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2.1 Introduction

The menisci are semilunar discs of fibrocartilaginous tissue which play critical roles in knee joint biomechanics [1]. Despite, it has been described in the past as nearly useless with perhaps some minor roles on joint nutrition and stabilization [2]. These complex structures are primarily composed of an interlacing network of collagen fibers (predominantly type I collagen) interposed with cells, and an extracellular matrix (ECM) of proteoglycans and glycoproteins.

Menisci are placed within each knee, between the correspondent lateral and medial femoral condyles and tibial plateaux. It has been now recognized that its removal determines deleterious joint consequences, particularly on the long term [3].

Due to the pivotal role of meniscus in maintaining knee homeostasis and proper joint functioning/stability, novel regenerative treatments have been attempted to develop as an alternative to traditional repair procedures or meniscectomy.

The basic science knowledge concerning human meniscus require re-appreciation given the overturn on therapeutic approach, i.e. from meniscectomy to preservation or substitution; and the nearly universal arthroscopic surgical approach opposing to open surgery.

The biological characterization of this tissue, although not yet completely accomplished, has evolved significantly in the last few years. This is true concerning recognition of different cellular populations, understanding its ultrastructure [4], cells and extracellular matrix segmental distributions, biomechanical properties, biologic interactions and mechanism for triggering the response to injury.

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2.2 Anatomy and Biomechanics

In early eighties, a biomechanical study stated the importance of medial meniscus on load transfer. Kurosawa et al. showed that total meniscectomy reduces the total contact area by a third to a half in the fully extended knee [5]. Another report stated its major importance in load transfer and the possible consequences of meniscal excision, not only in articular surface, but also on the subchondral bone, proximal tibia's trabecular bone and cortex [6]. The menisci are not firmly fixed on the tibia and follow knee anteroposterior translation during joint motion. Due to its anatomical features (including stronger attachment to medial collateral ligament), the medial is less mobile. In the stable knee (functioning central pivot ligaments) the medial meniscus has little participation on anterior tibial displacement constraint. The anterior cruciate ligament stops anterior knee motion prior to significant contact of femoral condyle with posterior horn of medial meniscus and tibial plateau [7].

There are major differences between both femorotibial compartments on knee joint to be considered. Lateral tibial plateau is prone to have a more convex shape, opposing to concave shape on medial compartment [1, 7]. This fact helps to understand that the loss of the lateral meniscus leads to a least femorotibial congruence. Furthermore, according to Walker et al., the lateral meniscus carries most of load transfer on lateral compartment, while in the medial force transmission is distributed between the exposed cartilage surfaces and respective meniscus [8]. *In vitro* trials stated about 70 and 50 % of load transmission through the corresponding menisci in the lateral and medial compartment respectively [9].

Regarding gross morphology, medial meniscus resembles a “C”, whereas lateral meniscus is more sharply curved (Fig. 2.1). There is a great variability in medial meniscus anterior horn insertion types, but insertions of the lateral meniscus are less variable and quite closer [10–12]. These variants must be taken into account when performing any kind of meniscus substitution.

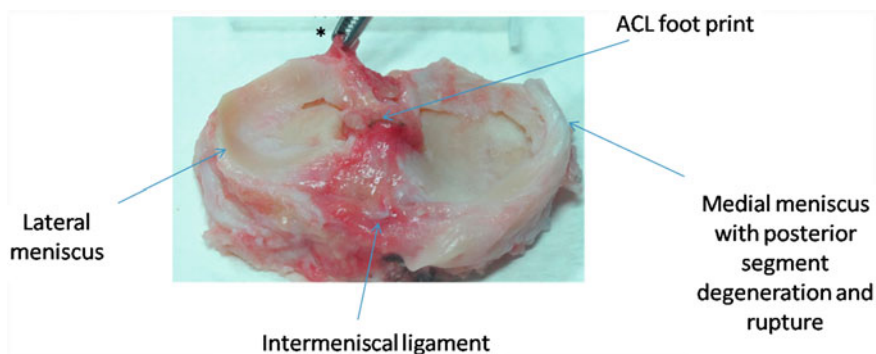


Fig. 2.1 Human specimen photo with menisci in place; ligament of Humphrey also present (attached with forceps*)

The biomechanical response of the menisci to loads acting on tibiofemoral joints result from their macro-geometry, their fine architecture and their insertional ligaments. The collagen bundles of the superficial layer are randomly orientated mimicking articular hyaline cartilage [13] (Fig. 2.2). This way it lowers friction between menisci, femur and tibia during joint motion.

In the bulk of the meniscal tissue, under these surface layers, two distinct regions of different collagen fibers are present: the inner one-third bundles have a radial pattern, whereas the outer two-thirds are oriented in a circumferential manner.

Accordingly, it has been suggested that the inner third may function in compression and the outer two-thirds function in tension. Furthermore, some radially-orientated collagen fibers can also be found within the bulk of the meniscal tissue acting as “tie fibers”, and resisting longitudinal splitting of the circumferential collagen bundles [14].

Viscoelastic behavior (rubber-like at high loading frequencies; at lower frequencies viscous dissipation occurs) of the meniscus relates with ECM composition (not much dependent of collagen content; higher with increasing glucosaminoglycans (GAGs) content and lower with increasing water content. Accordingly, regional variations can be observed in terms of viscoelastic properties [15]. It has been demonstrated a regional and zonal variation in glycosaminoglycan coverage, size, and cellular density in animal meniscal tissue [16]. Similar studies on human tissue have been required, particularly in the era of Tissue Engineering aiming to replicate menisci in laboratory for clinical application [17]. Pereira et al. have recently presented the first biomechanical segmental characterization of fresh human meniscus [18].

The anterior intermeniscal ligament (or transverse geniculate) connects the anterior fibers of the anterior horns of medial and lateral menisci. Its prevalence is estimated around 60 % and its functional relevance remains unclear [19].

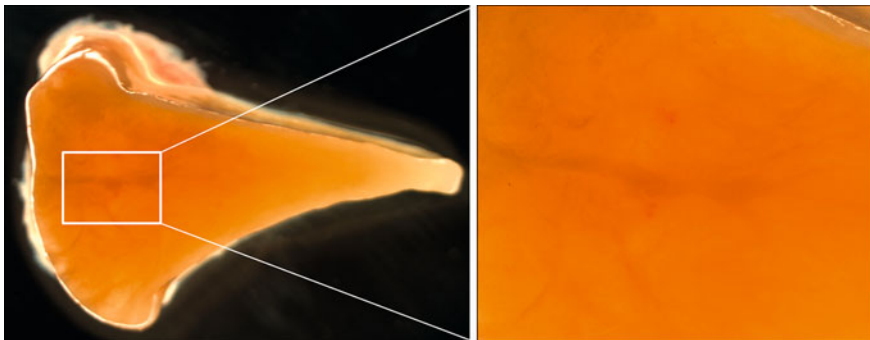


Fig. 2.2 Stereomicroscopy images of human meniscus where it is possible to observe the bundles

Two ligaments are known to connect the posterior horn of the lateral meniscus to the lateral side of the medial condyle of the femur—meniscofemoral ligaments.

The ligament of Humphrey runs anterior to the posterior cruciate ligament (PCL), while the ligament of Wrisberg runs posterior to the PCL. Their estimated prevalence is 74 % for Humphrey ligament, 69 % for Wrisberg ligament, and both ligaments found together in around 50 % of knees [20].

The functional relevance of these ligaments has been demonstrated by Gupte et al., who demonstrated that menisco-femoral ligaments contributed 28 % to the total force resisting posterior drawer at 90° of flexion in the intact knee, and 70.1 % in the PCL-deficient knee [21]. Probably this issue will remain a research topic aiming to improve meniscal repair or replacement techniques.

2.3 Extracellular Matrix and Cellularity

Considering composition by wet weight, the meniscus has high water content (72 %). The remaining 28 % consists of an organic component, mostly ECM and cells [22]. Collagens comprise the majority (75 %) of the organic matter, followed by GAGs (17 %), DNA (2 %), adhesion glycoproteins (<1 %), and elastin (<1 %) [22, 23]. These proportions vary according to age, injury, or pathological conditions [24].

Collagen is the main fibrillar component of the meniscus. Different collagen types exist in various quantities in each region of meniscus. In the red–red zone, type I collagen is predominant (80 % composition in dry weight), but other collagen variants (e.g., type II, III, IV, VI, and XVIII) are present at less than 1 %. In the white–white zone, collagen makes up to 70 % dry weight, of which 60 % is type II collagen and 40 % is type I collagen [25].

Elastin is another fibrillar component, although its relevance is not completely understood. The combination of mature and immature elastin fibers has been found in very low concentrations (<0.6 %) in the adult meniscus [26, 27].

Proteoglycans are the major component of ECM. These molecules are comprised of a core protein which is decorated with GAGs. The main types of GAGs found in normal human meniscal tissue are chondroitin-6-sulfate (60 %), dermatan sulfate (20–30 %), chondroitin-4-sulfate (10–20 %), and keratan sulfate (15 %) [23]. Aggrecan constitutes the major large proteoglycan of the meniscus, while biglycan and decorin are the main small proteoglycans [28]. Their main function is to enable the meniscus to absorb water, whose confinement supports the tissue under compression [22]. Regional variation of these molecules has also been observed, with the inner two-thirds containing a relatively higher proportion of proteoglycans than the outer one-third [28].

Adhesion glycoproteins are also important components of the meniscus matrix, as they serve as a link between ECM components and cells. The main adhesion glycoproteins present in the human meniscus are fibronectin, thrombospondin, and type VI collagen [29].

Considering shape classification and territorial ECM, chondrocyte-like, fibroblast-like, and intermediate cells were identified in the meniscus [30]. Classification of meniscus cells is controversial and different terms are being used (i.e. fibrocytes, fibroblasts, meniscus cells, fibrochondrocytes, and chondrocytes) [31].

It is apparent that outer zone cells have an oval, fusiform shape and are similar in appearance and behavior to fibroblasts. Thus, they may be described as fibroblast-like cells [4]. These cells also display long cell extensions, which facilitate communication with other cells and the ECM. The matrix surrounding the cells is mainly comprised of type I collagen, with small percentages of glycoproteins and types III and V collagen [32].

In contrast, cells in the inner portion have rounded appearance and are embedded in an ECM comprising largely type II collagen intermingled with a smaller but significant amount of type I collagen and a higher concentration of GAGs. This relative abundance of type II collagen and aggrecan in the inner region is more reminiscent of hyaline articular cartilage. Therefore, cells in this region are classified as fibrochondrocytes or chondrocyte-like cells [4].

A third cell population has also been recognized in the superficial zone of the meniscus. These cells have somewhat peculiar morphology, i.e. are flattened, fusiform and lack the cell extensions. It has been suggested that these might be specific progenitor cells with more regenerative capacities [33].

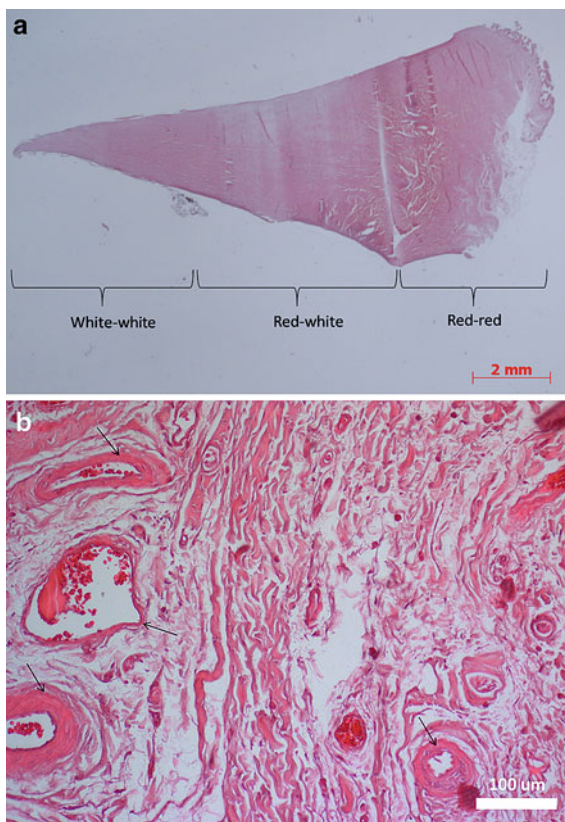
Outer meniscus cells seem to migrate quicker and exhibited lower adhesion strengths as compared to inner meniscus cells [34].

Meniscus cells isolated from outer (vascular), inner (avascular), and horn (mixed) can be induced towards chondrogenic, adipogenic and osteogenic lineages. Outer cells are more plastic and can also go to osteogenesis [35]. The distribution of different cells in the meniscus architecture (segments and zones) has recently been focus of research and it is a relevant insight in the ambitious goal of achieving a tissue engineered implant [18].

2.4 Vascularization and Innervation

Three classical zones according to vascularization continue to be used as references: red–red; red–white e white–white (Fig. 2.3a, b) perfectly shows the blood vessels at red–red zone, which arise mainly from medial and lateral inferior and middle geniculate arteries. Radial branches from a perimeniscal plexus enter the meniscus at intervals, with a richer supply to the anterior and posterior horns [36]. Vessels supplying the body are limited to the meniscus periphery with a variable penetration of 10–30 % for medial meniscus and 10–25 % for lateral one, except in the fetus. There is an avascular area adjacent to the popliteus tendon [37].

Fig. 2.3 Microscopy image of a section of human meniscus stained with haematoxylin and eosin (**a**), and respective magnification of red-red zone where it is possible to observe the blood vessels (*black arrows*) (**b**)



The perimeniscal tissue is richly innervated. Most nerves are associated with vessels. Smaller nerves and axons run radially in convoluted patterns. Single axons course through the perimeniscal tissue, and many nerves are seen in the interstitial tissue of the peripheral zone of the meniscus and in the anterior and posterior horns. The inner menisci core has no nerve fibers [36].

Studies of the vascular and nerve supply of the meniscus in humans have potentially important clinical applications. It has been established that meniscal vasculature is related to the ability of meniscal tissue to heal well, although some healing of meniscal tissue has also been described in avascular portions of the meniscus.

In the fetus, the vascular supply is more extensive, with vessels extending to the inner one-third. There is also a significant nerve supply that is similar in distribution to the vascular supply.

2.5 Conclusions

Progressive insights in meniscus structure, biology and biomechanical properties are uprising. Such knowledge plays a determinant role in the development of further therapeutic options for full repair of these structures known to be critical to the long lasting physiological functioning of the knee joint.

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