Chapter 2
Synovial Knee Joint

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Abstract The knee is a synovial knee joint that allows flexion, extension and also a slight ability to rotate medially and laterally, being able to move on two planes, being known as a modified hinge joint. The main features of a synovial joint are the articulating cartilage, the joint capsule, the joint cavity, the bursae and the ligaments. The joint capsule is composed by the synovium and a fibrous capsule, keeping the synovial fluid that fills the joint cavity inside the joint. The most common injuries or diseases that affects this complex biomechanical system are arthritis, bursitis and dislocations. In fact, the synovium the central area of pathology in a number of inflammatory joint diseases, such as rheumatoid arthritis (RA) and spondyloarthritis (SpA).

2.1 Introduction

The knee is the largest synovial joint in the body and one the most complex biomechanical system known. The purpose of synovial joints, also known as diarthroses, is to allow movement. The knee supports flexion and rotation, promoting complete stability and control under large variety of conditions [1]. The knee is composed by four main bones—the femur or thigh bone, the tibia or shin bone, the

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fibula or outer skin bone and patella or knee cap (Fig. 2.1). The foremost movements of the knee joint occur between the three bones: femur, patella and tibia.

The patella, located at top centre, is small and is flat triangular—shaped bone that moves and rotates with knee [2]. The distal end of the femur has a medial and a lateral condyle, the structure of these condyles is important in the movement of the tibia on the femur. The proximal end of the tibia form a plateau with medial and lateral sections. The menisci intensify the shape of plateaus and serve to increase the conformity of the joint and help the rotation of the knee [3] (Fig. 2.1). Therefore, the structure of the femur, tibia, and patella highly contributes to the stability, strength and flexibility of the knee joint, with static and dynamic restrictions of the ligaments and crossing the joint [1].

The knee is composed by tendons and ligaments that are essentially constituted by connective tissues. The former connect muscle to bones and the latter connect bone to bone. Whether the tendons as ligaments are made of strands of elastic proteins. Ligaments prevent bones from moving too far and tendons help in the movement of muscles. The patella is inside a tendon, the patellar tendon which annexes the quadriceps muscles on the front of thigh and cover the patella [4].

The knee has important ligaments, such as the lateral ligaments of the femorotibial joints. Accordingly, the external condyle stays in position on the superior articular surface of the tibia by the external lateral ligaments (fibular collateral) and the anterior cruciate ligament that represents an internal ligament. The internal condyle stays in position by internal lateral ligaments (tibial collateral) and the posterior cruciate ligament that represents an external lateral ligament [5].

Moreover, knee joint include the tibiofemoral joint, a condyloid joint between the condyles of the femur and tibia, and patellofemoral joint, that it is between the

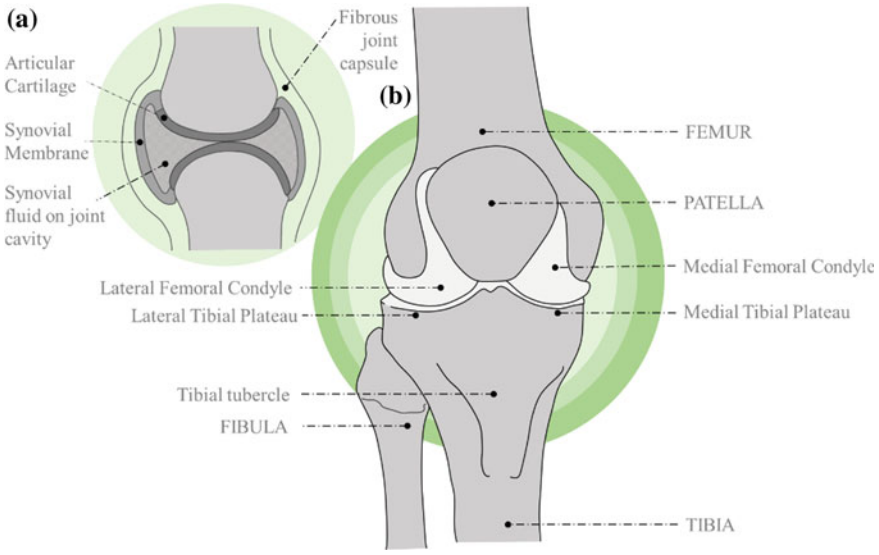

Fig. 2.1 Structure of synovial joint (**a**) and the anatomy of the knee (**b**)

posterior surface of the patella and the patellar surface of the femur. The upper tibiofibular joint often communicates with the femorotibial joint [6]. The tibiofemoral joint provides transmission of body weight from femur to the tibia, allowing a rotation along with a little degree of tibial axial rotation. The patellofemoral joint allows along with the tibialis anterior and ankle joint support the body to start the gait cycle [7].

The knee joint is separated in three articulations, one articulation between each femoral condoyle, corresponding to meniscus, other relative tibial condyle and other between the femur and patella.

The structure of synovial joint is different from cartilaginous (synchondroses and symphyses) and fibrous joints (such as gomphoses and syndesmoses). The key structural differences are related the existence of capsules surrounding the articulating surfaces of a synovial joint and the presence of lubricating synovial fluid within those capsules (synovial cavities).

The articular capsule that lining a synovial joint is constituted by fibrous capsule (thick outer layer) and synovial membrane (inner layer) [8]. The joint capsule is vital to the function of synovial joints. It protects the joint space, allowing stability by restricted movements, promoting active stability through nerve endings and may form articular surface for the joint, lined with synovium and forms a sleeve around the articulation bones to which it is attached [9]. The synovial membrane is highly vascular, it is constituted by connective tissue, it is responsible for the secretion of viscid synovial fluid that serve to lubricates and nourishes the joint [8].

The synovium (synovial membrane or stratum synovial) is a thin highly organized structure that is present between the joint cavity and the fibrous joint capsule [10], lining the joint capsule and producing the synovial fluid. This specialized mesenchymal soft tissue, essential for the appropriate function of the locomotor apparatus [11], covers the spaces of diarthrodial joints, tendon sheaths and bursae. The synovial fluid, secreted by the synovial membrane, is responsible by the (1) joint lubrication (which reduces friction and avoids shock between the surfaces of cartilage) and (2) nourishment (supplying oxygen and nutrients). This non-Newtonian fluid is composed by hyaluronic acid (synthesized by the synovial membrane) and lubricin (also named as Proteoglycan 4). Synovial cells, also known as synoviocyte, synovial lining cell or (synovial) intimal cell, comprise the main types A (showing ultrastructural resemblances to the macrophage series of cells) and B (with abundant endoplasmic reticulum and appear like fibroblasts synoviocytes) [12].

The synovial membrane includes the continuous surface layer of cells (intima) and the underlying tissue (subintima) [13]. Likewise, the lining layer is formed by condensed cells (macrophages and fibroblasts [10, 13]), one- to four-cells thick, and a loosely organized subliming layer, in contact with synovial fluid, that includes blood and lymphatic vessels, a cellular content of both resident fibroblasts and infiltrating cells in a collagenous extracellular matrix [10, 13]. In contrast to the compact layer of the synovial lining layer, the sublining is more amorphous, consisting of loose connective tissue that forms a microanatomic base for the synovial lining. The sublining allows for the transfer of both molecular and cellular elements from circulating blood to the synovial lining and the synovial fluid space

[10], since between the intimal surfaces is a small amount of fluid (usually rich in hyaluronan). Together, this structure provides a non-adherent surface between tissue elements. Synovium is derived from ectoderm and does not contain a basal lamina [13]. The synovium is the central area of pathology in a number of inflammatory joint diseases, including rheumatoid arthritis (RA) and spondyloarthritis (SpA) [13]. Synovitis is defined as inflammation of the synovium, the joint lining and responsible for the knee lubrication.

2.2 Synovial Membrane

The synovial membrane of the knee-joint is the largest in the body. This membrane start at the upper edge of the patella, on the lower part of the front of the femur that communicates with a bursa interposed between the tendon and the front of the femur [14].

The synovial membrane is a specialized mesenchymal tissue covering the spaces of diarthrodial joints, bursae, and tendon. This membrane has two layers, the inner layer, constituted by macrophages or synoviocytes, and outer layer, composed of two to three layers of synoviocytes over connective tissue with fibroblasts, secreting collagen, and other extracellular matrix proteins. The outer layer has few macrophages and lymphocytes, blood vessels with contain nutrients to the synovial membrane and the adjacent avascular cartilage and fat cells [15]. The synovial membrane is surrounding the cavity of joints, taking the space with synovial fluid. It has an important role in nutrition of the articular cartilage. The synovial fluid lubricates the ends of the bones making possible them to move often. The inefficiency to keep the level of metabolism starts destructive process [16, 17].

Most investigators believe that rheumatoid arthritis is primarily an inflammatory disease of synovial membrane of the joints [18]. The main characteristics of rheumatoid arthritis (RA) are chronic inflammation and progressive joint destruction. The synovial lining layer is thickened and hyperplastic, and synovial villi form. The sublining layer contains proliferating blood vessels and is invaded by inflammatory cells such as lymphocytes, plasma cells, and macrophages [19]. Aggressive resident synovial cells invading and destroying cartilage and bone in the joints of patients with RA is observed being the induction of apoptosis in synovial cells suggested as a successful strategy for the treatment of RA [19].

2.3 Synovitis

Synovitis is known as inflammation of the synovial membrane (synovium). Synovitis is characterized by thickening of the synovial membrane/capsule, increased synovial fluid and joint effusion, with the associated symptoms: pain, stiffness in the joint, swelling, warmth and redness over the area. Early synovitis is

initially classified in clinical practice on the basis of the extent, location, and symmetry of the joint involvement [20]. This condition could play an important role in the pathophysiology of osteoarthritis [21, 22] and is regarded as a potential target for novel treatment strategies [23]. It can be either a result of rheumatoid arthritis, gout, cancer, and injury or occur independently on its own.

Synovitis is noticeably associated with a wide spectrum of infectious agents, and the mechanisms underlying this association are varied and complex, being the inflammatory process usually completely solved with the prompt and successful eradication of the organism [20].

The incidence of joint degeneration is higher for the knee joint [24]. The treatment of the inflammation depends on the cause, being the milder cases solely solved by conservative measures (such as rest, ice, compression and elevation) and the severe cases require an arthroscopic surgery (open synovectomy and arthroscopic synovectomy [25]). The treatment approaches to be applied are then related to the extent and level of injury, damage, from viscosupplementation methodologies to the joint replacement implants.

Chronic synovitis where conservative measures fail, can be treated effectively by the operation (open and arthroscopic synovectomy) through resecting the inflamed synovium. The arthroscopic synovectomy is the ideal operation owing to the fast recovery, less postoperative pain and cosmetic effect [25]. The use of the intra articular injection of a viscosupplement aims to support the synovial fluid function, mimicking its rheological behavior and also the biological functions. The most common material applied has been hyaluronic acid (HA), due to its leading characteristics, for instance it can reduce the production of pro-inflammatory mediators [26] and it is existent on normal synovial fluid, being responsible for the viscoelastic properties, important for the lubrication of the tissue surfaces in diarthrodial joints [27]. Nonetheless, due to its high costs [28] and some limitations, new studies with other promising materials are emerging to replace HA on this very challenging application [29].

Clinical trials are used to evaluate the safety and effectiveness of new treatments. ClinicalTrials.gov. is a website, maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH), which provides access to a database with information on clinical studies, on a wide range of diseases and conditions. Information is provided and updated by the sponsor or principal investigator of the clinical study. A search on this database, using relevant keywords returned the registered clinical trials related with the application of biomaterials in knee joint diseases (Table 2.1). Table 2.1 summarizes some of those studies.

Table 2.1 A summary of clinical trials regarding synovial knee joint interventions with biomaterials

Trial ID	Denomination	Objectives	Interventions	Patients age (years)	Time-frame	Period time
NCT01211119	Novel one-step repair of knee meniscal tear using platelet-rich fibrin	Analyse if PRF implantation can help regeneration process of meniscectomized knee and T2 map MRI can evaluate the process in those patients with meniscal injuries	No platelet-rich fibrin (PRF)	20–45	1 month	2011–2013
NCT01425021	Retrieval and analysis of orthopedic implants at revision arthroplasty surgery	Evaluate safety, efficacy, performance and durability of biomaterial and implant designs used in joint replacements	NA	18–85	10 years	2010–2015
NCT02609074	Pilot clinical trial of CPC/rhBMP-2 (calcium phosphate cement scaffold/recombinant human bone morphogenetic protein-2) microffolds as bone substitute for bone regeneration	Analyse safety and preliminary efficacy of bone tissue repairing capacity and to test standard clinical and rehabilitation protocols	Procedure: minimally invasive internal fixation surgeries; Device: CPC/rhBMP-2 micro-scaffolds and CPC paste (group control)	16–70	1, 2, 3, 4, 6, 8 and 12 months post-operation	2013–2015
NCT00945399	Phase III protocol comparing a microfracture treatment to a CARTIPATCH® chondrocyte graft treatment in femoral condyle lesions	Compare the clinical improvement between the microfracture-treated group and CARTIPATCH® chondrocyte graft-treated group	Procedure: CARTIPATCH procedure and Microfracture	18–45	18 moths	2008–2014

2.4 Final Remarks

The synovial knee joint plays an important role as it provides unique movements (flexion, extension and a small degree of medial and lateral rotation) while supporting the body's weight. To do so, it is composed by different tissues such as bones (femur, tibia, and patella), strong ligaments, joint capsule, bursae, and articular fat pads. This complexity, which confers the foremost knee joint characteristics, also consents the incidence of some complications, mainly related with lesions and arthritis (such as rheumatoid arthritis, osteoarthritis, gout, bursitis, and tendonitis). Besides anti-inflammatory drugs, with an important role on relieving pain, inflammation, fever and even swelling, products capable of treating the problem from its source is of major interest to fully solve it. In fact, the current strategies for treatment of the inflammation can range from the simple conservative measures up to arthroscopic surgeries. Thus, biomaterials capable of mimic the affected structures, and even loaded with the necessary drugs for their recovery, are emergent and promising technologies currently being developed.

References

1. Goldblatt JP, Richmond JC (2003) Anatomy and biomechanics of the knee. Oper Tech Sports Med 11(3):172–186
2. Scott WN, Colman C, Gotlin RS (1996) Dr. Scott's knee book: symptoms, diagnosis, and treatment of knee problems including torn cartilage, ligament damage, arthritis, tendinitis, arthroscopic surgery, and total knee replacement. Simon and Schuster, New York
3. Blackburn TA, Craig E (1980) Knee anatomy a brief review. Phys Ther 60(12):1556–1560
4. Pujari A, Alton NS (2010) The healthy back book: a guide to whole healing for outdoor enthusiasts and other active people. Skipstone
5. Fullerton A (1916) The surgical anatomy of the synovial membrane of the knee–joint. Br J Surg 4(13):191–200
6. Saavedra MÁ, Navarro-Zarza JE, Villasenor-Ovies P, Canoso JJ, Vargas A, Chiapas-Gasca K, Hernández-Díaz C, Kalish RA (2012) Clinical anatomy of the knee. Reumatol Clin 8:39–45
7. Flandry F, Hommel G (2011) Normal anatomy and biomechanics of the knee. Sports Med Arthrosc Rev 19(2):82–92
8. Fenn S, Datir A, Saifuddin A (2009) Synovial recesses of the knee: MR imaging review of anatomical and pathological features. Skelet Radiol 38(4):317–328
9. Ralphs J, Benjamin M (1994) The joint capsule: structure, composition, ageing and disease. J Anat 184(Pt 3):503
10. Kiener HP, Karonitsch T (2011) The synovium as a privileged site in rheumatoid arthritis: cadherin-11 as a dominant player in synovial pathology. Best Pract Res Clin Rheumatol 25 (6):767–777
11. O'Connell JX (2000) Pathology of the synovium. Am J Clin Pathol 114(5):773–784
12. Revell P (1989) Synovial lining cells. Rheumatol Int 9(2):49–51
13. Smith MD (2011) The normal synovium. Open Rheumatol J 5(1):100–106
14. Gray H (1918) Anatomy of the human body. Lea & Febiger, Philadelphia
15. de Sousa EB, Casado PL, Neto VM, Duarte M, Aguiar DP (2014) Synovial fluid and synovial membrane mesenchymal stem cells: latest discoveries and therapeutic perspectives. Stem Cell Res Ther 5(5):112

16. Bobick J, Balaban N (2008) The handy anatomy answer book. Visible Ink Press, Michigan
17. Korochina K, Polyakova V, Korochina I (2016) Morphology of synovial membrane and articular cartilage in the knee joint in experimental chronic heart failure. Bull Exp Biol Med 160(3):376–380
18. Fujii K, Tsuji M, Tajima M (1999) Rheumatoid arthritis: a synovial disease? Ann Rheum Dis 58(12):727–730
19. Ospelt C, Gay S (2008) The role of resident synovial cells in destructive arthritis. Best Pract Res Clin Rheumatol 22(2):239–252
20. El-Gabalawy H (1999) The challenge of early synovitis: multiple pathways to a common clinical syndrome. Arthritis Res 1(1):31–36
21. de Lange-Brokaar B, Ioan-Facsinay A, Yusuf E, Visser A, Kroon H, Andersen S, Herb-van Toorn L, van Osch G, Zuurmond A-M, Stojanovic-Susulic V (2014) Degree of synovitis on MRI by comprehensive whole knee semi-quantitative scoring method correlates with histologic and macroscopic features of synovial tissue inflammation in knee osteoarthritis. Osteoarthr Cartil 22(10):1606–1613
22. Haugen I, Mathiessen A, Slatkowsky-Christensen B, Magnusson K, Bøyesen P, Sesseng S, van der Heijde D, Kvien T, Hammer H (2015) Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: Is erosive hand osteoarthritis a separate inflammatory phenotype? Osteoarthr Cartil 24(4):647–654
23. Oei E, McWalter E, Sveinsson B, Alley M, Hargreaves B, Gold G (2014) Non-contrast diffusion weighted imaging for the assessment of knee synovitis: a comparative study against contrast-enhanced MRI. Osteoarthr Cartil 22:S252
24. Park J, Lakes RS (2007) Biomaterials: an introduction. Springer, Berlin
25. Pan X, Zhang X, Liu Z, Wen H, Mao X (2012) Treatment for chronic synovitis of knee: arthroscopic or open synovectomy. Rheumatol Int 32(6):1733–1736
26. Migliore A, Procopio S (2015) Effectiveness and utility of hyaluronic acid in osteoarthritis. Clin Cases Miner Bone Metab 12(1):31
27. Swann D, Radin E, Nazimiec M, Weisser P, Curran N, Lewinnek G (1974) Role of hyaluronic acid in joint lubrication. Ann Rheum Dis 33(4):318
28. Wen DY (2000) Intra-articular hyaluronic acid injections for knee osteoarthritis. Am Fam Phys 62(3):565–572
29. De Sousa RPRA, Gertrudes ACF, Correia C, da Silva Morais AJ, da Mota Martins Gonçalves C, Radhouani H, Gomes CAV, dos Santos TSXC, de Oliveira JMAC, do Sameiro Espregueira-Mendes JDC (2015) Viscosupplement composition comprising ulvan for treating arthritis. Google Patents