chains may be different in the two tissues. Another report, which demonstrated an elevated basal level of small leucine-rich proteoglycan (SLRP) cleavage in the aged meniscus, also showed that the proteolytic pathways are different in the two tissues [25]. Additionally, a significant difference was found in tissue concentrations: in the adult meniscus, only

2.8 mg/g wet weight of tissue is present, compared with 20 mg/g wet weight in adult cartilage. According to histochemical examination, zonal variation of proteoglycan distribution in the meniscus is considered a cause of this difference. The zonal variation of ECM components was also reported in a porcine study, and this is consistent with adaptation to higher compressive loading and deformation during knee flexion. These functional and morphological differences might be the cause of the difference in the age-related changes between the meniscus and the articular cartilage. A decrease with aging in fibronectin, a glycoprotein that enhances molecular adhesion in the ECM, has been found to contribute to cartilage fibrillation [26]. Thus, even in the meniscus, surface roughening or fibrillation might occur with gradual loss of fibronectin. However, age-related change of fibronectin in the meniscus has not been researched. Moreover, surface fibrillation might indicate a loss of progenitor cells, which exist in the superficial layer, and thus might be a factor that decreases healing potential.

Calcium deposits

Calcium deposits in the meniscus are often seen in the aged knee, and are common findings in patients with calcium pyrophosphate dihydrate (CPPD) crystal deposition disease. Almost all the articles mentioned calcium deposits in the OA meniscus, but little is known about whether OA or calcium deposits occur first. It was found that up to 20% of elderly people without a history of joint disorders had a calcified meniscus [27]. It was also reported that meniscal calcification is potentially a predisposing factor for cartilage lesions. Although this report compares OA meniscal cells with normal meniscal cells, another report demonstrated that even normal cells could induce calcium deposition. Moreover, the relative content of elements in human menisci, such as sulfur, calcium, and phosphorus, are reported to increase progressively with advancing age. Mechanical stress may induce the release of chemokines, which encourage calcium pyrophosphate formation. According to these reports, aging could change the regulation of calcium homeostasis.

Clinical relevance

Aging can be defined as a result of time-dependent accumulation of molecular and cellular damage. Thus, meniscus aging alone is probably not the cause of daily injury. Progression to degeneration or degenerative tears induces damage. Degeneration of the meniscus begins within the substance of the tissue rather than on the surface, while tissue fibrillation and disruption are first seen at the inner rim, followed by spread to the articular surfaces of the meniscus over time, and then to total disruption or loss of meniscal tissue, mainly in the avascular zone. Subsequently, meniscal dysfunction leads to pathogenesis and progression of knee OA as one of the major risk factors. The precise mechanism of age-related degenerative tears is not fully understood, but a stiffened meniscus with compositional changes might become vulnerable to degeneration or damage with repetitive loading or microtrauma. Degenerative horizontal tears, which are often seen in the clinical setting, are considered a result of extensive mucoid degeneration inside the meniscus. Arthroscopic views show age-related degenerative tears. In the cardiac mitral valve, myxomatous degeneration occurs in conjunction with an accumulation of proteoglycans, and spaces between collagen fibrils are occupied by abnormal proteoglycans or aggregates [28]. In the aged meniscus, accumulation of abnormal proteoglycans or imbalances of proteoglycans might also be the source of pathological change. Posterior root tears, especially in the medial meniscus, are also seen in the elderly. Transition of fiber orientation from the

body to the insertion on the meniscus, in addition to age-related vulnerability, might be responsible..

Conclusion

Compositional and environmental changes presented in this review represent age-related changes in the knee meniscus. These changes could lead to meniscal tissue vulnerability. Meniscal dysfunction is then induced through degeneration or degenerative tears, and knee OA then develops. Further studies could elucidate the more precise mechanisms of meniscal aging and could lead to a novel method for slowing these changes or healing of the meniscus.

Reference

1. Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. Clin Geriatr Med 2010;26:371–86
2. Merkel KH. The surface of human menisci and its aging alterations during age. A combined scanning and transmission electron microscopic examination (SEM, TEM). Arch Orthop Trauma Surg 1980;97:185–91.
3. Adams MA. Intervertebral disc tissues. In: Derby B, Akhtar R, editors. Mechanical properties of aging soft tissues. Springer International Publishing; 2015. p. 7–36.
4. Shane Anderson A, Loeser RF. Why is osteoarthritis an age-related disease? Best Pract Res Clin Rheumatol 2010;24:15–26.
5. Vo NV, Hartman RA, Patil PR, Risbud MV, Kletsas D, Iatridis JC, et al. Molecular mechanisms of biological aging in intervertebral discs. J Orthop Res 2016;34: 1289–306.
6. Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016;12:412–20.
7. Rodier F, Campisi J. Four faces of cellular senescence. J Cell Biol 2011;192:547–56.
8. Song Y, Greve JM, Carter DR, Giori NJ. Meniscectomy alters the dynamic deformational behavior and cumulative strain of tibial articular cartilage in knee joints subjected to cyclic loads. Osteoarthritis Cartilage 2008;16:1545–54.
9. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007;35:1756–69.
10. Fairbank TJ. Knee joint changes after meniscectomy. J Bone Joint Surg Br 1948;30B:664–70.
11. Hugle T, Geurts J, Nuesch C, Muller-Gerbl M, Valderrabano V. Aging and osteoarthritis: an inevitable encounter? J Aging Res 2012;2012:950192.
12. Englund M, Guermazi A, Lohmander LS. The meniscus in knee osteoarthritis. Rheum Dis Clin North Am 2009;35:579–90.
13. Katsuragawa Y, Saitoh K, Tanaka N, Wake M, Ikeda Y, Furukawa H, et al. Changes of human menisci in osteoarthritic knee joints. Osteoarthritis Cartilage 2010; 18:1133–43.
14. Howell R, Kumar NS, Patel N, Tom J. Degenerative meniscus: pathogenesis, diagnosis, and treatment options. World J Orthop 2014;5:597–602.
15. Loeser RF. Aging process and the development of osteoarthritis. Curr Opin Rheumatol 2013;25:108–13.
16. Rath E, Richmond JC. The menisci: basic science and advances in treatment. Br J Sports Med 2000;34:252–7.
17. Clark CR, Ogden JA. Development of the menisci of the human knee joint. Morphological changes and their potential role in childhood meniscal injury. J Bone Joint Surg Am 1983;65:538–47. [18] Arnoczky

SP, Warren RF. Microvasculature of the human meniscus. Am J Sports Med 1982;10:90–5.

18. Herwig J, Egner E, Buddecke E. Chemical changes of human knee joint menisci in various stages of degeneration. Ann Rheum Dis 1984;43:635–40.
19. Ghosh P, Taylor TK. The knee joint meniscus. A fibrocartilage of some distinction. Clin Orthop Relat Res 1987:52–63.
20. McDevitt CA, Webber RJ. The ultrastructure and biochemistry of meniscal cartilage. Clin Orthop Relat Res 1990:8–18.
21. Ingman AM, Ghosh P, Taylor TK. Variation of collagenous and non-collagenous proteins of human knee joint menisci with age and degeneration. Gerontologia 1974;20:212–23.
22. McNicol D, Roughley PJ. Extraction and characterization of proteoglycan from human meniscus. Biochem J 1980;185:705–13.
23. Scott PG, Nakano T, Dodd CM. Isolation and characterization of small proteoglycans from different zones of the porcine knee meniscus. Biochim Biophys Acta 1997;1336:254–62.
24. Fox AJ, Bedi A, Rodeo SA. The basic science of human knee menisci: structure, composition, and function. Sports Health 2012;4:340–51.
25. Makris EA, Hadidi P, Athanasiou KA. The knee meniscus: structure–function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 2011;32:7411–31.
26. Declercq HA, Forsyth RG, Verbruggen A, Verdonk R, Cornelissen MJ, Verdonk PC. CD34 and SMA expression of superficial zone cells in the normal and pathological human meniscus. J Orthop Res 2012;30:800–8.
27. Muhammad H, Schminke B, Bode C, Roth M, Albert J, von der Heyde S, et al. Human migratory meniscus progenitor cells are controlled via the TGF-beta pathway. Stem Cell Reports 2014;3:789–803.

How to citation this article: Dr Ayesha Bahar Hashmi, Dr Aisha Syed, Dr Muhammad Umar Farooq, “Meniscal changes with relation to Age- An Article Review”, ijmacr- January – February - 2020, Vol – 3, Issue -1, P. No. 49-56