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Exploration of articular cartilage biomechanical response during gait of patient with knee osteoarthritis using finite element models.

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Abstract

Knee osteoarthritis (OA) is one of the most prevalent forms of arthritis and one of the leading causes of disability. The pathological traits consist of articular cartilage degradation and bone thickening, among other factors. Since evaluating the changes in the cartilage is difficult to accomplish via medical tests, finite element (FE) models are arising as an alternative. However, they are too simple and do not consider changes through the gait cycle. Thus, the aim of this project is to evaluate the articular cartilage response of knee osteoarthritic patients during gait cycle through a FE model, using data from real patients.

Three knee condition were evaluated: 1) healthy, 2) with OA referred to conservative treatment, and 3) with OA referred to surgery. For each condition, knee reaction force, rotation angles and time of full gait cycle was obtained from data of real patients. The biomechanical response was addressed by using a 3D knee FE model that considers the femur and tibia as rigid bodies, and the cartilages and menisci as composition-based materials. Two gait simulations were performed: a) full extension, and b) with angles of rotation. Emphasis is placed on contact pressure and water and proteoglycan content at cartilage zones most affected by OA according to clinical observations.

Lateral articular cartilage receives significantly more contact pressure than the medial in all conditions. Nonetheless, an average pressure difference between both cartilages changes from 36.86% to 4.92% when cases 1) and 3) are compared. Similar outcomes were observed water and proteoglycans content. When rotation is considered, OA patients showed cartilage-cartilage contact, aspect not seen for healthy condition.

Overall, this study provides valuable information for clinician in OA treatment decision making. Moreover, the effect of the biomechanical environment found in this study on cartilages cells need to be further study, to develop novel strategies to face knee OA.

Keywords

Articular Cartilage; Finite Element Model; Gait Cycle; Knee Osteoarthritis.

Prologue

Knee osteoarthritis is one of the most affected types of arthritis, and it is estimated that by the age of 55 – 65, up to 85% of all people will suffer some degree of this pathology, amongst these my grandmother, and maybe the one of some of those who are reading this. Therefore, when Dr. Carlos Ruiz Wills talked to me about this project, I thought it would be a great chance to contribute my humble grain of sand.

This project is done in collaboration with Hospital del Mar and the BCN Medtech Research unit with the Biomechanics and Mechanobiology Team. In this study we work with data from a healthy patient, and of two patients suffering from knee osteoarthritis, one referred to a conservative treatment and another to a knee replacement surgery. All the data came from the HOLOA's project which aimed to design a predictive and exploratory knee model.

The model which we are working with is a three-dimensional modified and improved model of the right knee. We are taking special look to some parameters which can help to make a decision related to the most optimal treatment. Through this work we see relevant differences between the patients indicating how bad is the condition that the patient is suffering.

Moreover, we also study two different types of simulations. On the one hand, full-extended knee simulations in which we do not have into account the angles of rotation of the knee. And on the other hand, simulations in which we do have into account the angles of rotation. Throughout this analysis relevant findings showed up in the second type of simulations, denoting more realistic outcomes for this condition.

There is a clinical need for medical practitioners when determining if a patient suffering from knee osteoarthritis must be referred to a conservative treatment or to a surgery. Currently, it is still bias when determining this decision, depending on how much pain states the patient that is suffering. A replacement surgery may lead to some complications like the requirement of an additional surgery, anesthesia complications, infection, allergic reactions, knee stiffness and loss of motion amongst others. Therefore, prostheses must be inserted bearing all these possible drawbacks in mind and remembering that there is no turning back.

Although being at a premature stage, the outcomes obtained from this project represent a first step to provide physicians with parameters not obtained throughout medical regular explorations, aiming to refer patients to the most optimal treatment.

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1. Introduction

1.1. The problem and motivation

Osteoarthritis (OA) is the most common form of arthritis and one of the leading causes of disability. Pain, deformity, instability and reduction of motion and function characterize the condition, and severe OA is the main reason for joint replacement surgery [1]. It is known that by the age of 55–65, up to 85% of all people will have some degree of OA in one or more joints [2]. The universal increase in life expectancy makes OA one of the most important causes of incapacity, being hip and knee OA the most prevalent types of this illness [3]. Although still not completely elucidated, the etiology is considered multifactorial with genetic, constitutional, and environmental components [1].

The diagnosis of OA occurs by the study of imaging tests like X-rays and Magnetic Resonance Imaging (MRI). Through X-rays cartilage does not show up but, cartilage loss is revealed by narrowing of the space between the bones of the joint. Also, it may show bone spurs, subchondral cysts formation, bone remodeling and effusion. On the other hand, MRI uses radio waves and a strong magnetic field to produce detailed images of bones and soft tissues, including cartilage. Thus, it can help to provide more information in complex cases. OA may be also determined by laboratory tests like joint fluid tests which can help to confirm the diagnosis. Synovial fluid analyses serve to test whether the inflammation is caused due to an infection or another cause rather than OA [3].

When it comes to the study of OA it is important to evaluate the cartilage damage. To do so, researchers work with different methods. These approaches may be *in-vivo*, *in-vitro* and *in-silico* models. *In-vivo* models use animals or place sensors inside the tissue, *in-vitro* models experiment with cells, corpses, or tissue samples and finally, *in-silico* computerized models help to simulate behaviors on a computer screen. Even so, there have been significant advances when studying OA, there are still lot of improvable approaches to help physicians and patients suffering from this illness.

There are two different ways to treat knee OA; conservative and non-conservative treatments. The first ones are those in which a surgery is not involve while the second ones involve invasive procedures like Total Knee Arthroplasty (TKA) which will be described later. Often, physicians have troubles when deciding whether to refer a patient to one medical procedure or another. This is because at present, guidelines for patient selection for TKA are, at best, based on medium-term data with no externally validated method of patient selection in existence. A clinician's decision to consider a TKA is based on their interpretation of the pathoanatomy of the knee arthritis which is usually reached by careful examination of radiographs [4]. This means that they do it from a subjective perspective depending on the degraded cartilage, but they do not have objective parameters to choose the optimal treatment.

1.2. Objectives

After knowing the importance of investigating knee OA and the challenging decision physicians must go through when determining which treatment would be the best for each patient, it can be observed a clear clinical need; to know more about the cartilage composition when suffering from OA. Thus, in the present study are used data from a collaboration project, entitled HOLOA, between the UPF and the Hospital del Mar. Which aims to provide objective parameters for the medical specialists to help them when choosing which treatment will be the most suitable for each patient.

In order to do it, Finite Element Models (FEMs) based on real patient data will be used to evaluate the response of articular cartilage (AC) in a gait cycle. Emphasis will be placed on changes in water content, proteoglycan content and cartilage contact pressure.

For this, three conditions will be studied. The first one consists of a model of a person with a healthy knee, the second model is from a patient suffering from knee OA referred to a conservative treatment and the third one consists of a patient suffering also from knee OA but referred to an arthroplasty replacement, more concretely a TKA. In this way, differences between the distinct patients will be studied, especially amongst the two last ones. And clinicians will be supplied with non-subjective bias and will make more optimal diagnoses.

2. State of the art of knee osteoarthritis

2.1. The knee joint

The knee is the central joint of the lower limbs. As it can be seen in Figure 1, it is formed by the union of two very important bones, the femur and the tibia, and joins the thigh and the leg. Inside it has a small bone, the patella, which articulates with the anterior and inferior portion of the femur, as well as two fibrocartilage discs, the menisci that act as “shock absorbers". The AC is the tissue that covers the bone surfaces that are part of the joints. It is responsible for supporting and distributing the loads that are transmitted between the surfaces and providing a smooth sliding movement practically free of friction due to its low coefficient of friction. It is also surrounded by a joint capsule and ligaments, which give it stability. The most important ligaments are the external lateral ligament, the internal lateral ligament, the anterior cruciate ligament, and the posterior cruciate ligament. In addition, important muscles are inserted into it and allow flexion and extension movements of the knee and leg [5].

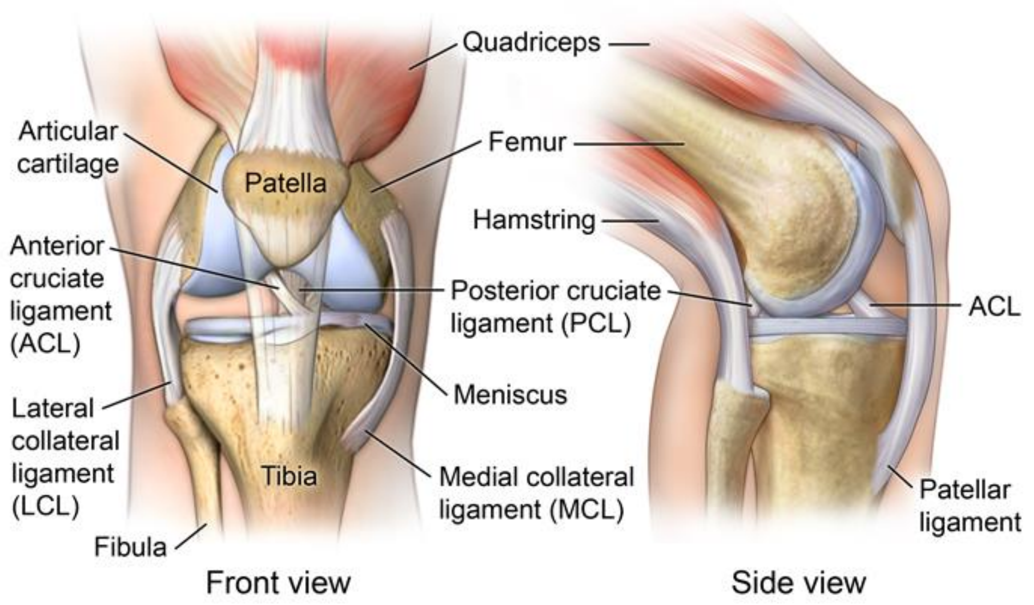


Figure 1. Knee anatomy from the front (left) and the side (right) *view. Image from [5].*

In the case of a healthy knee, it can flex and straighten without difficulty, thanks to the ACs mentioned above, which cover, protect, and cushion the ends of the bones that make up the knee. OA wears down these cartilages [2,5,6]. The pathologic traits of OA consist of AC degradation together with subchondral bone thickening, osteophyte formation, synovial inflammation, ligament degeneration, and capsule hypertrophy (Figure 2) [7].

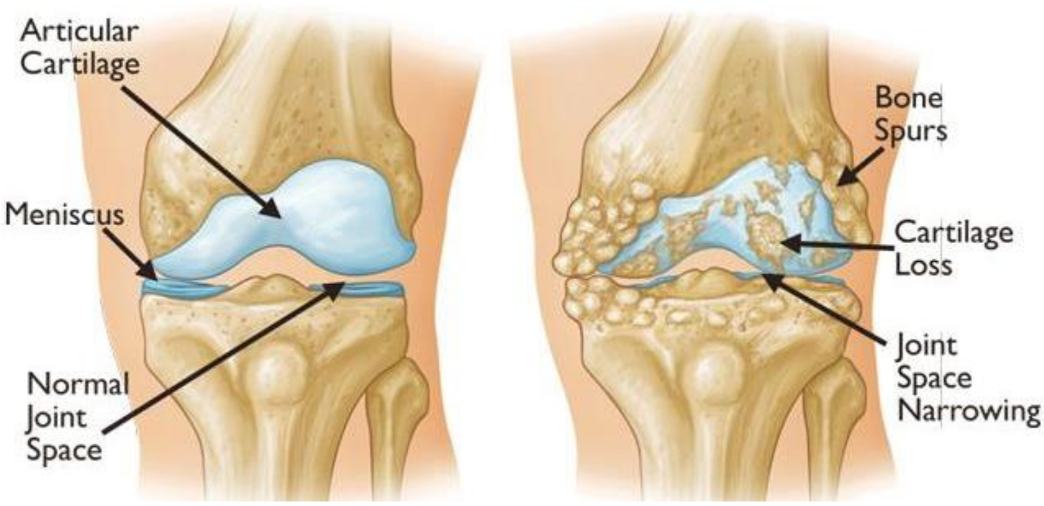


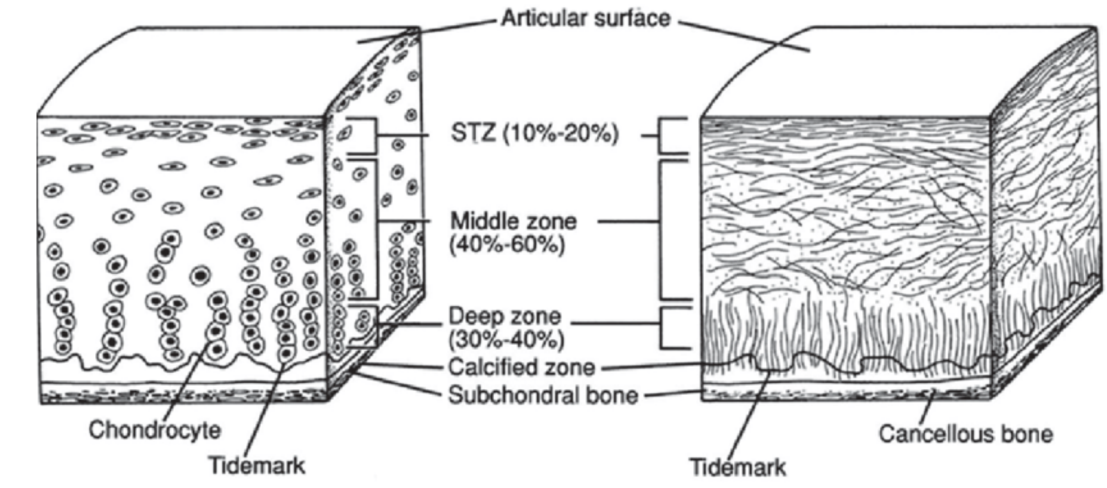
Figure 2. *Normal knee on the left. Osteoarthritic knee on the right.*
Image from [31].

2.2. Articular Cartilage

As aforementioned, in the knee OA the AC wears away. As the cartilage deteriorates, the protective space between the bones decreases and this results in bone rubbing on bone and produces painful bone spurs. AC is composed of hyalin cartilage which is a particularly smooth type of cartilage which allows for easy articulation, increased weight distribution, and shock absorption. Cartilaginous connective tissues are avascular, aneural and alymphatic. AC consists of cells, called chondrocytes, and an extracellular matrix (ECM) that gives it its peculiar mechanical properties and is mainly composed of water, collagen molecules and negatively charged proteoglycans (PGs) [2,8,9]. The chondrocytes are cells highly specialized in the production and maintenance of the ECM. They account for about 10% of the total tissue volume, with variations from joint to joint, and the entire mass of AC, except for chondrocytes, constitutes the ECM [8,9].

It is important to remind that the composition and disposition of the ECM varies between the AC layers. It is composed of four different layers: superficial, transitional, deep and calcified layer. The differences between them are mainly characterized by the disposition of the collagen fibers type II, and by the quantity of water and PGs (Figure 3)[2,7,8,9].

- In the superficial layer, chondrocytes are quite flat in shape. There is a low concentration of collagen molecules and PGs but the highest concentration of water. Collagen fibers are densely packed, have a small diameter, and are arranged parallel to the articular surface.
- In the transitional zone, chondrocytes are rounder in shape. There is a higher concentration of collagen molecules and PGs but a lower concentration of water. The collagen fibers have a larger diameter and are more randomly arranged. This zone is a bridge between the superficial and the deep zone.
- In the deep zone, there are collagen fibers of larger diameter, the concentration of PGs is the highest and the concentration of water the lowest. Collagen fibers have their largest diameters and are arranged perpendicular to the subchondral bone. This type of arrangement provides more resistance to compressive forces.
- In the calcified cartilage layer, very few chondrocytes are found in this zone. It acts as a transition layer between the cartilage and the subchondral bone, allowing a strong adhesion between the two types of tissues.



re 3. Schematic illustration of the orientat, collagen II fibers in the articular cartilage. a) shape of the chondrocytes, b) orientation of the chondrocytes. Image from [8].

ECM is constantly being remodeled by the action of different anabolic and catabolic factors. The ECM consists of water, which accounts for the 60-80% of the total weight, and a dry tissue weight composed by macromolecules which the most important ones are collagen and PGs. Structural macromolecules (collagen, PGs and non-collagenous proteins) account for 20-40% of the total weight. From this 20-40% of the total weight, collagen forms approximately 50–75% of dry tissue weight. AC contains primarily type II collagen (80–85%), with smaller amounts of collagen types V, VI, IX, X, and XI. On the other side, PGs account for 30-35% of the dry tissue weight [2,8,9].

Osteoarthritic articular surface displays swelling which progresses with fibrillation and finally to full-thickness erosions that expose the subchondral bone. This phenomenon is accomplished in a healthy knee due to the resulting ion concentration in the AC is higher than in the surrounding synovial fluid. Then, a Donnan osmotic pressure due to the charge difference between the external and internal environment of the tissue is created due to the excess of ion particles within the matrix. As a results of this pressure difference, the fluid flows into the tissue to maintain osmotic balance [10,11]. However, various proinflammatory mediators may be important in the development of OA, provoking an exaggerated swelling to help healing the damaged joint. Normal AC swells by less than 2–4% when immersed in saline, but cartilage from joints with OA can swell by typically 10% or more in severely affected tissue [12].

2.3. Knee OA Risk factors

Despite recent advances in epidemiologic and genomic research on OA, traditional risk factors such as age, female sex and obesity remain the most important ones for incident knee OA. Among these, obesity, putting aside whether it is through biomechanical or metabolic stress, is the most important modifiable risk factor for the development and progression of the knee OA [13,14]. There are other risk factors such as suffering from joint injuries, infections and occupations that require heavy labors and repetitive bending of the knees. [7].

2.4. Kellgren and Lawrence Scale

The first formalized attempts at establishing a radiographic classification scheme for OA were described by Kellgren and Lawrence (KL) in 1957 [15]. After concluding that there was wide disagreement when diagnosing the gravity of OA among different observers, KL endeavored to establish a classification scheme with an associated set of standardized radiographs for OA of diarthrodial joints. As it can be seen in Figure 4, they proposed a five-grade classification scheme and examined plain radiographs of eight joints including the distal interphalangeal joint, metacarpophalangeal joint, first carpometacarpal joint, wrist, cervical spine, lumbar spine, hips, and knees to calculate the inter- and intraobserver reliability of each [15]. These early results would predict the future application of their classification scheme to the knee specifically. Currently, the KL classification is the most widely used clinical tool for the radiographic diagnosis of OA. However, it is still very demanding choosing the most suitable treatment for each patient [16].

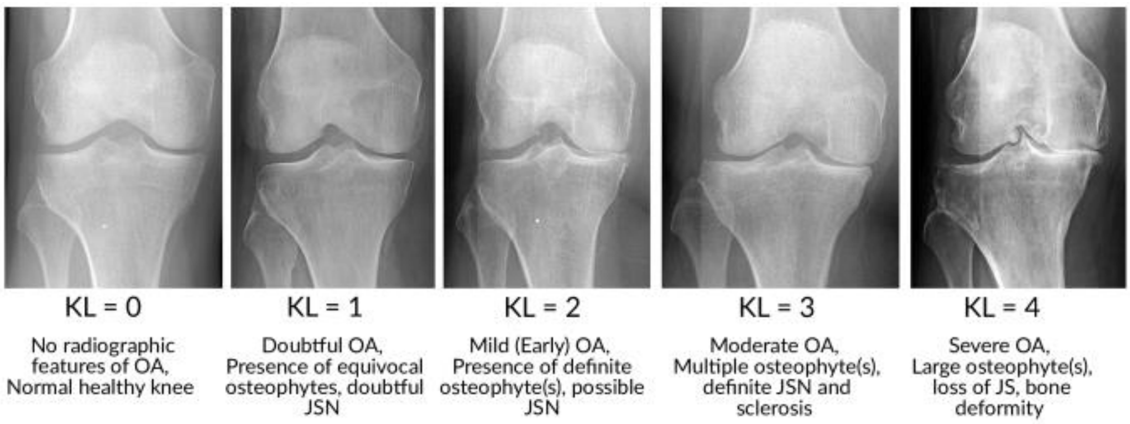


Figure 4. Examples of knee X-Rays showing the stages of knee osteoarthritis severity according to KL grading. For the OA detection problem, KL<2 is defined as non-OA and KL>=2 is classified as OA [16].

2.5. Knee OA Treatments

Depending on the degradation of the cartilages the first step to address OA would be conservative or non-conservative treatments. The first mentioned are medical treatments that avoid invasive methodologies. These include non-pharmacological procedures like education, weight loss, occupational therapy, physical therapy (Ultrasounds, Cryotherapy, thermotherapy, massage, etc.) and physical exercises. They also include pharmacological treatment like the use of oral analgesics and anti-inflammatories to address the issue of pain. To tackle the pain, intra-articular corticosteroid injections are also seen as an effective way in the short-term and are often used when signs of inflammation arise. Another approach are the hyaluronic acid injections because this acid is a natural complex sugar and a normal component of synovial fluid and cartilage in the knee. Its viscosity and elasticity allow it to act as both a joint lubricant and shock absorber, respectively. Thus, hyaluronic acid injections are also applied to treat OA. One more method is the usage of platelet-rich plasma (PRP) which has expanded over the past several years not only for including the treatment of tendon and ligament injuries, but also the treatment of cartilage injuries such as in knee OA. PRP include several growth factors that help in the structural reparation of the AC. Other injectables are also used to treat this pathology (Figure 5)[8,14,17].

On the other side, joint arthroplasty constitutes a major advance in the treatment of chronic refractory joint pain. Joint arthroplasty can be partial (PKA) or total (TKA). These surgeries involve the implantation of a knee prosthesis to partially or totally replace the damaged joint in order to perform its function and allow the patient to regain mobility in the affected area. The artificial knee is designed to comply with all the characteristics of the native knee, it only differs in that it lacks sensitivity, therefore, the pain caused by joint wear does not exist. Hence, knee arthroplasty is a common surgery that reduces pain and improve function and quality of life in patients with knee disorders like OA (Figure 5)[18,19,20].

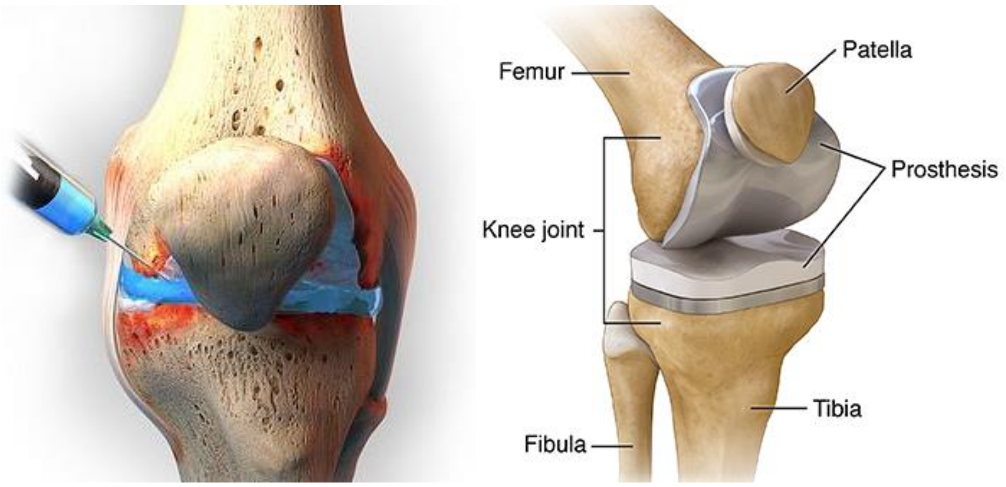


Figure 5. Injectable (intra-articular corticosteroid, PRP or hyaluronic acid) used for the treatment of knee OA, image from [17] (left). Total Knee Arthroplasty, image from [19] (right).

Despite a good outcome for many patients, approximately 20% of patients experience chronic pain after TKA. Chronic pain can affect all dimensions of health-related quality of life, and is associated with functional limitations, pain-related distress, depression, poorer general health and social isolation. The assessment of this pain has been inadequate during the past years. However, there are encouraging trends for increased use of validated patient-reported outcome measures. Risk factors for chronic pain after TKA should be considered before the surgery to determine or not if that patient is valid to go through the surgery, this is the reason why these risk factors must be known to help to the development of the interventions. The causes of chronic pain after TKA are not yet fully understood, although research interest is growing and it is evident that this pain has a multifactorial etiology, with a wide range of possible biological, surgical and psychosocial factors that can influence pain outcomes [21,22].

At present, the objectives for the treatment of knee OA are to decrease pain and stiffness, maintain or improve morbidity and minimize disability. The main controversy related to knee OA is that the criteria used to send patients to a knee replacement or not are subjective and some in cases could have been avoided because the surgery was not totally necessary [19,20].

2.6. The gait cycle

Human walking involves repetitive patterns known as gait cycles. The gait or locomotion cycle consists of two basic components, the stance phase and the swing phase. The first one, starts when the foot first touches the ground and ends when the same foot leaves it, and it is about 60% of the total cycle. On the other side, the swing phase begins when the foot leaves the ground and ends when it touches the ground again, which stands for the 40% of the total gait cycle. As shown in Figure 6, associated to these two main phases there are the following subphases: Heel Strike (A), Loading response (B), Midstance (C) and Terminal Stance (D) for the stance phase. Preswing I, Initial & Mid-swing (F) and Terminal swing (G) for the swing phase [23]. During the gait cycle the knee undergoes a rotational phase and the force of the human weight applies down in the vertical.

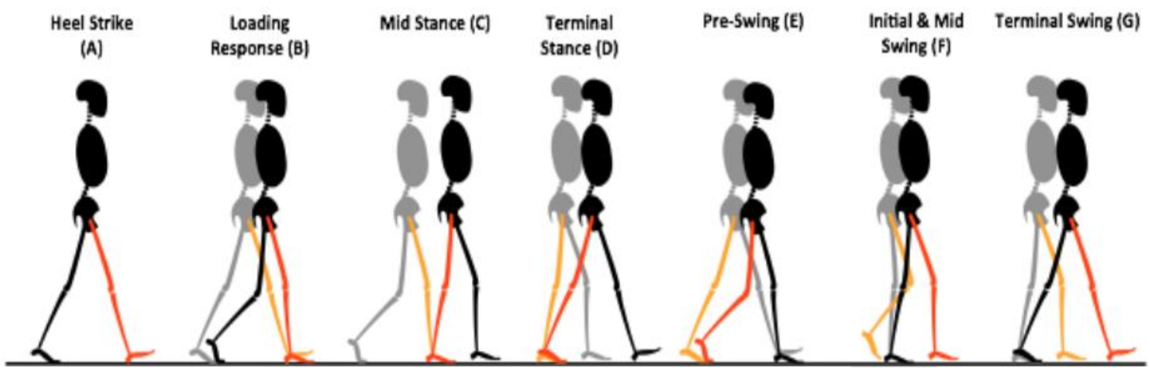


Figure 6. Sub-phases of the human gait cycle [23].

2.7. Models for knee OA

Several gait analyses have been conducted to study the biomechanics of the knee OA. Some of these are *in vivo* models which may give the most accurate reflection of the naturally occurring whole-joint disease. Nonetheless, are not easy to execute since the patients would have to undergo many radiological tests which can lead to long-term negative effects if done excessively. *In vitro* models are easier to manipulate that the ones mentioned before and can provide relevant information. However, they are difficult to achieve since the focused of what is being studied is the knee on its gait cycle and through an *in-vitro* model it is practically impossible to replicate it. The use of corpses via *ex vivo* models are also an option, but the conditions are different from an alive tissue no matter how well the tissue is conserved [24,25].

On the other side, several studies have been made via *in silico* models which means via artificial organs, synthetic materials that resembles cartilage and menisci and, computational simulations thanks to mathematics. These models provide a non-invasive way to explore what is happening in the knee. Nevertheless, they do not represent the whole system of the human being but only a part of it. Also, they tend to be simplified and do not represent the reality on its totality.

2.7.1. Finite Element Models in the study of OA

Several studies of knee OA with Finite Element Models (FEMs) have been published during the last decades. In these research projects, simplifications can be done in order to obtain representations of complex models hard to accomplish in real life [2,26,27,28,29]. In brief, by the use of finite element (FE) methods, simplified and computerized models of an object or set of objects are created to analyze specific results. They are widely used in mechanical engineering discipline such as aeronautical, biomechanical, and automotive industries because they help tremendously in producing stiffness and strength visualizations and in minimizing weight, materials, and costs.

W. Wilson et al [2] provided an overview of computational descriptions developed for investigating the initiation of OA via the determination of the stresses and strains in the AC. To accomplish their objective, they used a FE analysis. They concluded that computational models enable calculations of stresses and strains in the different components of AC. Thus, it can be a useful tool to study the onset and development of mechanically induced cartilage damage, as well as for understanding the mechanical behavior of healthy and degenerated cartilage. However, they did not work with a three-dimensional model. Hence, the approximations to reality were minimized.

Yuan Guo et al [26] simulated a three-dimensional FEM of a gait cycle of a healthy human knee joint. It was constructed by the (FE) software ANSYS and it included complete femur, tibia, fibular, patellar and the main cartilage and ligaments. They achieved to study the pressure distribution of AC of knee joint in walking and it was proved to be accurate and valid by comparing with research data of other scholars. Results of this paper gave an operational platform for three-dimensional modeling of personal human knee joint and *in-vivo* biomechanical studying. Nonetheless, in this study they did not work on knee OA nor its affections, they only considered a healthy knee.

Lan Li et al [27] developed a three-dimensional FEM of knee OA to evaluate the intra-articular changes in the biomechanical behavior after meniscus tears and meniscectomy. Thanks to the use of a realistic total-knee FEM, they achieved to explore the biomechanical changes under aggravating degenerative meniscus tear and after meniscectomy. In conclusion, the results of their FE simulation concerning the stress on the meniscus of the intact knee were similar to those of previous studies, indicating that the analytical results obtained by the use of the model used in the study were reliable. However, they focused the study on the menisci, and they did not provide information about the AC which, as it was seen above, has an incredibly important role in OA.

Michael E. Stender et al [28] developed two three-dimensional FEMs to investigate the poromechanics of the bone cartilage unit (BCU) which is the functional combination of soft (AC) and calcified tissues (calcified cartilage, subchondral cortical bone, and subchondral trabecular bone) in synovial joints. The BCU is often afflicted by OA leading to severe pain and loss of joint function. This work presented an approximation of the behavior of the BCU as a complete poromechanical unit, and the corresponding consequences of alterations in permeability in tissues of the BCU with OA. The obtained results helped to elucidate the role that permeability plays in the poromechanics of the BCU as well as to guide future experimental and computational studies aimed at preventing and/or alleviating the symptoms of OA. Nevertheless, in this paper they focused on changes in permeability only.

D. Tarnita et al [29] presented a complex three-dimensional model of the human knee joint, containing bones, ligaments, menisci, tibial and femoral cartilages. Their purpose was to investigate the role of the AC in the developing of the OA. A FE analysis was performed to simulate and analyze the biomechanical behavior. The results showed that the contact areas of initial cartilage damage change with overweight and misalignment, determining the increase of the stress magnitude and the damage magnitude which could determine progressive cartilage erosion. However, as they state, these results were expected and similar with those obtained by other authors (Figure 7).

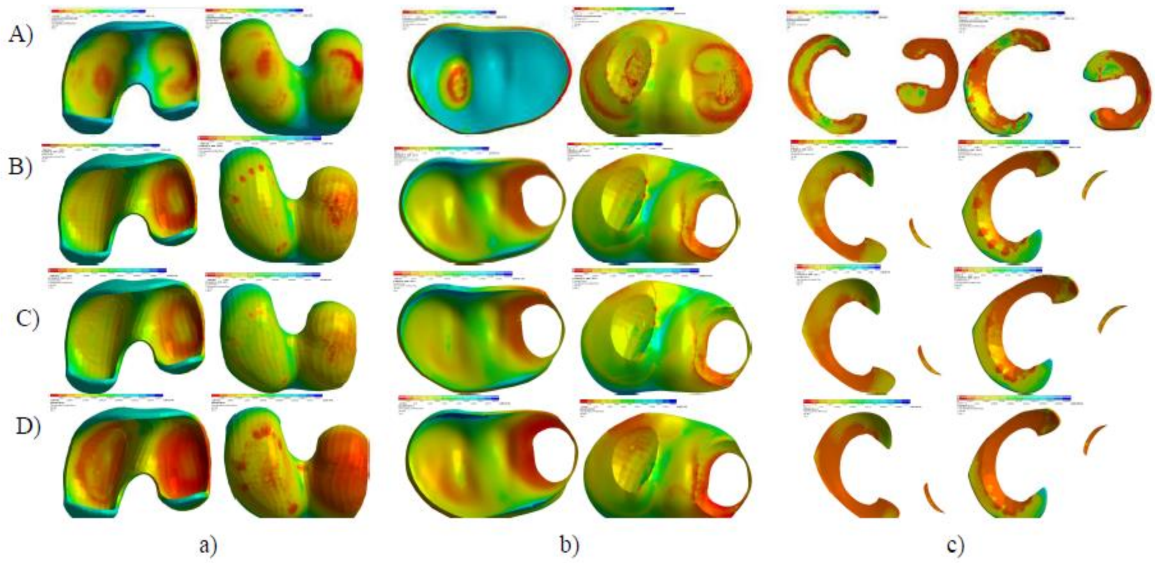


Figure 7. Equivalent maximum stress on a) femoral cartilage; b) tibial cartilage; c) menisci. Image from [29].

3. Materials and Methods

The overall pipeline with general steps is seen in Figure 8. Three main steps have been completed to achieve the final results. The first step was the extraction of all the necessary data for the study. For this, patients needed to go through a motion lab which is a tool for extracting and processing experimental motion capture data for muscular simulations. These data are the angles, the forces and the total time of the gait cycle (see Table 2). Next, the BCs must be applied for the correct functioning of the model. The third step was to simulate the gait cycle of the different conditions. And finally, the obtention and analysis of the results.

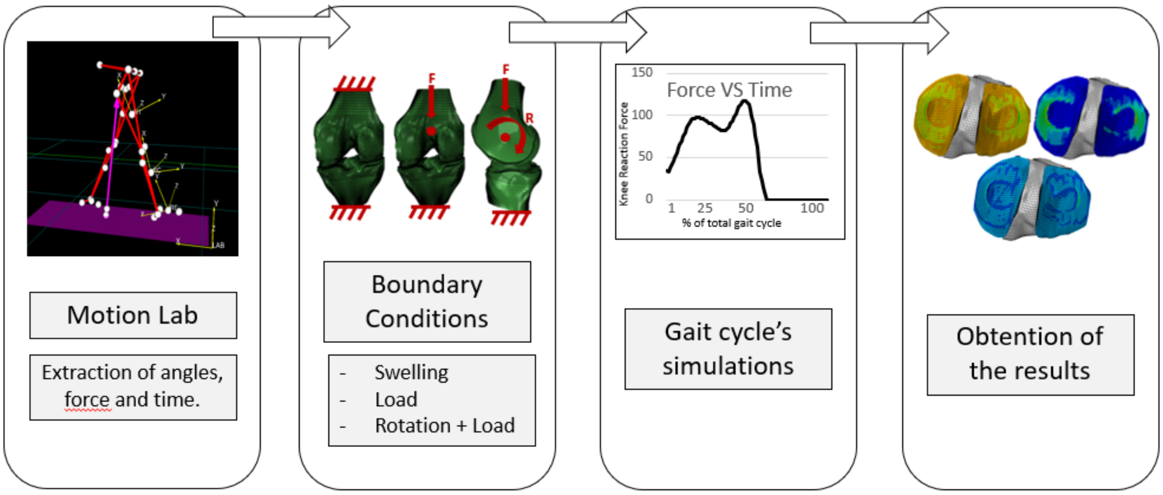


Figure 8. General pipeline to perform gait cycle simulations of a complex knee model.

3.1. Data

The data came from the HOLOA's project. In this project, patients suffering from knee OA were recruited to get their gait acquisitions. This was done in collaboration with Hospital del Mar and the UPF. They provided the dataset of both conservative and non-conservative. The UPF supplied the data of the healthy person that we used as control which belongs to a student of the UPF.

We have raw data of more than forty patients suffering from OA who have been referred to a conservative treatment or to a TKA. Nonetheless, we are going to use one patient referred to a conservative treatment and another one to the non-conservative. In Table 1, the information of the sex, the age, the weight, and the Body Mass Index (BMI) of the three subjects is presented. In Table 2 the information of the angles of rotation, the force directly applied to the knee in direction to the ground and the partial times of the gait are recruited.

Table 1. Sex, age, weight, and BMI of the healthy, conservative and TKA subjects.

	Healthy	Conservative	TKA
Sex	Female	Female	Male
Age	20 – 30	60 – 67	68 – 75
Weight (Kg)	59	77.52	106.28
BMI	Low	High	High

3.2. Model

The knee model (see Figure 9) which we are working with is a three-dimensional model of the right knee. It was obtained from the Open-Knee database [30, 31] and was later improved and modified by Dr. Carlos Ruiz Wills[1]. It consists of seven parts which are the femur, the articular cartilage femoral (ACF), the lateral and the medial meniscus (LM and MM), the lateral and the medial articular cartilage tibial (ACT) and the tibia. There are some which are in contact between them; the femur with the ACF, the ACF with the meniscus, the LM with the ACT lateral, the MM with the ACT medial and the ACT medial and lateral with the tibia.

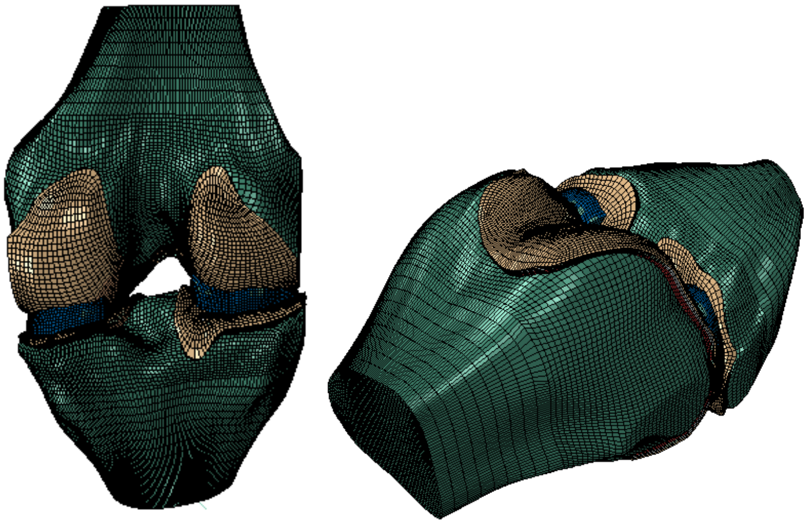


Figure 9. View of different materials of the 3D right knee model. Green is for the bones considered rigid bodies. Yellow for the cartilages and blue for the menisci, both considered composition-based materials.

On the one hand, femur and tibia were considered rigid bodies. As such, they do not deform with any load applied. Hence, the deformation must be zero in all directions.

$$\varepsilon_x = \varepsilon_y = \varepsilon_z = 0 \qquad (1)$$

Where ε_i is the deformation.

[1] Dr. Carlos Ruiz Wills – carlos.ruiz@upf.edu

On the other hand, cartilages and menisci are considered composition-based materials. Hence, in mechanical terms this means that they have large deformations and in practice that they act as biphasic materials. According to the biphasic theory [32] the tissue is assumed to consist of an incompressible solid matrix, hydrated with an incompressible fluid. The total stress equals the sum of the solid and fluid stress [33].

$$\sigma_{total} = \sigma_{sol} + \sigma_{liq} = \sigma_{eff} - pI \qquad (2)$$

Where σ_{total} is the total stress, σ_{eff} is the effective stress tensor, p is the hydrostatic fluid pressure and I is the unity tensor.

The stress in the nonfibrillar solid matrix is given by the next modified Neo-Hookean law [34],

$$\sigma_{eff} = \frac{1}{6}\frac{Ln(J)}{J}G_m I\left[-1 + \frac{3(J + n_{s,0})}{(-J + n_{s,0})} + \frac{3JLn(J)n_{s,0}}{(-J + n_{s,0})^2}\right] + \frac{G_m}{J}\left(B - J^{2/3}I\right) \qquad (3)$$

where G_m is the shear modulus, J is the deformation gradient and $n_{s,0}$ the solid fraction.

The liquid part acts as the following equation

$$p = \mu_w + \Delta\pi \qquad (4)$$

being $\Delta\pi$ the swelling pressure gradient and μ_w the chemical potential of water.

The osmotic swelling of the AC, as it is explained by [35, 36, 37], is represented by biphasic swelling theory. This theory is based on the hypothesis that electrolyte flux can be neglected in mechanical studies of charged materials. This means the ion concentrations can always be assumed in equilibrium. When the distinction between extra- and intra-fibrillar water is considered, the effective fixed charge density should be expressed as mEq fixed charges per ml extra-fibrillar water and not based on the total fluid content as is usually done. The osmotic pressure gradient $\Delta\pi$ is then given by:

$$\Delta\pi = \varphi_{int}RT\sqrt{c_{F,exf}^2 + 4\left(\frac{\gamma_{ext}^{\pm}}{\gamma_{int}^{\pm}}\right)^2 c_{ext}^2} - 2\varphi_{ext}RTc_{ext} \qquad (5)$$

where the $C_{F,exf}$ fixed charge density based on the extra-fibrillar fluid fraction and $C_{ext}$the external salt concentration. $C_{F,exf}$ is given by:

$$C_{F,exf} = \frac{n_f c_F}{n_{exf}} \quad (6)$$

with $n_f$the total fluid fraction, n_{exf} the extra-fibrillar fluid fraction and c_F the normal fixed charge density in mEq per ml total fluid.

The permeability (k) was assumed to be strain-dependent following the papers of Wilson et al. [38, 39].

$$K = K_0 \left(\frac{1 - C_{ref}}{1 - n_{exf}}\right)^M = \alpha(1 - n_{exf})^{-M} \quad (7)$$

Where K_0 is the initial permeability, M a positive constant, C_{ref} is a reference value constant over the depth of the tissue and α a positive material constant.

In this project, the collagen fibers of the meniscus and cartilage are modelled as viscoelastic. They are represented by a linear spring with stiffness E1, parallel to a nonlinear spring with stiffness E2 in series with a linear dashpot with damping constant η (Figure 10). This is called the standard linear solid (SLS) model, also known as Zener model.

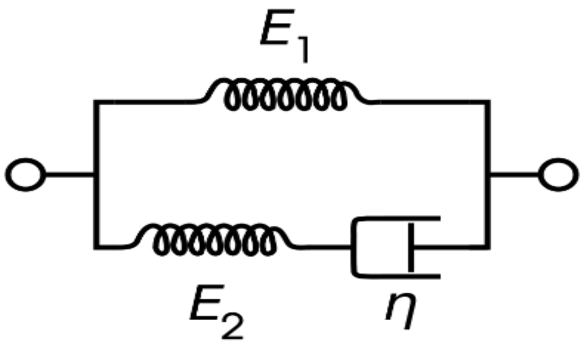


Figure 10. Schematic model for viscoelastic collagen fibrils. Image from [40].

3.3. Simulations

Simulations of full gait cycle have been accomplished in this project. There are three different conditions modelled:

a. Healthy person.
b. Patient suffering from knee OA referred to a conservative treatment.
c. Patient suffering from knee OA referred toa TKA.

Inside these categories, two situations are modelled:

1. Full-extended knee simulations.
2. With rotation angle knee simulations.

Situation 1) implies having into account the force, which is meant by the load of the body in direction to the ground applied to the knee while the gait cycle, without having into account the angles of rotation. Situation 2) implies that both force and rotation are used. Gait simulations were achieved using real data from patients to extract angles of rotation, force and time. In Figure 11 is seen how the gait cycle was divided into three sections because we need to extract the information from the peaks in which there is an increment or decrease of the load. All the values along the force peaks (FPs) are seen in Table 2.

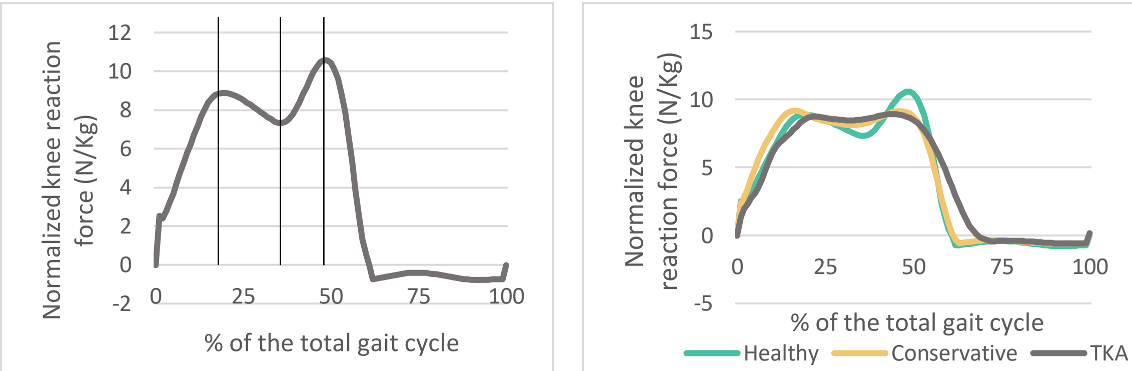


Figure 11. On the left the graphic are observed the divisions of the three sections of the force peaks. As it can be observed there are three sections which correspond to the first, the second and the third. On the right it appears the gait cycle of all the conditions.

Table 2. Values of the force (N), the angle (°) and the time (sec) for the three conditions: healthy, conservative and TKA. Each column corresponds to the three FP of the gait cycle.

	1			2			3		
	Force (N)	Angle (°)	Time (sec)	Force (N)	Angle (°)	Time (sec)	Force (N)	Angle (°)	Time (sec)
Healthy person	524.215	2.1	0.242	431.931	-1.9	0.1936	623.394	0.4	0.1573
Conservative tratment	695.0017	13.5	0.18992	617.182	11.4	0.17805	692.276	13.2	0.17805
TKA	928.5735	9.09	0.273	902.5875	7.3	0.13	950.619	6.1	0.169

3.4. Boundary Conditions (BCs)

A pre-step for swelling was done for the simulations with and without rotation. The bottom of the tibial and femoral bone was fixed in all translational and rotational degrees of freedom for applying the free swelling. Next, a reference point located in the central region between lateral and medial femoral epicondyles, was coupled to the femoral surface using the constraint method in Abaqus. An axial compressive load was applied to the femoral condyle reference point. For the simulations with rotation, apart from applying the load, a rotation was also applied tin the reference point aforementioned. This process simplified is seen in Figure 12.

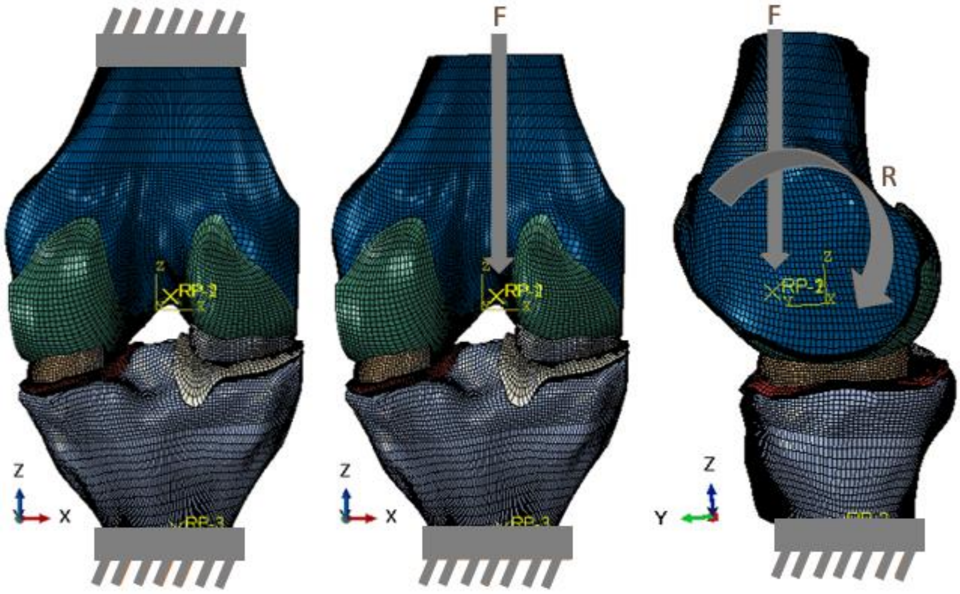


Figure 12. Application of the BCs.

All simulations were performed with Abaqus 2012 (Simulia, Providence, RI, USA). Results were evaluated in the ACT medial and lateral. For this, the average of the nodes in which the contact pressure is higher has been accomplished and all the parameters have been studied in the nodes seen in Figure 14. The parameters analyzed were the contact pressure, the content of water and the content of proteoglycans. All calculations were performed in a server (SGI UV1000 Intels Xeons, 224 CPU, 2.66 GHz, with 6.14 TB RAM) using 8 cores for each simulation.

4. Results

4.1. Contact Pressure

Figure 13 shows the distribution of contact pressure for the conditions of healthy, conservative and TKA. It can qualitatively be seen that the OA patients referred to TKA present higher values of contact pressure than the other cases. Within all conditions, the values decrease with the second FP but increase again with the third one. In some zones, the pressure is higher, and it is maintained during the three FP.

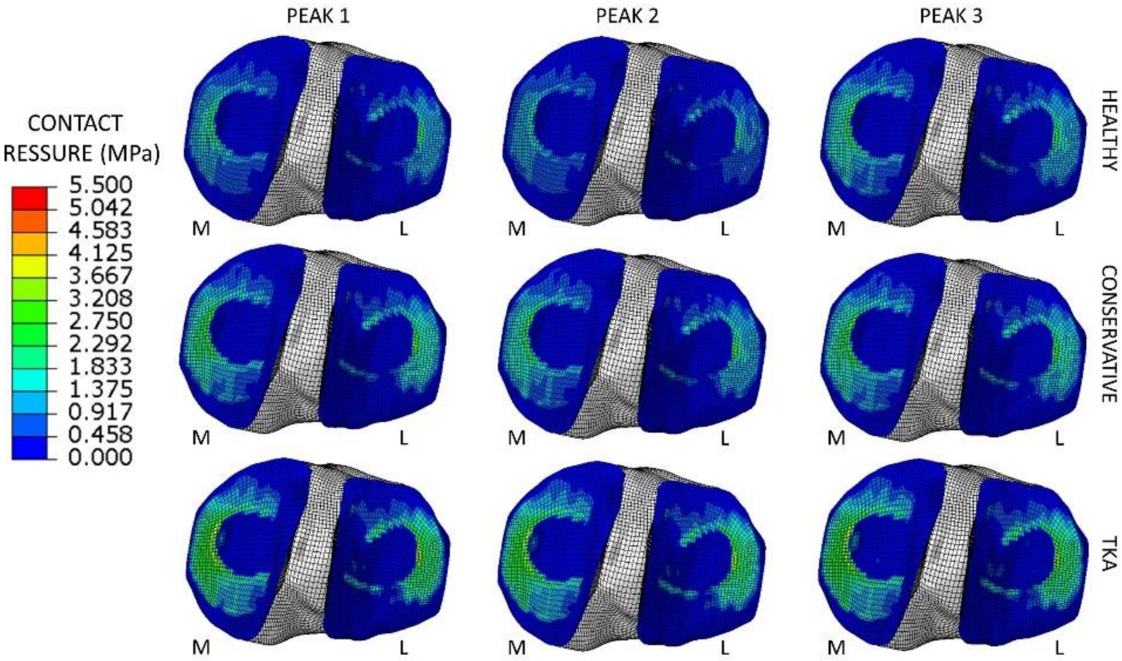


Figure 13. Top view of lateral (L) and medial (M) articular cartilage contact pressure distribution at the three FPs.

For the quantitative study, the average of the nodes in which there are the highest contact pressure values has been done in both the ACT lateral and the ACT medial. The zones indicated in Figure 14 are the ones with the highest values in contact pressure.

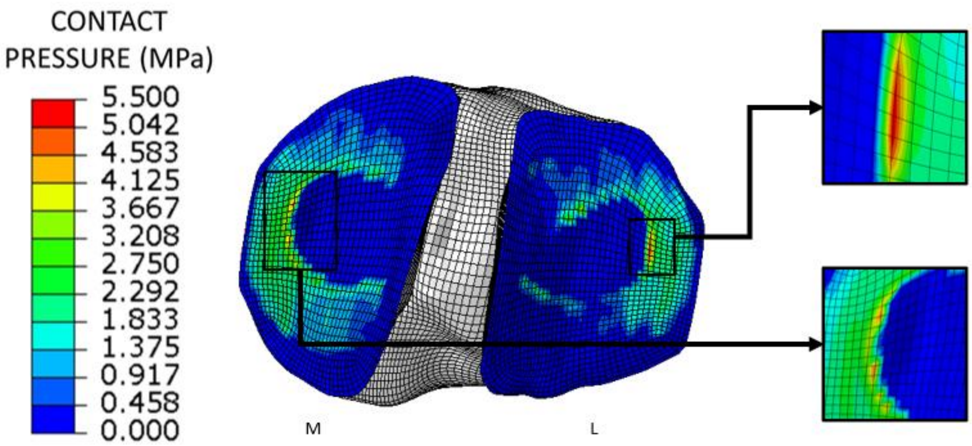


Figure 14. Nodes from lateral (L) and medial (M) articular cartilage in which there are the most severe changes in contact pressure.

Table 3 shows the quantitative results of the contact pressure for the three conditions: healthy patient, OA patient referred to conservative treatment and OA patient referred to TKA. In all cases, the ACT lateral receives higher pressure than the ACT medial, except in the third FP of the TKA patient which the contact pressure is a little bit higher in the ACT medial. In the cases suffering from knee OA the values are remarkably higher than the healthy case, specifically the one referred to TKA which has the most severe condition.

To compare properly the differences of contact pressure between both ACT, the relative differences (RDs) have been calculated following the formula $RD = \left(\frac{LAT-MED}{MED}\right)100$. In Table 3 are also shown the results together with the average values of each patient. It is seen that the healthy patient has the highest values of RDs, meaning that the differences between both cartilages are higher than among the other cases. The case of TKA is the one having more similar values of contact pressure amongst both cartilages being the RD in the third FP practically zero. Another remarkable found is that in the second FP there are the highest differences throughout all cases.

Table 3. Values of the contact pressure in MPa. Relative differences of the values of contact pressure of the ACT lateral versus the ACT medial in percentage. FP accounts for FP. ACT accounts for Articular Cartilage Tibial. TKA accounts for Total Knee.

	CONTACT PRESSURE (MPa)								
	Healthy			Conservative			TKA		
	ACT Lateral	ACT Medial	RD(%)	ACT Lateral	ACT Medial	RD(%)	ACT Lateral	ACT Medial	RD(%)
First FP	3.02	2.45	23.27	3.81	3.44	9.71	4.72	4.62	2.12
Second FP	2.51	1.91	31.41	3.37	2.95	12.46	4.58	3.97	13.32
Third FP	3.36	2.95	13.89	3.62	3.33	8.01	4.54	4.57	-0.66
Average	2.96	2.44	22.85	3.60	3.24	10.06	4.61	4.39	4.92

Figure 15 shows all values of the contact pressure clustered by cartilage, lateral and medial. Patients suffering from knee OA have higher contact pressure during the gait cycle in both the ACT lateral and medial, being the one referred to TKA with the highest values. The healthy case presents higher pressure in the third FP for both cartilages, while this is not seen in the osteoarthritic cases. In the lateral cartilage and for the TKA case, pressures are maintained practically at the same values during the whole gait.

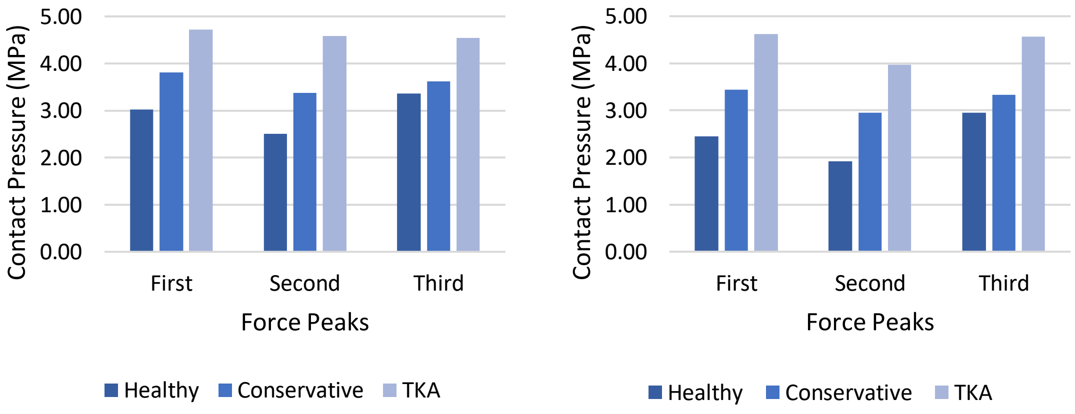


Figure 15. Comparative graphic of the contact pressure in MPa between the three patients in lateral (left) and medial (right) articular cartilage.

4.2. Water content

Figure 16 shows the water content distribution at tibial articular cartilage. In general, the water contact decreases along the three FPs. The values of water content are in their lowest in the patient with OA referred to TKA. The case of the healthy patient, in general presents more water content during the three FPs in comparison to the others.

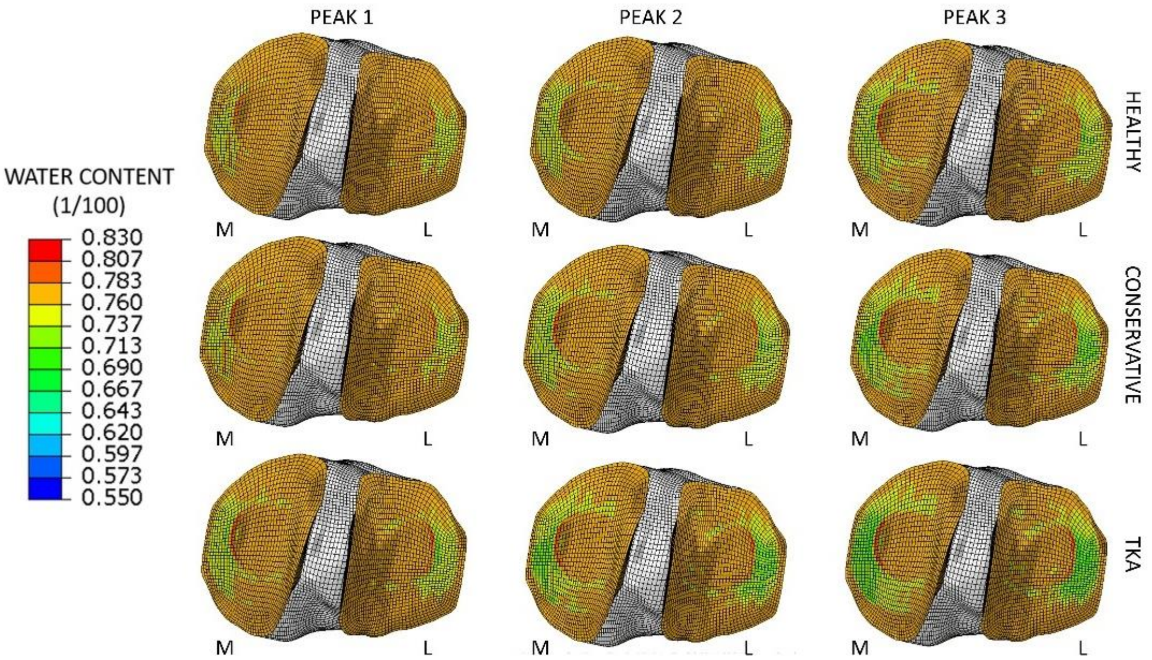


Figure 16. Top view of lateral (L) and medial (M) articular cartilage water content distribution at the three FPs.

In Table 4 are shown the quantitative results of the water content. According to the average values, there is more content of water in the ACT lateral cartilage in the healthy and conservative cases. However, in the case of the TKA patient, there is more water content in the ACT medial than in the ACT lateral.

Table 4. Values of the water content in % of the total weight. Relative differences of the values of water content of the ACT lateral versus the ACT medial in percentage.

	WATER CONTENT (% of the total weight)								
	Healthy			Conservative			TKA		
	ACT Lateral	ACT Medial	RD(%)	ACT Lateral	ACT Medial	RD(%)	ACT Lateral	ACT Medial	RD(%)
First FP	76.01	75.03	1.29	75.89	75.91	-0.03	75.27	76.39	-1.48
Second FP	75.71	74.00	2.31	75.24	74.49	0.99	74.43	75.20	-1.03
Third FP	74.97	73.97	1.33	74.48	74.13	0.47	73.40	75.06	-2.25
Average	75.47	74.33	1.64	75.20	74.84	0.48	74.37	75.55	-1.59

In Figure 17 is observed that the patients suffering from knee OA have lower water content during the gait cycle in ACT lateral and higher in ACT medial than the healthy person. The one referred to TKA presents the most extreme values.

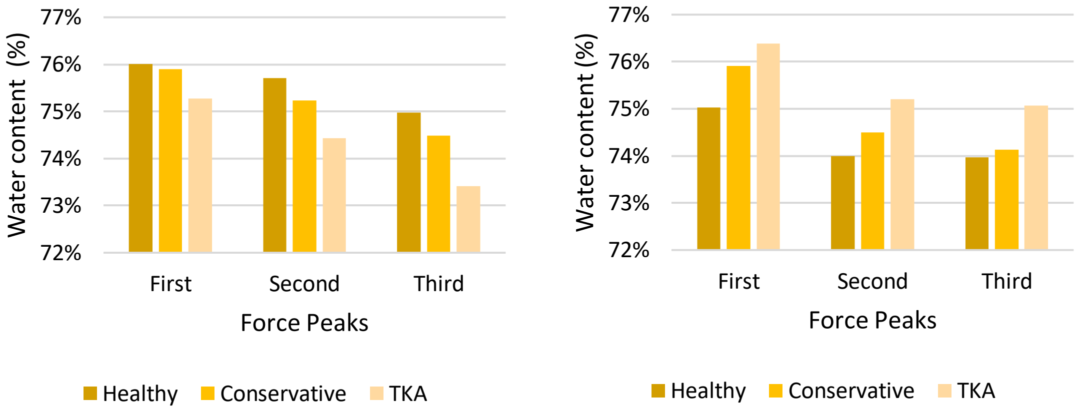


Figure 17. Comparative graphic of the water content in % of the total weight between the three patients in lateral (left) and medial (right) articular cartilage.

4.3. Proteoglycan's content

In Figure 18 the fixed charge density distribution as a measure of PG content is shown. It can be seen qualitatively that clearly the OA patient referred to TKA has lower values of PGs content in the three FPs than the other cases. The condition of the healthy patient is the one with the highest values of PGs content in the three FPs. Also, the third FP presents the highest content of PGs in comparison to the two FPs before.

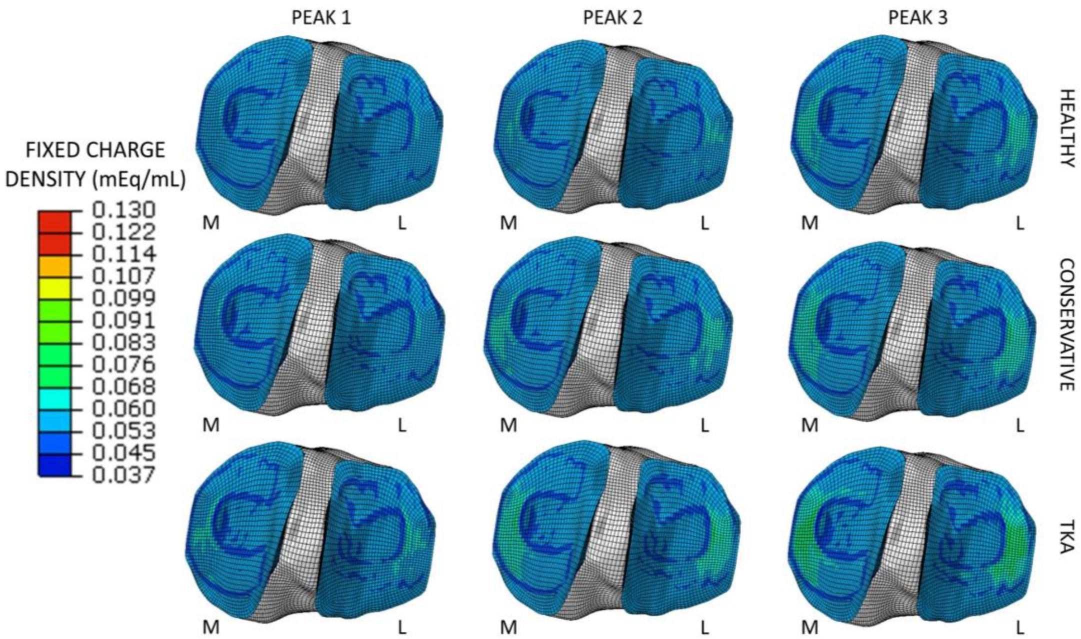


Figure 18. Top view of lateral (L) and medial (M) articular cartilage fixed charge density (mEq/mL) distribution at the three FPs.

In Table 5 are shown the quantitative results of the PGs content. Each file accounts for the first, the second and the third FP of the gait cycle. Here it is stated that in the zones studied, the quantity of PGs increases as the FPs increase as well.

In Table 5 is seen that the RDs are positive in the healthy patient and the OA patient referred to a conservative patient but negative in the OA patient referred to TKA. However, the values of the healthy patient are more positive than the ones for the conservative patient. This means that in the first two cases there is higher PGs content in the ACT medial than in the ACT lateral while in the TKA patient there is a lower PGs content in the ACT medial than in the ACT lateral.

Table 5. Values of the PG's content in % of the total weight.

	PROTEOGLYCANS CONTENT (% of the total weight)								
	Healthy			Conservative			TKA		
	ACT Lateral	ACT Medial	RD(%)	ACT Lateral	ACT Medial	RD(%)	ACT Lateral	ACT Medial	RD(%)
First FP	5.59	5.90	-5.51	5.62	5.63	-0.12	5.80	5.49	5.44
Second FP	5.68	6.23	-9.55	5.82	6.06	-4.05	6.07	5.47	9.93
Third FP	5.91	6.25	-5.69	6.06	6.20	-2.27	6.41	5.94	7.44
Average	5.73	6.13	-6.92	5.83	5.96	-2.14	6.09	5.63	7.60

In Figure 19 is observed that the patients suffering from knee OA have higher PGs content during the gait cycle in ACT lateral and lower in ACT medial, being the one referred to TKA with the most extreme values.

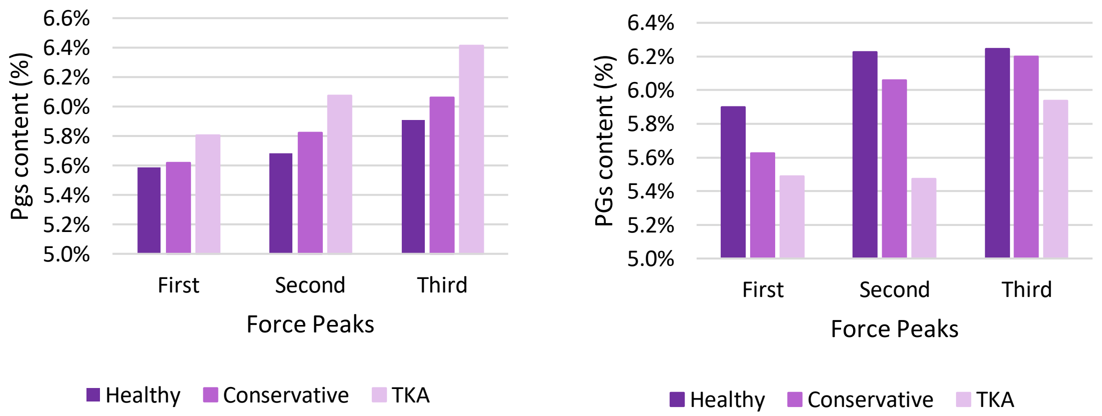


Figure 19. Comparative graphic of PGs content in % of the total weight between the three patients in ACT lateral (left) and ACT medial (right).

4.4. Rotation and force simulations

Figure 20 shows the difference of the full-extended knee simulation versus the simulations having into account both rotation and force. In the OA cases, it is seen cartilage – cartilage contact, something not seen in the other full-extended knee simulations.

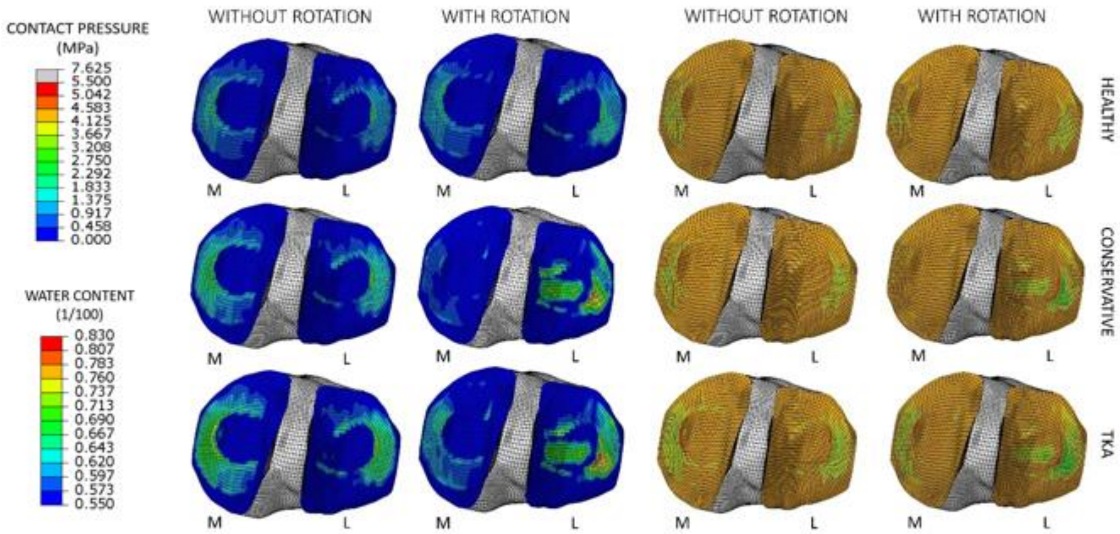


Figure 20. Top view of lateral (L) and medial (M) articular cartilage contact pressure (in blue) and water content (in orange) distribution at the first FP of the full-extended knee versus with rotation angle knee simulations.

In Figure 21 are seen the similitudes between the with rotation angle knee simulation of the TKA patient and an image of the removed cartilage of that patient in vitro. Fig. 21B shows areas with no cartilage (more beige color) and not damaged areas (pinker color).

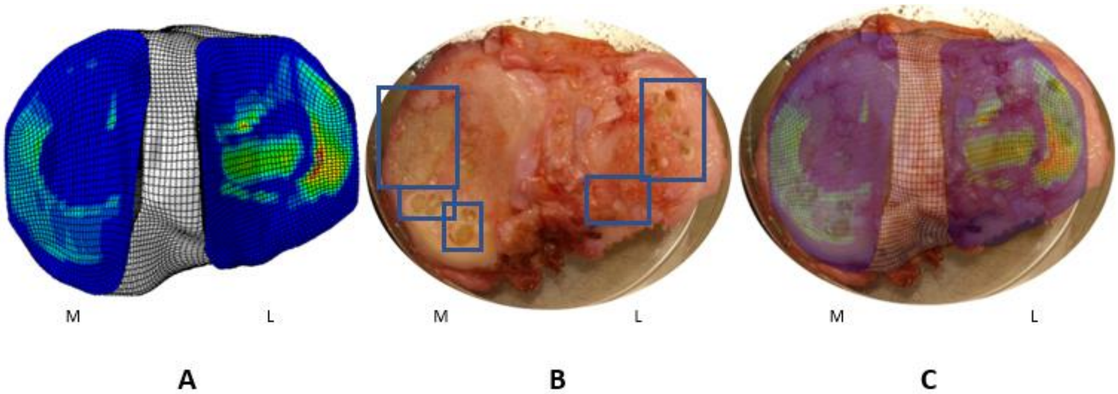


Figure 21. A) Top view of contact pressure in TKA condition through FEM with rotation angle knee simulation. B) In vitro extracted cartilage of the TKA patient with the most damaged zones marked. C) Comparison of the simulation and the in vitro model.

5. Discussion

The fundamental objective of this thesis was to simulate through a FEM the gait cycle of three different conditions to observe changes in the contact pressure, the water and PGs content. Through this work, not only differences between healthy and OA patients have been obtained but also between patients with different degrees of severity of the pathology. Furthermore, two different types of simulations have been accomplished and will be discussed along this section.

In Figure 13 is seen that the values of the contact pressure in the AC are higher for the cases of patients suffering knee OA; being the highest for the patient referred to a TKA. This has sense, since the patients suffering from knee OA also have obesity. As explained during the introduction section this is one of the risk factors of knee OA. In comparison to the healthy knee, OA patients for conservative treatment and TKA present a 31.39% and 80.14% of more weight, respectively. It is normal the heavier the person is, more weight will the knee charge so more probability to suffer pain and having a worse condition. It is also important to mention that in this project we are having into account the same type of material properties for the three conditions, so the cellular interactions of the cartilaginous tissue due to the advanced age of the OA patients are not being considered.

An overload could lead to the activation of certain catabolic processes which could result in the degradation of the ECM, losing the shocking-absorbing properties of the cartilages. As the ECM changes in composition and structure, collagen II may be affected, giving rise to a loss of the tensile support for the tissue and predisposing the tissue for mechanical fault. This shows significantly altered mechanical environments of the cells within the cartilage matrix [41]. This effect could be significantly higher in the case of the medial cartilage since it may be less prepared to support large loads. The articular cartilage could resist large loads for a short period of time but not for too long. Repetitive cycles with these loads could lead to knee OA, damaging the medial cartilage strongly [42].

In Table 2, quantitative values are shown. In general, ACT lateral receives higher values of pressure than the ACT medial. As it is stated in literature [43, 44] the medial cartilage tends to be more damaged than the lateral. This suggests that the lateral is better prepared to resist higher loads than the medial. Thus, in the healthy case, a marked average relative difference between the pressure of the lateral cartilage over the media is presented. However, this difference is reduced with the patients suffering from the pathology, being even negative in the third peak of the patient referred to TKA. This could mean that the lateral has reached its maximum charge of load and the medial must charge a little bit more than it, even though it is not prepared for that. Hence, it results in the medial cartilage beginning to load more as the pathology progresses. This could be explained by the aforementioned hypothesis that the medial cartilage is not as prepared as the lateral to resist overloads so, it is easier to deteriorate and erode.

In some papers [45, 46, 47] it is said that people are thought to walk with relatively greater loads over the medial compartment compared to the lateral. This could explain the greater damages to the medial because an overload may induce to failure. However, in our cases it is seen that the lateral cartilage is the one presenting a greater load. This also has sense, because if the medial cartilage presented higher loads in all cases, it should present more capacity of resistance, something that it is clearly not seen. As aforementioned, literature and the present model states that the medial compartment is the one most affected. The fact that the medial cartilage is the one suffering more damage does not mean that it must present higher pressure values.

In Figure 16, it is seen that water content decreased in the zones in which the pressure values are higher. This behavior is normal because due to an application of a load, the water tends to expand through all the surface of the cartilage. If we look closer on the quantitative values in Table 3, it indicates that as the pathology gets worse, the water content decreases in the lateral cartilage. However, in the medial cartilage we see higher values of water as it deteriorates. Less content of water implies higher probability to suffer dehydration, so less capacity to resist compressive loads.

This argument concurs with the hypothesis that the lateral cartilage is naturally capable to support higher loads in comparison to the medial one. As it is observed, in the healthy case the ACT lateral presents more water content than the ACT medial. The interaction between collagen network, PG and water is believed to play an important role in the biomaterial and biomechanical properties of articular cartilage [48]. If the cartilage suffers dehydration, it could result in a joint-lubrication loss, and it may have little available fluid for stress sharing or to redistribute stress away from the loading site. Stresses are concentrated on the directly loaded surface, which can lead to cracking of the cartilage and possibly to subsequent rupture of the surface [49].

Nonetheless, as the osteoarthritic condition gets worse, it is observed that the medial cartilage presents higher content of water than the lateral. This could be due to the phenomenon of effusion-synovitis which results from the accumulation of excess fluid in the joint and is known to be an active component of the OA process, associated with both pain and structural progression [50]. If the medial cartilage is less prepared to support big loads, it could be more affected by the pathology than the lateral. Thus, the cartilage swells and it is more inflamed due to the excess of fluid accumulated and this could be the reason why the medial articular cartilage shows higher values of water.

During arthritis and other joint diseases, the PG level of cartilage matrix is diminished, leading to impairment of normal joint function [51]. This can be observed in Figure 19 in the medial cartilage. In the medial compartment, the OA cartilage presents less PG content compared to the healthy. This could imply that osteoarthritic tissue is storing less energy than healthy tissue so has worse elastic properties. The reduction in proteoglycan content in the surface region makes the tissue susceptible to mechanically-induced damage whereas healthy tissue is relatively unaffected by mechanical testing [42]. Nonetheless, the cartilage in the lateral compartment does not follow this behavior. This could be because as we have discussed along this section, it is not as affected by the pathology as the medial cartilage.

It could be speculated that under the load conditions, some catabolic processes may be activated like the protease's expression as MMP-3 which destroy the aggrecans. In the paper of Peggy M et al [52], it is proved that the elevation of MMP-3 following cell death was consistently found in the superficial zone of loaded cartilage. Thus, since MMP-3 can degrade PG and super-activate procollagenase, the increase of MMP-3 can therefore induce matrix degradation and PG depletion in mechanically injured articular cartilage, both of which are important to the development of OA. Nonetheless, this cannot be observed through our model because we are studying in tissue level not cellular.

It is also important to mention that changes in PGs content have a really close relation to the percentage of water content. If the water content increases but the PGs content remains the same, the percentage of PG will diminish. Otherwise, if the water content decreases the percentage of the PG content will increase. This could also explain this different behavior among the lateral and medial compartment.

Regarding the angle of ration of the knee, in the healthy condition there are not prominent changes between the two different types of simulations. This can be explained by the fact that the angle of rotation applied during the first peak is only of 2.1 degrees. Hence, both simulations expect similar results. However, in the OA conditions, noticeable changes appear. In full-extended knee simulations, it can be perceived the shape of the menisci when the pressure is applied in both lateral and medial cartilages. Nevertheless, in the with rotation angle knee simulations, not only the shape of the menisci can be observed but also cartilage – cartilage contact is noticed. Also, through the colormap it is observed that the zones in which there are the highest values of contact pressure are different in both types of simulations (Figure 20). The highest value of contact pressure for the TKA condition in the full-extended knee simulation is of 5.50 MPa whilst in the with rotation angle knee simulation is of 7.63 MPa.

Figure 21 clearly shows the importance of having the angles of rotations into account when simulating. In Fig 21C, when we overlap the image with the most damaged zones (Fig 21B) and the image extracted from our model (Fig 21A) in which there are seen the zones suffering more pressure, it is observed that the worn areas coincide. Hence, this indicates that including the angles of rotation in the simulations is basic to capture properly the effect caused in the cartilages. It is also seen that some parts of the cartilage are totally destructed, these areas correspond to the zones marked with the highest values of contact pressure.

Related to the application of this project in real life, it is essential to remind that nowadays, doctors are still facing a difficult decision when concluding the proper treatment for each OA patient. This may be altered by the intensity of pain that manifests the patient that is suffering, which may conditionate the decision depending on the hypersensitivity of each patient. Fortunately, this work could provide medical practitioners with objective parameters not able to get through medical explorations to confront this problem.

As any numerical study, this project presents some limitations that should be considered when interpretating the results. Only one patient was simulated for each group. This was due to the high computational cost that did not allow more samples per condition. In order to extrapolate the results, this should be fixed. Moreover, the geometry used in this model is generic and not patient specific which is good for capturing differences between groups but not for studying particular cases. This project has been accomplished with subjects of different ages, weighs, and sex. Therefore, some results may be altered due to these factors. Further investigations should ensure similar values of these variables to only differ in the grade of OA. However, the results obtained provide a good starting point to understand the changes produced during the gait cycle in the articular cartilage.

Another point to consider would be that the model does not present ligaments. Although it is known that they play an important role in the stabilization of the knee, proves in the full-extended knee have shown that not including them into the model did not affect the pressure values in the cartilage. Moreover, not including ligaments for the FEM reduces the computational cost. However, it has been reported that the instability of ligaments influences the gait cycle so, this should be considered to study in further projects.

Despite the comparison of the full-extended and with rotation angle knee simulations until the first peak, no complete gait cycle considering both angles of rotation and force has been accomplished. Thus, we propose to achieve complete gait cycle simulations having into account both, the angles of rotation and the force. This way, more realistic outcomes will be obtained.

6. Conclusions

Biomechanical changes in articular cartilage during gait was evaluated using a 3D FE knee model. Lateral cartilage bears more pressure than medial, yet the pressure at medial cartilage increases with OA. It can also be concluded that rotation angles are mandatory to explore the real mechanical response of the cartilage. Outcomes show a very different pattern in comparison to the full-extended knee simulations that allow a better approximation to reality and provide more information. However, full-extended knee simulations do also supply valuable results for the study of knee OA through FEM.

Overall, the information provided by FE models can be used in clinical practice to support the decision making for the best OA treatment, distinguishing amongst those patients who must undergo a surgery and those who do not.

7. Further work

Further work could be centered in the realization of a larger study with more samples simulating the complete gait cycle of both full-extended and with rotation angle simulations. Also, the proper development of novel strategies to face knee OA should be accomplished thoroughly the study of the impact in cartilage cells of the biomechanical environment found in this work. Cells response to the mechanical environment described in this study should be further explored through experiment or computational approaches such as agent-based modelling.

Moreover, we propose to analyze deeper the differences between the conservative and TKA groups to be able to provide objective parameters for physicians when determining if a patient should go to a conservative treatment or to surgery. In addition, an exhaustive analysis of femoral cartilages could also be implemented to complement the outcomes achieved with the current project.

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