ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN

SCIENZE E TECNOLOGIE DELLA SALUTE

Ciclo 37

Settore Concorsuale: 06/F4 - MALATTIE APPARATO LOCOMOTORE E MEDICINA FISICA E RIABILITATIVA

Settore Scientifico Disciplinare: MED/33 - MALATTIE APPARATO LOCOMOTORE

EFFECT OF NEURODEGENERATIVE COMORBIDITIES ON THE RISK OF REVISION OF KNEE JOINT REPLACEMENTS

Presentata da: Alessandro Panciera

Coordinatore Dottorato

Igor Diemberger

Supervisore

Cesare Faldini

Esame finale anno 2026

TABLE OF CONTENTS

ABSTRACT

Background:

As populations age, both joint arthroplasty procedures and neurodegenerative diseases like Parkinson's disease (PD) are increasingly common. While general risk factors for knee prosthesis failure are well known, the specific impact of PD on implant survival is less clear. Motor symptoms of PD—rigidity, bradykinesia, postural instability—could impair joint function and raise complication risks. Understanding this relationship is crucial for optimizing care in these patients.

Aim:

This study investigated whether patients with preoperative PD have a greater risk of revision after total knee arthroplasty (TKA). Secondary aims included determining causes of failure, comparing outcomes with total hip arthroplasty (THA), and assessing biomechanical factors through computer modeling.

Materials and Methods:

A retrospective cohort analysis was conducted using the Emilia-Romagna Joint Replacement Registry (RIPO) and administrative databases. Patients with PD who underwent TKA from 2003–2018 were compared to matched controls without neurodegenerative diseases. The primary endpoint was revision for any reason. Kaplan–Meier survival analysis and multivariate Cox regression were applied. THA outcomes were analyzed in parallel, and biomechanical modeling was performed to simulate joint forces in PD.

Results:

Of 52,573 TKAs, 551 were in PD patients. The revision rate was significantly higher in the PD group (8.4% vs. 3.5%), with a 2.7-fold increased risk (HR 2.7; 95% CI 2.1–3.7). Septic loosening and implant dislocation were more common in PD patients, while aseptic loosening rates were similar. For THA, long-term revision rates did not differ, but PD patients had more early complications, notably periprosthetic fractures. Biomechanical modeling showed no significant differences in joint loading.

Conclusions:

Parkinson’s disease independently increases the risk of TKA failure, primarily due to systemic frailty, infection, trauma and not mechanical overload. Tailored perioperative and multidisciplinary approaches are needed to improve outcomes in this population.

Introduction

Knee Osteoarthritis[1–3]

Knee osteoarthritis (OA), is a condition characterized by specific symptoms and radiographic changes typical of articular cartilage degeneration, generally affecting both the femoral and tibial components of the joint. The onset of symptoms is typically insidious, with a progressive course leading to a gradual worsening of the clinical picture. Knee OA may be primary (idiopathic) or secondary: it is defined as primary when, following thorough differential diagnosis, all possible secondary causes are excluded.

The knee is, by far, the joint most frequently affected by osteoarthritis, followed by the lumbar spine and the hip. This predisposition is due to the high loads the knee must bear during daily activities. When the knee is neutrally aligned, the medial region bears approximately 60–70% of the load forces, making it the compartment most frequently involved in the degenerative process.

The prevalence of knee OA is slightly higher in females, with an incidence that increases directly with age: radiographic changes consistent with osteoarthritis are present in around 60% of patients over the age of 65. In addition to genetic predisposition, hormonal status plays a significant role in the development of primary knee OA: notably, estrogens exert a protective effect, which explains the increased incidence of knee osteoarthritis in women after menopause. Conversely, an excess of growth hormone (GH) may favor the early onset of the condition in both sexes. Other predisposing factors include being overweight, engaging in intense sporting activities, and physically demanding occupations.

Secondary knee OA, on the other hand, may be caused by numerous pathological conditions affecting the knee, such as the sequelae of articular fractures, meniscal or ligament injuries, or joint deformities. In particular, deformities lead to abnormal load distribution and thus promote the development of degenerative lesions. Overall, the main isolated risk factor for knee osteoarthritis is axial malalignment of the lower limb in either varus or valgus, as the mechanical axis and adduction moment are closely correlated.

Articular damage initially affects the cartilage, which, owing to its limited regenerative capacity, undergoes progressive degeneration leading to exposure of the underlying subchondral bone. Typically, degeneration begins in the medial tibial plateau, the area subjected to the greatest load. The process then extends first to the entire medial femorotibial compartment and subsequently to the other compartments of the knee. In the early stages, the meniscal cartilages undergo a metaplastic process of calcification which, together with degeneration, alters joint mechanics. In advanced stages, large periarticular osteophytes form; these represent a compensatory attempt by the organism to increase the articular surface in response to overload, but ultimately further impair joint function.

During the presymptomatic phase, the degenerative process also involves the capsuloligamentous structures, which, due to progressive restriction of movement, retract and thicken, resulting in reactive fibrosis that may also affect the flexor muscles. Clinically, this manifests as a flexed posture of the knee. Capsular thickening and fibrotic involvement of the muscles lead to an irreducible flexion of the joint, with consequent reduction of the load-bearing surface and acceleration of the degenerative process; moreover, the reduction in range of motion forces the knee to bear body weight in a semi-flexed (mid-flexion) position, which may unmask any underlying joint instability.

The clinical onset of knee OA generally occurs after the age of 55, even though the degenerative process begins much earlier and progresses slowly and asymptomatically. In the presence of secondary knee OA, onset may occur at a younger age. Its presentation is typically subtle rather than acute, which is why patients often come to clinical attention with radiographic evidence of advanced osteoarthritis but only recent or mild pain symptoms. When the knee becomes symptomatic, pain is usually localized to the anteromedial region and may radiate proximally or distally. The knee pain exhibits the typical characteristics of osteoarthritic pain: in the early stages, it appears on awakening or after periods of inactivity, improves progressively with movement throughout the day, and subsides with rest; in advanced stages, pain persists throughout the day, worsening with weight-bearing, postural changes, and walking. Functional limitation manifests as progressive reduction in joint mobility, due both to anatomical changes and reflex antalgic contractures. The progression of the disease leads to increased deformity of the articular ends, reduced flexion-extension movements, and, in advanced cases, progressive flexion contracture. It is not uncommon for patients to report, in their medical history, episodes of sudden swelling and pain in the knee, often resolving spontaneously with cryotherapy, NSAIDs, and rest; occasionally, they may report having undergone infiltrations or arthrocentesis of the affected joint.

On inspection, the knee at rest generally presents in a moderately flexed position. Clinical assessment reveals marked tenderness during movement, often accompanied by crepitus or palpable clunks. These pathological signs are reflected in impaired gait: the patient may exhibit an antalgic limp or, during the stance phase of walking, a varus thrust. Any ligamentous instability is detected during physical examination.

First-line investigation, generally sufficient to confirm the diagnosis of knee OA, is weight-bearing radiography of the knee, performed in anteroposterior and lateral projections. It is also advisable to obtain a panoramic radiograph of the lower limbs in the standing position, in order to assess possible axial deformities of the entire limb that may involve the knee.

The typical radiographic features of osteoarthritis include joint space narrowing, subchondral bone sclerosis, prominence of the tibial spines, presence of subchondral cysts, osteophytes, and joint deformity (see Figure 1).

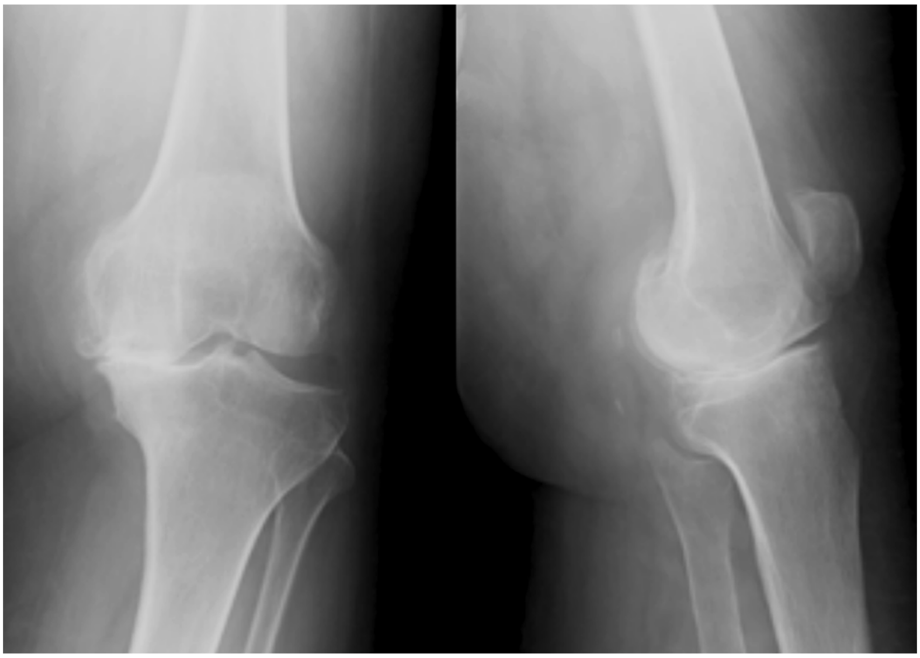

Figure 1: Radiographic assessment of a severely osteoarthritic knee with varus deviation. The radiograph shows the classic signs of osteoarthritis, such as osteophytes, deformity, joint space narrowing, subchondral bone sclerosis, and prominent tibial spines.

In cases of severe deformities or in the context of significant bone loss, a CT scan may be useful to complete the diagnostic process, especially for the purpose of surgical planning. Magnetic resonance imaging (MRI), in osteoarthritic disease, should be considered a third-line examination, the role of which is to exclude secondary causes of pain, such as neoplastic lesions of the soft tissues, early-stage diseases or conditions not diagnosable with conventional radiology (such as osteonecrosis and synovitis), or to rule out other potential differential diagnoses (complex regional pain syndrome, osteoid osteoma, etc.). Furthermore, MRI allows, in doubtful or complex cases, for the appropriate treatment to be correctly defined.

Knee OA can be classified based on radiographic findings into five grades of severity, according to the classification published in 1957 by Kellgren-Lawrence (Table 1).

Kellgren-Lawrence Classification	
Stage	**Description**
0	Absence of radiographic signs of osteoarthritis
1	Initial narrowing of the joint space (<2 mm) and possible osteophytes
2	Presence of osteophytes associated with joint space narrowing
3	Multiple osteophytes, joint space narrowing, subchondral sclerosis and early deformities
4	Large osteophytes, severe reduction of joint space, severe subchondral sclerosis and marked bone deformities

Table I: Kellgren-Lawrence Classification

The treatment of knee osteoarthritis in its early stages is typically conservative. It is based on weight control and strengthening the muscles with exercises that do not overload the joint (cycling, swimming), complemented by postural gymnastics, anti-inflammatory drug therapy (NSAIDs or corticosteroids) and pain relief (opioids, paracetamol), as well as cycles of joint injections (hyaluronic acid, corticosteroids, platelet gel). However, the patient must be informed about the progressive nature of knee OA and the fact that it is only possible to reduce symptoms, but in no way to alter the natural course of the disease. Knee OA is therefore destined to progressively worsen, until it reaches a severity such that the pain and functional limitation are no longer tolerable for the patient.

When the patient can no longer tolerate the symptoms and conservative approaches have failed, surgery is indicated. Surgical treatment of knee OA essentially includes three types of intervention: corrective osteotomies (see Knee Osteotomies), unicompartmental prostheses and total prostheses (see Knee Prosthetic Replacement). The choice between these three options depends on the patient's history, age, functional demands and the clinical-radiological picture; in particular, it is essential to consider the range of motion (ROM), ligament stability, the type of bone deformity and its reducibility. Each of these surgical options has consequences for the patient's lifestyle and the future functionality of the joint: clear information and shared therapeutic decision-making are therefore fundamental.

Kinematics of the Knee

Axes and Alignment of the Knee[2]

At the femoral level, two distinct axes can be identified: specifically, the anatomical axis and the mechanical axis. The anatomical axis of the femur is defined as the mid-diaphyseal axis equidistant from the femoral diaphyseal cortices. The mechanical axis of the femur, on the other hand, is described as the axis passing through the center of rotation of the hip (center of the femoral head) and the center of rotation of the knee (center of the tibial spines). There is an angle of about 6° between the anatomical and mechanical axes of the femur, corresponding to the physiological valgus of the femur, which is due to the presence of the femoral neck introducing a lateral component, while the mechanical axis runs proximodistally and is almost perpendicular to the ground, forming an angle with the vertical between 0° and 3°, which is greater in females owing to a wider pelvis compared to males.

At the tibial level, an anatomical and a mechanical axis can also be identified, defined respectively as the mid-diaphyseal axis equidistant from the tibial diaphyseal cortices, and the axis passing through the center of rotation of the knee and the center of rotation of the ankle (center of the tibial plafond). Unlike the femur, in the tibia the two axes (anatomical and mechanical) can be considered superimposable, as the angle between them is virtually zero in physiological conditions, within a range of 0°-3°.

In biomechanical studies of the knee, it is essential to consider the mechanical angles of epiphyseal deformity of the distal femur and proximal tibia, respectively defined as the "lateral distal femoral angle" (LDFA) and the "medial proximal tibial angle" (MPTA), both of which have a physiological range between 85° and 90°. The LDFA is defined as the laterally open angle between the mechanical axis of the femur and the line tangent to the distal surface of the femoral condyles: values >90° indicate a varus epiphyseal deformity, and 90° indicate valgus. Physiologically, most knees present mean values of LDFA and MPTA of 88° and 87° respectively, corresponding to a slightly valgus distal femur paired with a slightly varus proximal tibia. The angle between the lines tangent to the distal femoral condyles and the tibial plateau is the so-called "joint line convergence angle" (JLCA), with mean values of 0°-2° in physiological conditions.

To describe the alignment of the knee on the frontal plane, it is necessary to consider the lower limb as a whole. The mechanical axis of the lower limb is defined as the axis passing through the center of rotation of the hip and the center of rotation of the ankle. If the mechanical axis of the lower limb passes through the center of the knee within a range of about 3 degrees, the knee is defined as neutral, while it is referred to as varus or valgus if the axis passes inside or outside the center of the knee, respectively. For an angular description of knee alignment, the mechanical hip-knee-ankle angle (mHKA) is defined as the angle between the center of rotation of the hip, the center of rotation of the knee, and the center of rotation of the ankle, with positive values (valgus) if the angle opens externally and negative values (varus) if the angle opens internally.

At birth, there is an anatomical varus of the knee of about 15°, which persists until the onset of walking. As the child begins to walk, the axis gradually aligns to neutral and then to valgus, finally reaching, around 6-8 years of age, the definitive alignment represented by an anatomical valgus of 5°-7° (which corresponds to a total mechanical axis within the normal range). There has long been debate in the literature regarding what constitutes the physiological mechanical alignment of the knee. Recent studies have shown that there is a large variability in alignments within the population that can be considered physiological, in addition to the classic frontal neutrality, particularly thanks to the "coronal plane alignment of the knee (CPAK) classification" by MacDessi et al. (10.1302/0301-620X.103B2.BJJ-2020-1050.R1) introduced in 2021. This system takes into account two new angular variables, specifically the arithmetic hip-knee-ankle angle (aHKA) and the joint line obliquity angle (JLO). The aHKA angle is obtained by subtracting MPTA-LDFA, and its value is correlated with the constitutional alignment of the knee on the coronal plane: specifically, constitutional varus alignment if aHKA is negative (MPTA > LDFA) and valgus if aHKA is positive (LDFA > MPTA). If the values of MPTA and LDFA are equivalent within a confidence margin, aHKA of about 0° corresponds to neutral alignment on the coronal plane.

The JLO angle is obtained by summing MPTA + LDFA, and its value is correlated with the joint line obliquity on the coronal plane: specifically, distal apex obliquity if JLO is 180°.

The CPAK classification, by considering the combination of aHKA and JLO calculated on a large sample of healthy, asymptomatic knees, has outlined nine types of constitutional alignment on the coronal plane, greatly expanding the concept of physiological knee alignment, which is no longer considered such only in cases of neutral alignment (Figure 7). From a percentage perspective, the most frequent types of constitutional alignment in the healthy population are neutral alignment with distal apex joint line (39.2%), and varus alignment with distal apex joint line (26.4%). The percentages for the other CPAK types are shown in Figure 2.

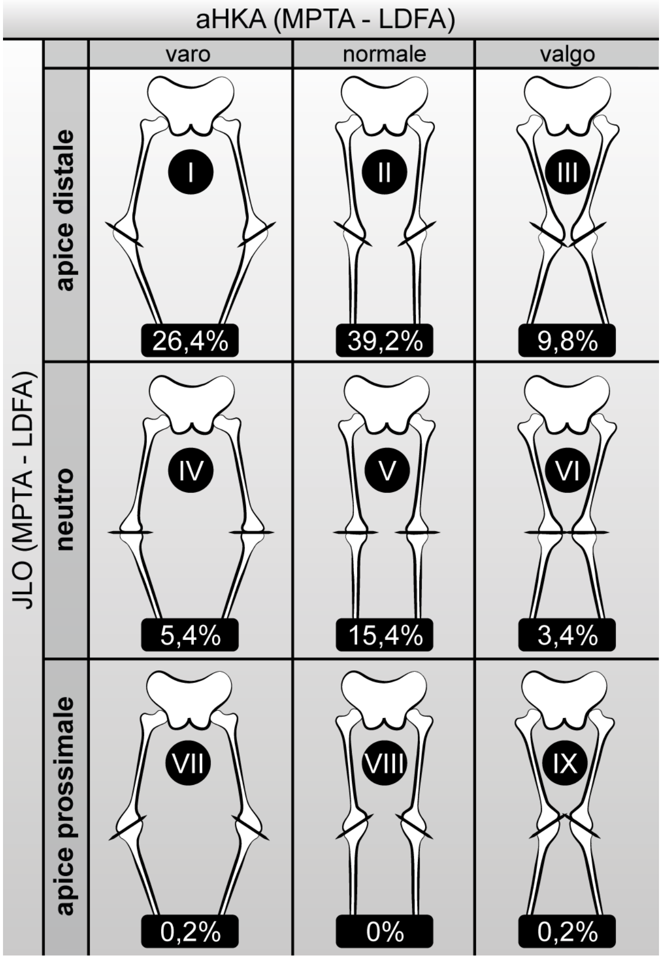

Figure 2: By combining the three types of aHKA (varus, neutral, valgus) with the three types of JLO (proximal apex, neutral, distal apex), it is possible to define nine types of constitutional knee alignment. The distribution and percentage values of the nine types of constitutional alignment according to the CPAK classification are shown.

According to the distribution data for constitutional knee alignments, it can be observed that, around neutral values, in valgus alignment types, angular values up to 6° of deviation can be considered within the physiological range, while in varus alignment types, angular values up to 8°-10° are regarded as physiological.

The introduction of new concepts of physiological knee alignment has recently led to a reconsideration of the indications for corrective osteotomy surgery in cases of valgus and varus axial deviations in young patients, with such procedures increasingly limited to cases presenting pathological axial deviation outside the safe ranges, symptomatic cases, or those with a known secondary cause (post-traumatic, Blount's disease, patellofemoral dysplasia, etc.).

Movements

Defined as a condylar joint, the tibiofemoral articulation classically presents six degrees of freedom (flexion/extension, internal/external rotation of the tibia relative to the femur, varus/valgus, anteroposterior glide, compression/distraction, and mediolateral translation). The most important movement of the knee joint is represented by the flexion-extension of the leg upon the thigh, and the other movements serve to optimize this primary motion.

Flexion-extension:

This is the movement that occurs in the sagittal plane and considers the relative position of the femoral and tibial axes. The reference position is represented by full extension, that is, when the femoral and tibial axes are parallel and coplanar in the sagittal plane. However, in the physiological knee, it is possible to achieve further passive extension of about 5°-10° from the reference position; it is important to distinguish this physiological passive extension from hyperextension, a pathological condition typical of certain neurological or post-traumatic disorders (characteristic of the pathological picture known as “genu recurvatum”).

The range of active motion in flexion is variable and depends on the relative position of the hip. Specifically, active flexion is physiologically possible up to 140° when the hip is flexed, whereas with the hip in extended position, flexion is possible up to 120°. This variability is secondary to the action of the hamstring muscles and the rectus femoris muscle, both of which are biarticular and thus their action is influenced by both knee and hip position. Passive flexion of the knee is possible up to about 160°. The axis around which the knee flexion-extension movements occur is essentially horizontal and forms an angle of about 81° laterally with the femoral shaft (a deviation from 90° considering the 3° between the vertical line and the mechanical axis of the femur, and 6° between the mechanical and anatomical axes of the femur). For this reason, in complete knee flexion, the leg axis does not lie directly posterior to the femoral axis but is slightly medial, bringing the heel into contact with the ischial tuberosity. Numerous biomechanical studies have been conducted to identify the transverse axes around which flexion-extension of the knee occurs. The primary axis is not considered fixed, but variable in its spatial position depending on the degree of knee flexion-extension, theoretically drawing a helical image at the condylar level: with increasing degrees of flexion, the area of contact between the condyles and the tibial plateau moves increasingly posteriorly. The position of the primary axis of rotation traces a sort of J-shape at the femoral condyles, thus referred to as the J-curve. This occurs as a result of the phenomenon of posterior rolling of the femur relative to the tibia, known as "femoral roll-back", regulated by the action of the posterior cruciate ligament; this phenomenon allows the knee to achieve flexion greater than 90° without mechanical conflict between the two bones.

Recent studies of joint kinematics, based on three-dimensional reconstructions of the femoral anatomy, have revisited these concepts, demonstrating that the articular portion of the femoral condyles, along which flexion-extension movement occurs, can be considered as a cylinder, with the radius of the medial condyle slightly larger than the lateral condyle, but with the center of rotation lying on the same axis crossing the condyles.

In light of these studies, three reference axes have been introduced around which the complex movements of the knee develop:

- Transverse axis of flexion-extension of the tibia on the femur (FEA or primary axis)
- Transverse axis of flexion-extension of the tibia on the femur (FEA or primary axis)
- Transverse axis of flexion-extension of the patella (secondary axis)
- Transverse axis of flexion-extension of the patella (secondary axis)
- Longitudinal axis of internal/external rotation of the tibia
- Longitudinal axis of internal/external rotation of the tibia

Of these, the primary and secondary transverse axes are involved in the flexion-extension movement. Unlike previously thought, these axes are now considered fixed and do not change their spatial position during knee flexion-extension. The primary transverse axis passes through the condyles and represents the axis about which the tibia flexes and extends around the (considered fixed) femoral condyles. The secondary transverse axis represents the axis around which the patellofemoral compartment flexes and extends and is parallel to the first, located anterior and proximal to the primary axis.

The knee extensor apparatus interacts at the level of the femoral trochlea, acting as a pulley and thus facilitating extension of the leg upon the thigh. In fact, the presence of the patella changes the direction of the force vectors produced by the quadriceps. Furthermore, by increasing the lever arm on which these forces act, the patella guarantees an increase of over 50% in the torque produced by the quadriceps muscle.

The patella travels an excursion of about 7-8 centimeters in the craniocaudal direction during a full flexion-extension movement, approximately twice its length. During the movement, the relative relationships of the articular surfaces change: in particular, the point where the two surfaces have the maximum area of contact is at about 45° of flexion. Normally the patella moves only in the vertical plane, and the possibility of transverse movement during flexion should be considered pathological; conversely, in full extension, lateral displacement of the patella is possible due to the absence of important restraining structures.

The action of the knee extensor musculature is of fundamental importance for the antigravity function it serves to allow the upright position. In fact, when the knee is extended or slightly flexed in a standing position, the vector of body weight passes posteriorly to the primary flexion-extension axis of the knee: for this reason, the knee tends to flex further in the absence of a compensatory mechanism provided by the extensor musculature. Conversely, when the knee is hyperextended, the body weight vector passes anteriorly to the flexion-extension axis: in this condition, the tendency for spontaneous hyperextension is immediately limited by the tension of the posterior capsule and ligaments. For this reason, knee hyperextension is a position that can be maintained even passively and does not require effective musculature to perform its antigravity function.

Internal and external rotation of the tibia on the femur

The anatomical design of the joint allows the tibia to rotate on the femoral condyles, although this movement can only be performed when the knee is flexed. This movement occurs around the longitudinal axis of the tibia and is assessed with the knee at 90° of flexion, both actively and passively. Rotations of the tibia on the femur are very important due to their close relationship with the flexion-extension movement. In fact, complete knee extension is invariably accompanied by an external rotation of the tibia, whereas the initial degrees of flexion are always associated with an internal rotation of the tibia and external rotation of the femur. This mechanism is known as the screw-home mechanism. The medial tibial plateau is larger than the lateral one and is characterized by greater congruence between the articular surfaces; during the last 20° of extension, the less congruent lateral plateau externally rotates to maintain articular congruence. This mechanism allows full extension to be achieved and stabilizes the knee during standing (the external rotation of the tibia puts tension on the fibers of the anterior cruciate ligament). Once full extension is reached, the action of the popliteus muscle is essential to "unlock" the knee and bring it back into flexion. The function of this muscle is closely dependent on the kinematic condition of the lower limb: in a closed kinetic chain (foot fixed to the ground and immobile), the popliteus muscle externally rotates the femoral condyles on the tibial plateau, whereas in an open kinetic chain (foot free) the popliteus muscle internally rotates the tibia on the condyles.

If only the geometry and bony anatomy were considered, the contact between the condyles and the tibial plateau would occur over a very limited area, resulting in high contact stress. The main role of the menisci is precisely to redistribute this contact over a larger area, thus reducing the load on the articular surfaces. In addition, the menisci help to stabilize the sliding and rolling movements of a curved surface (distal femur) on an irregular one (proximal tibia). To this end, during flexion-extension of the tibia on the femur, the menisci move; in extension, they translate anteriorly, pushed by the femoral condyles and pulled by the menisco-patellar ligaments; in flexion, they slide posteriorly as they are pushed by the condyles and by the insertions of the semimembranosus and popliteus muscles. However, the extent of this movement is not the same in both menisci: in particular, the lateral meniscus is characterized by mobility that is about double that of the medial meniscus (12 mm vs 6 mm).

In summary, during extension there is a proximal glide of the patella, a posterior translation of the tibia, and an internal rotation of the femur (with corresponding external rotation of the tibia). In flexion (initiated by the tendon of the popliteus muscle which "unlocks" the screw-home system), opposite movements occur, namely distal glide of the patella, anterior translation of the tibia (femoral roll-back), and external rotation of the femur (with corresponding internal rotation of the tibia).

Articular Stability

A joint is defined as stable if contact between the articular surfaces is maintained throughout its entire range of movement. The knee, due to the limited congruence between its bony surfaces, relies on specific structures to ensure adequate stability:

- Passive stabilizers (ligaments and capsule)
- Passive stabilizers (ligaments and capsule)
- Active stabilizers (muscles and tendons)
- Active stabilizers (muscles and tendons)

Simply put, the collateral ligaments resist varus and valgus stresses, whilst the cruciate ligaments prevent translation of the tibia relative to the femur and also control rotational movements. It is important to note, however, that the cruciate ligaments also contribute to knee stability in the coronal plane. Other key stabilizers of the knee include the pes anserinus tendons (sartorius, gracilis, semitendinosus) and the semimembranosus for the medial compartment, as well as the iliotibial band, biceps femoris tendon, and popliteus tendon for the lateral compartment.

The knee is completely stable in the coronal plane when fully extended. This stability is provided by the action of the cruciate ligaments (particularly the anterior cruciate ligament), the collateral ligaments, and the congruence afforded by the menisci. When the knee is flexed, the anterior cruciate ligament's contribution to coronal plane stability diminishes, with only the anteromedial bundle remaining taut, while the posterior cruciate ligament becomes essential for joint stability.

During flexion, coronal plane stability of the knee is mainly ensured by the medial and lateral collateral ligaments. However, the collateral ligaments are more relaxed in flexion than in extension; as a result, most knee instabilities become evident in flexion, whilst instability in extension is extremely rare. The slackening seen in flexion is secondary to the femoral insertions of the collateral ligaments, which move proximally in extension, thereby tightening the ligaments.

Anteroposterior stability of the knee is provided primarily by the cruciate ligaments, and secondarily by the posterior joint capsule and both the flexor and extensor muscle groups. The cruciate ligaments play a vital role in allowing the knee to function as a hinge joint for flexion and extension, whilst limiting anteroposterior translational movements.

Knee Arthroplasty

Total knee replacement (TKR) is one of the most successful surgical procedures in the history of modern medicine, capable of relieving pain and restoring joint function in patients with end-stage osteoarthritis of the knee.

The idea of restoring the function of an arthritic knee by modifying and resurfacing the articular surfaces began to take shape in the minds of surgeons as early as the 19th century. In 1860, Verneuil was the first to suggest interposing soft tissues between the articular surfaces of the femur and tibia to facilitate the gliding of the two bones in cases of wear. Following this example, a variety of materials were used for this purpose, such as nylon, pig’s bladder, fascia lata and cellophane. These materials produced poor results and their use soon declined. Independently, Ferguson had the idea of acting directly on the articular surfaces, shaping them so as to use the subchondral bone as a new weight-bearing and gliding surface. Usually, after this procedure the range of motion was acceptable, but the joint became unstable if the resection was too wide, while, conversely, if the resection was too limited and the joint space too tight, spontaneous early arthrodesis occurred. Because of the poor results, these procedures did not find widespread application and were therefore temporarily abandoned. It was only in 1940 that Campbell and Smith-Petersen introduced the concept of interposing a metal component between the two articular ends for the knee, taking their cue from what had already been done for the hip. Around the same time, McKeever and MacIntosh attempted a hemiarthroplasty of the tibia in cases of varus or valgus deformity, but this also produced unsatisfactory results and high failure rates.

Since then, the development of prosthetic implants has continued, essentially dividing into three lines: primary prostheses ("resurfacing"), constrained prostheses ("hinged"), and later unicompartmental prostheses. From a historical point of view, it is important to first discuss the development of total knee prostheses, therefore the primary and the constrained types. The former offered the advantage of preserving ligament integrity and better distributing the load (with a lower risk of loosening), while the latter were technically easier to implant as the intramedullary stems always ensured good alignment of the implant and not having to keep the ligaments functionally intact made the surgical technique simpler. The first surgeon to propose a constrained prosthesis was Walldius in the 1950s; however, the failure rate was very high, mainly because a simple constraint such as that proposed by the surgeon (simple hinge design) could not replicate the complex movements of the knee joint, and so the implants often underwent aseptic loosening due to relative overload. For many years, surgeons developed almost "customized" prosthetic designs in the absence of true standardization and thus achieved highly variable results. The real revolution in knee prosthesis design occurred in the 1970s with the work of Gunston and Freeman. The former was the first to propose a polycentric prosthesis (i.e. with a variable radius of curvature) and had the idea of using a metal-polyethylene coupling (inspired by what Charnley had done for the hip), all fixed to the bone with acrylic cement. Gunston's prosthesis preserved the collateral and cruciate ligaments to absorb stress and consisted of a high-density polyethylene tibial plateau that articulated with a rounded metal femoral prosthesis, which only replaced the posterior portion of the condyles. Although Gunston's was the first cemented knee prosthesis, it was Freeman's subsequent work that had the greatest influence on the development of knee prosthetic replacement and surgical technique. In particular, in 1973 Freeman listed the characteristics that every prosthetic implant should have to achieve acceptable results (the so-called “Freeman principles”), which are still valid today:

- It is always necessary to have a possible salvage procedure available in case of implant failure.
- It is important to minimize the risk of implant loosening: avoid excessive degrees of constraint (where not necessary), reduce friction as much as possible and distribute loads evenly at all points of the bone-prosthesis interface.
- Minimize the production of debris (or at least ensure that any produced are as harmless as possible).
- Minimize the risk of infection.
- Standardize the procedure for positioning the prosthetic components, making it reproducible.
- The prosthesis must guarantee a minimum range of motion between 5° of hyperextension and 90° of flexion.
- The prosthesis design must counteract excessive rotational movements.
- The soft tissues (especially the collateral ligaments) must contribute to joint stability by opposing excessive movement in any direction, particularly varus-valgus.

In the mid-1970s, three prosthetic designs were introduced: in 1976 Ranawat developed the bicondylar prosthesis at the Hospital for Special Surgery; subsequently Coventry proposed the geometric prosthesis and, lastly, Townley worked on the anatomical prosthesis.

It is precisely on the design of the bicondylar prosthesis (Total Condylar Prosthesis - TCP) that the rationale for the design of many implants still in use today is based. This prosthesis involved sacrificing both cruciate ligaments and consisted of a symmetrical cobalt-chrome femoral component with a flat trochlear groove, a polyethylene tibial component characterized by a median intercondylar eminence separating the two hemiplates and providing rotational stability, and a small stem to minimize the risk of prosthetic loosening. Patellar replacement was also envisaged, using a polyethylene hemisphere fixed with a single peg. This prosthesis was later refined by Insall, increasing the range of motion permitted by introducing the cam-post mechanism (a cam on the femoral side and a post on the tibial side), which encouraged posterior translation of the femur once flexion exceeded 70°, thus mimicking the action of the posterior cruciate ligament. It is on the basis of this implant that the prostheses we use today, particularly the posterior-stabilized ones, have been developed.

Today, the orthopaedic surgeon essentially has to choose between two types of implants: primary prostheses (which involve resurfacing the distal femur and proximal tibia with metal components, only partially altering the rest of the joint and its tissues) or constrained prostheses (which provide high stability to the prosthetic knee but deprive it of one or more of its physiologically allowed degrees of freedom).

In cases of mild deformity and good ligament function (the majority of cases), primary implants are preferable, as they guarantee better long-term survival, better functional outcomes and a lower complication rate. However, there are some situations where joint instability, significant bone loss or severe initial deformity force the surgeon to opt for a constrained implant to ensure adequate function and stability of the knee.

Primary prosthetic implants can be divided into those that closely resemble the original joint (anatomical implants) and those that do not reproduce the normal anatomical features of the knee but mimic its biomechanics (functional implants).

The main focus of this debate is the preservation or not of the posterior cruciate ligament. In fact, while the anterior cruciate ligament is often absent in longstanding arthritic knees, the same cannot be said of the posterior cruciate, which continues to play a fundamental role in femoral rollback during flexion. Whether or not the posterior cruciate ligament is preserved significantly influences prosthesis design: in anatomical prostheses that preserve the posterior cruciate (known as “PCL retaining” or “CR Cruciate Retaining”), the insert must be as flat as possible to guarantee femoral rollback. In functional prostheses (“PCL substituting”, “PS Posterior Stabilized”), the cruciate ligament is sacrificed during surgery and, to ensure full flexion, a concave insert is used with a mechanism called “post-cam” between the condyles (which serves both to recreate rollback and to prevent posterior impingement).

Although sacrificing an intact and functional ligament may seem an excessively aggressive choice from a surgical point of view, preserving the posterior cruciate brings some important disadvantages which must be considered when approaching prosthetic replacement: first, it is very difficult to achieve correct soft tissue balance while retaining the native ligament; moreover, in the event of subsequent PCL rupture, instability in flexion and paradoxical anterior translation of the tibia relative to the femur may occur (a problem partially solved with new generation anterior stabilized implants – “AS Anterior Stabilized”).

In summary, based on whether the ligaments are preserved or not, there are five different types of primary knee prostheses:

- Sacrifice of the ACL and preservation of the PCL (CR TKR)
- Sacrifice of the ACL and substitution of the PCL with posterior stabilization (PS TKR)
- Sacrifice of both cruciates and substitution of both (bi-cruciate substituting BCS-TKR)
- Sacrifice of the ACL and substitution of the PCL with anterior stabilization (AS TKR)
- Preservation of both cruciate ligaments (bi-cruciate retaining BCR TKR)

The most widely used primary knee prostheses today are PS TKRs (sacrifice of the ACL and substitution of the PCL). Their design derives from the TCP prosthesis with a major modification: the introduction of the post-cam mechanism, which allows a greater range of motion and reproduces rollback. With the development of implants, many different sizes of components have also been introduced, allowing the implant to be adapted to the patient.

Another ongoing debate concerns the morphology of the femoral component. Until a few years ago, all implants respected the original anatomy of the distal femur, whose radius of curvature decreases from anterior to posterior in the sagittal plane: if one reproduces the movement of knee flexion according to a stylized scheme, the axis of flexion-extension shifts along a sort of spiral. To reproduce these features, prosthetic implants have always had a so-called "J-curve" shape, with a decreasing radius of curvature from anterior to posterior, thus facilitating rollback and the achievement of full flexion.

In recent years, however, these prosthetic designs have been criticized. It has been hypothesized that a variable radius of curvature could, at increasing degrees of flexion, result in two negative effects: firstly, increased stress and wear of the polyethylene due to the progressive decrease in the contact area between the femoral and tibial components; secondly, a loss of tension in the collateral ligaments, generating instability at intermediate degrees of flexion ("mid-flexion instability") and pain, especially during activities such as climbing stairs or rising from a chair. These observations have led to the development of single-radius prostheses; the advantages of such implants consist of better stability throughout the range of movement, reduced polyethylene wear and an increased lever arm of the extensor mechanism (due to the fact that a single radius of curvature shifts the axis of flexion-extension of the tibiofemoral joint posteriorly). Although single-radius prostheses represent the latest development in knee prosthetics, it is not clear whether they provide better results than traditional prostheses: once again, the individual case and the experience of the surgeon are of crucial importance.

Another criticism of “traditional” primary prostheses is that they do not respect the physiological kinematics of the femoral condyles, in other words, the posterior translation of the lateral condyle during flexion while the medial compartment acts as a sort of pivot (Figure 7). Implants called “medial pivot” have therefore been developed, with a relatively static medial condyle and a hypermobile lateral condyle. The use of such implants is still extremely limited, and their superior long-term performance remains to be demonstrated.

The debate on the best prosthetic design remains lively, and the literature does not report significant differences between the various types of implants: the final choice therefore depends on the overall assessment of the patient and the preferences of the individual surgeon (Figure 3).

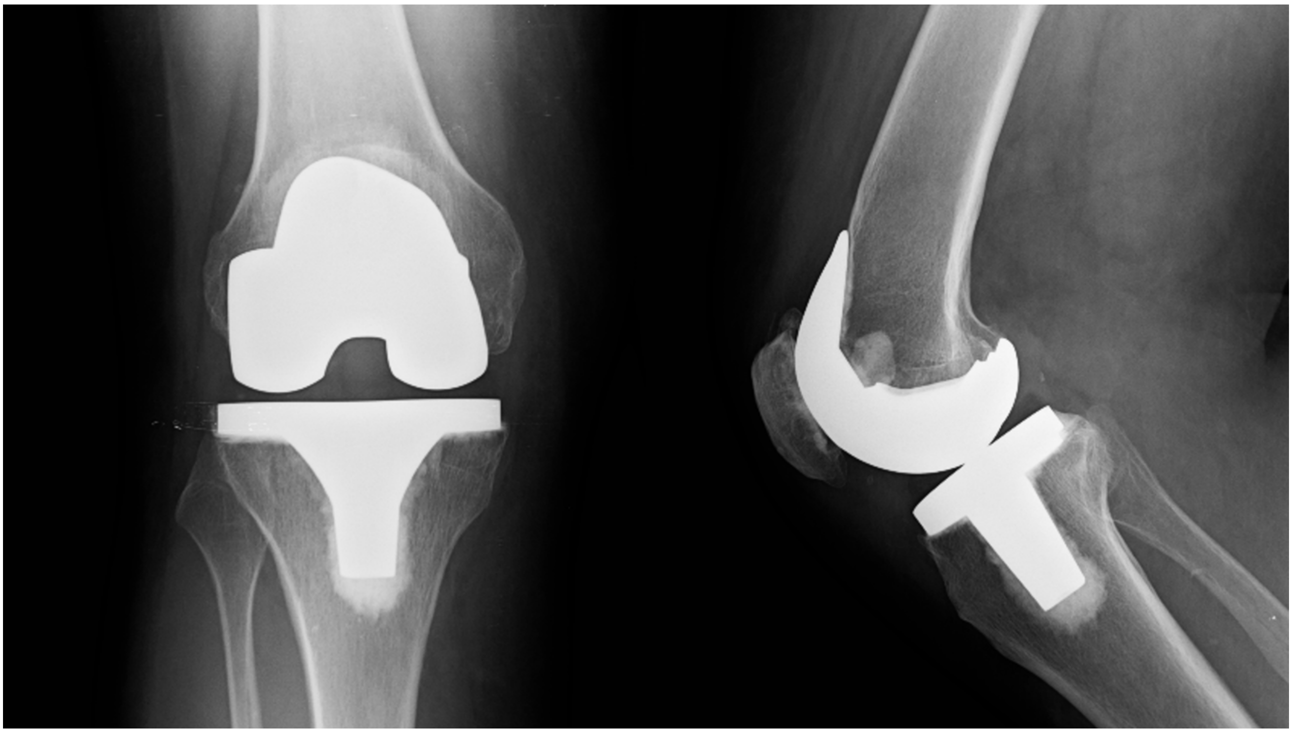

Figure 3: X-ray of a PS knee prosthesis with traditional design

The concept of constraint originates from the field of mechanics and refers to the limitation of a device's freedom of movement. When applied to orthopaedics, it means the restriction of movement within a joint, whether physiological (exerted by the joint capsule, ligaments or muscles), pathological (such as in cases of muscle contractures or osteoarthritic degeneration), or artificial (imposed by a prosthetic implant). The highest degree of constraint that can be applied to a mobile joint is a “hinged” movement, thus with only one degree of freedom: in the knee, this degree of freedom is rotation around a single horizontal axis (that of flexion-extension of the tibia on the femur), thereby sacrificing movements such as internal and external rotation of the tibia (screw-home mechanism), anterior-posterior translation of the femur (roll-back), and varus-valgus movements in the coronal plane. In the past, pure hinge prostheses were proposed by Walldius as an option for knee replacement; however, the excessive degree of constraint imparted to the knee led to such significant kinematic alterations that it resulted in early failure due to implant loosening. Over time, variants have been developed to achieve better implant survival rates without sacrificing the presence of constraint.

The two main types of constrained knee implants are:

- Semi-constrained ("Constrained" or CCK – Condylar Constrained Knee): These are used when the stability provided by the patient's collateral ligaments is insufficient, although ligament integrity is still required. This prosthetic design is characterized by an oversized post in the polyethylene insert, which completely fills the box of the femoral component. This feature provides excellent intrinsic stability in the coronal plane by compensating for the function of the collateral ligaments. The CCK prosthesis offers stability in the coronal plane but not in the sagittal plane; correct prosthetic positioning is therefore crucial. Given that the implantation technique for a constrained prosthesis is almost identical to that of a primary prosthesis, the CCK can be a useful salvage strategy, for example, in the event of an iatrogenic injury to the medial collateral ligament during surgery. Nevertheless, due to the increased mechanical stresses at the bone-prosthesis interface, it is recommended where possible to use prostheses with metaphyseal stems to better dissipate these stresses.
- Constrained (Hinged or "hinged"): These are used in cases of complete ligamentous instability (in such circumstances, a CCK implant would be subject to excessive stress and premature failure due to polyethylene wear). These are fully congruent prostheses characterized by a femoral pin that directly connects to the tibial post, permitting only flexion-extension movement. Nearly all prosthetic designs feature a rotating polyethylene insert ("rotating hinge prosthesis"), which helps to dissipate stresses and retain at least minimal rotational capacity. When implanting a constrained prosthesis

in the presence of intact collateral ligaments, these must be sectioned to avoid overloading the prosthetic implant.

Whichever constrained implant is chosen, it is important to remember that these are associated with a higher number of complications compared to primary implants. In particular, the loss of the joint soft tissues (which play a crucial role in absorbing energy and load stresses transmitted through the knee) means that all forces and torsional moments are transmitted to the prosthetic implant and the bone-prosthesis interface, encouraging loosening. For this reason, when using constrained or semi-constrained prostheses, it is always preferable to use intramedullary prosthetic stems, which allow for better force distribution. Secondly, the loss of the roll-back mechanism results in a reduced range of movement compared to primary prostheses.

Parkinson's Disease[4–9]

Although there are numerous neurodegenerative diseases presenting with symptoms affecting the musculoskeletal system, the most common and well-studied is Parkinson's disease (PD). Parkinson's disease is a chronic, progressive neurodegenerative disorder that affects the central nervous system, particularly a small area of the midbrain known as the substantia nigra pars compacta. In this region, the neurons responsible for producing dopamine degenerate and die off progressively. Dopamine is a crucial neurotransmitter that acts as a chemical messenger between neurons, playing an essential role in regulating voluntary movement, fine motor control, motivation, and pleasure. The reduction in dopamine levels disrupts the balance of the neural circuits in the basal ganglia, a group of subcortical structures that are essential for the planning, initiation, and smooth, harmonious execution of movements. This pathophysiological imbalance manifests clinically through a constellation of symptoms, mainly motor, which worsen over time and have a devastating and cumulative impact on the patient's entire musculoskeletal system.

This motor decline is accompanied by systemic physical weakness, making the person with Parkinson's particularly frail. The progression of the disease often leads to sarcopenia and a general state of deconditioning, exacerbated by numerous comorbidities typical of old age. This intrinsic frailty, combined with postural instability, results in a drastically increased risk of falls, which represent one of the most feared and frequent complications. Falls in a patient often already suffering from osteoporosis can have catastrophic outcomes, such as femoral fractures, which mark the definitive loss of independence. Furthermore, this systemic weakness compromises the body's ability to effectively counter pathogens, exposing the patient to a greater risk of infections, one of the main causes of complications and hospitalization in this population.

The cardinal motor symptoms of Parkinson's disease are four: bradykinesia, rigidity, resting tremor, and postural instability. Bradykinesia is not simply a slowing down, but a genuine difficulty in movement. It is the most disabling symptom of the disease and manifests as difficulty in initiating voluntary movements (akinesia) and a reduction in the speed and amplitude (hypokinesia) of movements themselves. A patient with bradykinesia struggles to perform everyday tasks such as getting up from a chair, buttoning a shirt, or turning over in bed. Their gait is characterized by small, shuffling steps ("marche à petits pas") and a marked reduction in arm swing, which normally serves to balance the body during walking. The face loses its expressiveness, becoming a "mask" (facial hypomimia), and handwriting becomes progressively smaller and almost illegible (micrographia). These symptoms have a significant influence on the musculoskeletal system. In particular, they can lead to disuse muscle atrophy: reduced mobility inevitably leads to generalized physical deconditioning. Muscles, no longer adequately stimulated, progressively lose mass and strength. This weakening is not a direct consequence of the neurological disease, but a secondary effect of lack of use, which, however, further aggravates movement difficulties. Lack of mobilization can lead to joint contractures, secondary to stiffening and shortening of the soft tissues (muscles, tendons, ligaments, and joint capsule). This process results in the formation of contractures, i.e., permanent limitations of joint movement. The most affected joints are the shoulders (frozen shoulder), hips, and knees, which tend to become stuck in a flexed position, worsening posture and walking.

Parkinsonian rigidity is an involuntary increase in muscle tone. Unlike spasticity, rigidity is constant throughout the entire range of passive movement and affects both flexor and extensor muscles. During medical examination, when the examiner passively moves a patient's limb, they perceive a resistance described as "lead-pipe" (uniform) or, if associated with tremor, "cogwheel" (jerky). Patients experience a sensation of tension, heaviness, and muscle soreness, often initially confused with rheumatic or arthritic pain. Rigidity typically affects the neck, trunk, shoulders, and hips, significantly altering posture. Rigidity has notable effects on the musculoskeletal system: it can cause pain due to constant and abnormal co-contraction of agonist and antagonist muscles, one of the most common and debilitating non-motor symptoms. Pain can be localized or widespread and worsens with fatigue. Rigidity, especially of the axial and flexor muscles of the trunk and limbs, is the main cause of the characteristic camptocormic or flexed posture. The patient tends to lean forward with head and shoulders, arms flexed and adducted, and hips and knees slightly bent. This abnormal posture completely alters body biomechanics. Poor posture shifts the center of gravity and abnormally overloads the joints, particularly the spine and knees. In the long term, this mechanical stress can accelerate degenerative joint processes (osteoarthritis) and cause secondary conditions such as chronic low back pain and knee pain.

Tremor is the best-known symptom of Parkinson's, as it is the most visible, although it is not present in all patients. It is a tremor that occurs when the limb is at rest, not supported against gravity, and typically disappears during sleep and diminishes with purposeful voluntary movement. It usually begins asymmetrically, in one hand, with a characteristic rhythmic "pill-rolling" movement. Although tremor can cause social embarrassment and some difficulty with fine tasks, its direct impact on the musculoskeletal structure is less severe than bradykinesia and rigidity. However, a persistent and wide-amplitude tremor can lead to muscle fatigue and pain in the affected limb. It does not directly cause deformity but contributes to overall energy expenditure and patient fatigue.

Postural instability generally appears in the more advanced stages of the disease and is caused by deterioration of postural reflexes, that is, those automatic mechanisms that allow us to maintain balance. The patient has difficulty adjusting posture to changes in position or correcting an unexpected loss of balance. Instability manifests as difficulty changing direction, a tendency to "freeze" or fall backwards (retropulsion) and, above all, frequent and sudden falls. It is the main risk factor for falls, which are among the most feared complications. Falls in an elderly patient, often already suffering from osteoporosis, lead to a very high incidence of fractures, particularly of the femur, wrist, and vertebrae. Furthermore, Parkinson's disease is a risk factor for the development of osteoporosis, increasing the rates of fracture in a "frail" population.

In conclusion, Parkinson's disease is a neurodegenerative condition with significant systemic implications that, through its motor symptoms, progressively dismantles the integrity of the musculoskeletal system. The interaction between bradykinesia, rigidity, and postural instability creates an inexorable functional decline, transforming the body into a rigid, weak, and unstable structure, subject to chronic pain, deformity, and fractures. Managing these patients therefore requires a multidisciplinary approach that integrates pharmacological therapy with physiotherapy aimed at countering rigidity, strengthening muscles, and preventing falls.

Epidemiology[10–14]

The ageing of the global population has led to an exponential increase in both the number of primary arthroplasty procedures and the incidence of chronic diseases, including neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD). Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. In industrialized countries, it has an incidence of approximately 12 patients per 100,000 people per year, with a preference for the male sex. In general, the estimated prevalence of the condition is about 1% of the population over the age of 60 and up to 4% of the population over 85 years old. Although risk factors for knee prosthesis failure, such as infection, obesity, and diabetes, are well studied, the specific impact of neurodegenerative comorbidities on the long-term outcome of the implant remains an area of research that is still little explored. Patients with these conditions present unique clinical challenges: in particular, those affected by Parkinson's disease exhibit characteristic movement disorders (rigidity, bradykinesia, tremor, postural instability) that can alter the biomechanics of the operated knee, causing abnormal loading on the implant and increasing the risk of falls and periprosthetic fractures.

Understanding whether and how these conditions influence implant survival is vital to improving patient selection processes, optimizing preoperative planning, personalizing postoperative management, and providing appropriate counselling to patients and their families. The current literature on knee prosthesis failure focuses mainly on mechanical causes (aseptic loosening, polyethylene wear, instability) and biological causes (periprosthetic infections). Some studies have analyzed the impact of systemic comorbidities, but neurological conditions are often grouped into a single heterogeneous category, without distinguishing between different etiologies and their specific pathophysiological mechanisms. Some small-scale retrospective studies have suggested an increased risk of complications (dislocations, fractures) and revision in patients with Parkinson's disease, but the results are not always consistent and often lack adequate statistical power or a well-defined control group. As for dementia, the data are even scarcer and sometimes contradictory, with some research showing no significant increase in revision risk, but a higher mortality rate. There is, therefore, a lack of large-scale studies, based on registry data or large cohorts, that could quantify the risk of revision, identify the specific causes of failure, and analyze implant survival times in these specific patient populations.

Biomechanics[15–18]

From a biomechanical perspective, recent decades have seen significant advances in understanding data derived from computer simulations of joint loading cycles. However, virtual modelling of the knee, particularly in the presence of significant pathological changes such as those associated with Parkinson’s disease, remains a complex challenge. These pathological conditions can alter both joint morphology and function, introducing elements of variability and uncertainty that make interpretation of the results more difficult.

The first approaches to musculoskeletal modelling date back to the 1970s and have since evolved constantly, leading to the development of standardized models of healthy adults that still serve as an established reference in the scientific literature. While these models provide a valid starting point, they often poorly represent the anatomical and functional specificities of patients with neurodegenerative diseases, showing significant discrepancies from images obtained with advanced imaging techniques. Furthermore, muscle function cannot simply be scaled proportionally to joint geometry, as there is notable variability between individuals due to genetic factors, age, health status, and physical activity level.

To overcome these limitations, highly detailed models have been developed, generated from individual patient imaging data (such as MRI or CT scans). These personalized models have demonstrated greater accuracy in estimating joint biomechanics, evaluating muscle force moments, and the transmission of forces through the joints. However, creating such a model requires a significant investment of time and resources, often resulting in slower analysis or clinical planning.

Currently, two of the main workflows used for biomechanical modelling are the INSIGNEO and STAPLE pipelines. The INSIGNEO pipeline, although highly detailed, can require up to ten hours to generate a single personalized joint model. STAPLE, on the other hand, largely automates the process, producing a joint model in about an hour, with accuracy comparable to INSIGNEO for skeletal and muscular reconstruction. It should be noted, however, that STAPLE does not natively integrate the muscle component, limiting itself to describing joint biomechanics. This limitation can be overcome by combining STAPLE with nmsBuilder on the MATLAB platform, thus enabling muscle component integration and the creation of a more complete and functional biomechanical model.

Using these pipelines, it is possible to generate gait simulations through the OpenSim platform, which allows for the assessment of contact forces at the femorotibial joint. Although the creation of personalized models represents the gold standard in terms of accuracy, the high complexity and clinical variability typical of Parkinson's disease often make this approach impractical for routine use. For this reason, a modern generic model was chosen, adapted to the specificities of a patient from the "5th Grand Knee Challenge", and subsequently modified to simulate the biomechanical changes typical of a subject with Parkinson's disease.

The literature review on muscle changes in Parkinson's disease has highlighted peculiar alterations in gait patterns compared to healthy subjects. These alterations involve the entire kinetic chain of the lower limb, with particular importance for the pelvic girdle and the flexion-extension dynamics of the ankle. Regarding the knee, there is a reduced range of movement in flexion-extension, mainly due to the generalized muscular rigidity caused by the disease. However, according to evidence from gait analysis, the specific effect of Parkinson's on knee biomechanics is relatively limited and mainly manifests as walking with rigid, extended knees, without substantial changes in the loads transmitted to the joint during gait.

To assess the impact of Parkinson's disease on the risk of knee prosthesis revision, reference was made to the work of Curreli et al., who analyzed the use of computer models to estimate the loads on prosthetic implants. In particular, this study showed that generic models, if appropriately adapted using well-defined bone landmarks, can adequately represent the loading conditions of a prosthetic implant. The study was based on experimental data produced within the fifth edition of the Knee Grand Challenge, using as reference a patient named PS, aged 86, 180 cm tall and weighing 75 kg.

Research Objectives

Research Hypothesis

Patients with a preoperative diagnosis of a neurodegenerative condition (and in particular Parkinson's disease) have a significantly higher risk of revision surgery for knee arthroplasty, for any reason, compared to a control population matched for age and sex.

Objectives

- To conduct an epidemiological analysis of the effect of Parkinson's disease on the incidence of knee prosthesis revision procedures.
- To demonstrate the presence of a biomechanical link between the severity of Parkinson's disease and the mechanical causes of implant failure.
- To extend the study to other neurodegenerative conditions or to other joints.

Materials and Methods

Study Design:

A retrospective cohort study was conducted using data from a joint prosthesis registry (RIPO – Registry of Prosthetic Implantology) and health administrative databases (SDO flows – Hospital Discharge Records).

RIPO – Registry of Prosthetic Implantology

The RIPO registry was established at the Rizzoli Orthopaedic Institute in 1990 and, since 2000, has included all Orthopedics departments in the Emilia-Romagna region, thus tracking all hip, knee, and shoulder prosthetic replacement procedures performed in the region. Furthermore, the registry's database contains information on the patients' clinical conditions, the surgical intervention, the type of implant and fixation used. The primary endpoint of the registry is the revision of at least one component of the prosthesis, enabling the assessment of surgical implant survival.

Data Source and Study Population:

By linking data from the RIPO registry with clinical information available in patients' medical records, it was possible to identify patients with Parkinson's disease who underwent total knee replacement between 1st January 2003 and 31st December 2018 in the Emilia-Romagna region. Specifically, a dedicated algorithm was used to identify patients with at least one hospital admission with a primary or secondary diagnosis of Parkinson's disease, coded as ICD-9 332.0, 332.1, 333.0, and 781 prior to the replacement surgery. Additionally, to be included, patients were required to have had at least two prescriptions for Parkinson's disease medications, identified with ATC code N04*, in the year preceding the prosthetic replacement. Patients diagnosed with Parkinson's only after the prosthetic replacement were excluded to avoid confounding factors. Moreover, patients not resident in Emilia-Romagna were excluded to minimize the risk of loss to follow-up, as any revision surgery performed outside the region would not be captured by RIPO, potentially introducing bias into the results.

The search of the RIPO database for the period considered led to the identification of 52,573 knee replacement procedures performed in Emilia-Romagna. Of these procedures, 52,022 (99.0%) were carried out in "normal" patients without a diagnosis of Parkinson's disease, while 551 (1.0%) were performed in patients with a confirmed diagnosis of Parkinson's disease. Of these, 276 were identified via medication prescriptions, 157 via ICD-9 codes, and 118 via both methods.

No other neurological condition was considered to avoid confounding factor due to an heterogeneity of clinical presentations (specifically when considering the musculoskeletal symptoms).

Definition of Cohorts:

Using diagnosis codes (ICD-9-CM), patients were stratified into two groups:

- Parkinson's Cohort (PD): Patients with a diagnosis of Parkinson's disease recorded before total knee replacement (TKR).
- Control Cohort: Patients who underwent TKR without a diagnosis of neurodegenerative diseases.

Statistical Analysis:

Descriptive statistics, such as median and range for continuous variables and frequency with percentage (%) for categorical variables, were used to present the data. The Chi-square test was employed to assess the statistical significance of qualitative data, whilst the t-test was used for continuous data. Kaplan-Meier survival analysis was performed, using revision as the endpoint and considering the last date of observation (31st December 2019 or the date of death available from the ER database) as the survival time for non-revised knee prostheses. The Wilcoxon test was used to compare survival between groups. The Wald test was performed to analyze the p-values obtained from Cox multiple regression analyses. The proportional hazards assumption was assessed using the Schoenfeld residuals method, and p-values < 0.05 were considered significant. Statistical analyses were conducted using JMP, version 12.0.1 (SAS Institute Inc., Cary, NC, USA, 1989–2007).

Results

In our population, 551 prosthetic replacement procedures were carried out in 491 patients affected by Parkinson's disease at the time of surgery, while 52,022 procedures were performed in 43,304 unaffected patients (Table 2). No significant difference was identified regarding the side distribution of prosthetic replacement in the two populations: in the Parkinson's disease group, 311 implants (56.4%) were on the right side, while in the control group, 27,600 implants (53.1%) were on the right side. As for gender distribution, a statistically significant difference was observed between the two groups: the prevalence of women in the PD population is 66.2% (365 cases), while in the control population, the female prevalence increases, reaching 71.0% (36,950 cases). This difference can be explained by the higher prevalence of PD in the male population, which therefore reduces the proportion of women. The mean age at the time of surgery was 72.2 years in the affected population and 71.4 years in the control population; this difference also proved to be statistically significant ($p<0.02$).
No statistically significant differences were found regarding the mobility of the tibial insert used (fixed-bearing or mobile-bearing), the material of the insert, or the material of the femoral component.

	PD group	***Control group***	
N° of implants (%)	551 (1,0%)	52.022 (99,0%)	
N° of patients	491	43.304	
Side DX (%)	311 (56,4%)	27.600 (53,1%)	
Gender Females (%)	365 (66,2%)	36.950 (71,0%)	Fisher's exact test (p=0,01)
Average age (range)	72,2 (42-89)	71,4 (21-95)	Student's t test (p=0,02)
Etiology Primary OA (%) Deformities (%)	82,6 10,8	84,4 9,8	Pearson's Chi-squared test (p=0,5)
Mobility of the bearing Fixed (%)	68,9	66,9	Fisher's exact test (p=0,34)
Material of the bearing Convention poly (%)	82,4	83,3	Pearson's Chi-squared test (p=0,21)

Cross-linked poly (%) Cross-lnk poly + vit E (%)	13,4 4,2	11,4 5,3	
Material of the prosthesis CrCo(%) Oxinium (%) Ceramized CrCo (%) Other (%)	 88,8 6,9 3,5 0,7	 88,4 7,4 3,7 0,5	 Pearson's Chi-squared test (p=0,82)

Table 2: Differences between the Parkinson's group and the control group. Only differences related to gender and mean age were found to be significant, whereas etiology, insert characteristics and implant material did not show significant differences.

The Kaplan-Meier method was used to calculate knee prosthesis survival. In this method, the X-axis represents the time elapsed since surgery in years, while the Y-axis shows the percentage of surviving procedures. As previously specified in the materials section, the endpoint was defined as the revision of any component (femoral component, tibial component and/or polyethylene insert). Secondary patellar replacement was not considered, as it is relatively common and more related to alterations in patellar tracking than to the underlying pathology. In the group affected by Parkinson's disease, out of 551 prosthetic replacement procedures with an average follow-up of 5.2 years, there were 46 failures requiring revision. Meanwhile, in the control group, out of a total of 52,022 primary implants with an average follow-up of 6.3 years, 1,823 revisions were recorded (Table 3).

Groups	**TKRs**	**Average follow-up (range)**	**TKR revisions**	**Revision incidence (n° revision/n° TKRs)**
PD group	551	5,2 (0-15,9 years)	46	8,4%
Control group	52.022	6,3 (0-16,0 years)	1.823	3,5%

Table 3: Results comparing the revision incidence between PD patients and the control group showed a significant difference.

The reported results show a significant difference between the two Kaplan-Meier curves, as indicated by a p-value less than 0.001 in the Wilcoxon test (see Figure 4).

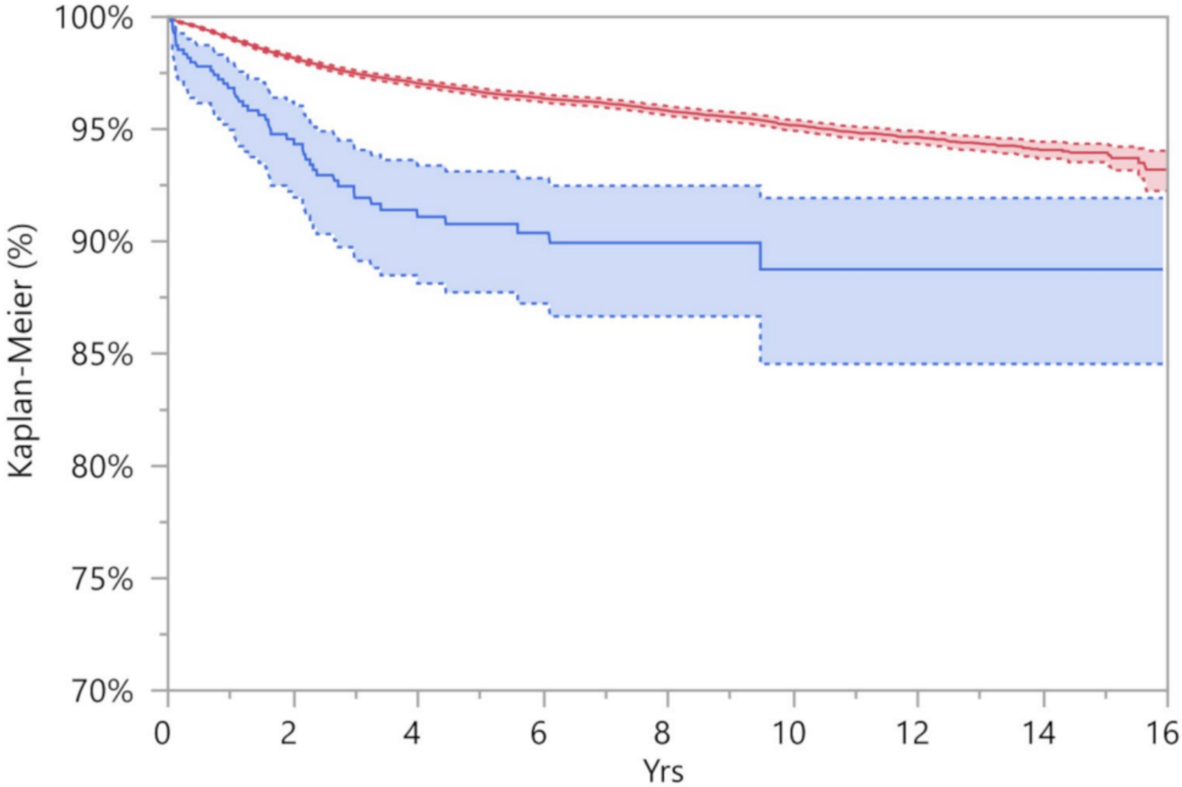

Figure 4: the Kaplan-Meier curves showed significant differences between the PD group (blue line) and the control group (red line). The dotted lines represent the confidence interval of 95%.

The survival analysis was therefore examined in greater depth (see Table 4) by assessing at various follow-up durations where the curves began to diverge. The difference between the two groups becomes apparent as early as the first year of follow-up, only to become more pronounced over time. At the one-year follow-up, the survival rate for patients with Parkinson's disease was 96.8%, compared to 99.1% in the control group. At the thirteen-year follow-up, the survival rate for the Parkinson's group dropped to 88.8%, whilst in the control group it remained around 94.3%. The parameter for the population at risk gradually decreases over time as the number of patients with long-term follow-up diminishes.

Survival rate % (Confidence Interval 95%)						
Group	**1 year**	**3 years**	**5 years**	**7 years**	**10 years**	**13 years**

PD group	96,8 (95,0-98,0)	91,9 (89,1-94,1)	90,8 (87,7-93,1)	89,9 (86,7-92,5)	88,8 (84,5-91,9)	88,8 (84,5-91,9)
At-risk population	497	355	254	172	*62*	*19*
Control group	99,1 (99,0-99,1)	97,5 (97,3-97,6)	96,7 (96,5-96,8)	96,1 (96,0-96,3)	95,2 (94,9-95,4)	94,3 (94,0-94,7)
At-risk population	47.176	37.737	29.446	21.659	*11.055*	*3.604*

Table 4: Results comparing the survival rate at various follow-up.

As highlighted in Table 5, an investigation was therefore carried out into the underlying causes of prosthetic implant failure. From the registry, we collected both the incidence rate and the percentage distribution of the various etiologies underlying revision. The causes of revision included are aseptic loosening, septic loosening, pain without signs of loosening, implant dislocation, periprosthetic fractures, implant instability, polyethylene insert wear, and joint stiffness. The group affected by Parkinson's disease shows an increased risk of septic loosening and implant dislocations, whereas for the other etiologies the frequency is similar between the two groups.

Cause of implant failure	**Control Group**			**PD Group**		
	Incidence	**%**	**Percentage distribution**	**Incidence**	**%**	**Percentage distribution**
Aseptic loosening	490/52.022	0,9	26,9	12/551	2,2	26,1
Septic loosening	460/52.022	0,9	25,2	16/551	2,9	34,8
Pain w/out loosening	186/52.022	0,4	10,2	3/551	0,5	6,5
Tibial aseptic loosening	166/52.022	0,3	9,1	4/551	0,7	8,7
Cause not reported	205/52.022	0,4	11,2	3/551	0,5	6,5
Other	63/52.022	0,1	3,5	4/551	0,7	8,7
Implant dislocation	57/52.022	0,1	3,1	3/551	0,5	6,5

Periprosthetic fracture	43/52.022	0,1	2,4	1/551	0,2	2,2
Implant instability	42/52.022	0,1	2,3	-	-	-
Polyethylene wear	35/52.022	0,1	1,9	-	-	-
Femoral aseptic loosening	33/52.022	0,1	1,8	-	-	-
Joint stiffness	28/52.022	0,1	1,5	-	-	-
Implant rupture	15/52.022	0,03	0,8	-	-	-
Total	1.823/52.022	3,5	100,0	46/551	8,3	100,0

Table 5: Causes of implant failure and their respective incidence and percentage distribution. The causes are reported in order based on their incidence in the control group

Finally, a Cox multivariate analysis was performed to identify independent variables that may influence the endpoint, in this case, implant revision. The Cox multivariate analysis was conducted on four independent variables: gender, age at the time of surgery, diagnosis of Parkinson's disease, and implant design. The proportionality of risk was assessed using the Schoenfeld residuals method. All four variables included in the model were found to be statistically significant, namely age at surgery ($p<0.0001$), gender ($p<0.0001$), diagnosis of PD ($p=0.0348$), and implant design ($p<0.0001$), with the following hazard ratios (HR):

- HR Parkinson group vs control group = 2.7 (95% CI 2.1–3.7). This means that patients with the diagnosis have a 2.7-fold higher risk compared to patients in the control group, considering the same age and gender.
- HR age ≤ 60 years vs age > 60 years = 2.2 (95% CI 1.9–2.5). This indicates that patients under 60 years of age have a 2.2-fold higher risk, all other factors being equal.
- HR gender M/F = 1.3 (95% CI 1.1–1.4). In other words, male patients have a higher risk, specifically 1.3 times greater, considering the same age and diagnosis.
- HR implant design (constrained implants vs unconstrained implants) = 1.7 (95% CI 1.3–2.1). This means that patients with constrained implants (semi-constrained or rotating hinge implants) have a 1.7 times higher risk, considering the same age and gender, compared to patients with unconstrained implant designs.

Extension to Other Joints

The natural progression of this study is represented by the extension of investigations carried out to other joints. The hip is undoubtedly the joint of greatest interest. Hip replacement is one of the most successful orthopaedic procedures, to the extent that it has been described as the operation of the century, thanks to the excellent clinical and survival outcomes it has demonstrated. This success has inevitably led to a progressive expansion of surgical indications to cover increasingly complex conditions. Among these, neurological disorders—and Parkinson's disease in particular—are recognized risk factors for increased complications following hip replacement surgery.

The typical symptomatology of Parkinson's disease has an even greater impact on the hip than that identified at the knee. Typically, a patient with Parkinson's experiences sagittal imbalance of the spine, which is compensated by flexion of the hip and, to a lesser extent, the knee, together with retroversion of the pelvis. This postural alteration, combined with bradykinesia, tremors, and muscular weakness, leads to early development of osteoarthritic degeneration and is associated with an increased risk of falls and consequently fractures of the femoral neck. The literature also presents data indicating that patients undergoing hip replacement surgery who are affected by Parkinson's disease show a higher rate of major complications, particularly dislocations, periprosthetic fractures, and aseptic loosening.

In a similar manner to the approach used for the knee, a study was conducted using data from the RIPO (Orthopaedic Prosthesis Implant Registry) of the Emilia-Romagna region. This made it possible to identify patients who underwent hip replacement surgery in the region between 01/01/2003 and 31/12/2019. To identify the number of patients affected by Parkinson's disease, the same criteria used for the knee were applied: specifically, at least one hospitalization with a primary or secondary diagnosis of Parkinson's disease, identified by ICD-9 codes 332.0, 332.1, 333.0, or 781 prior to the hip replacement, and at least two pharmaceutical prescriptions identified with the ATC code N04. Again, patients with a diagnosis of Parkinson's following surgery were excluded.

Of the 83,181 hip replacement procedures performed during the period of interest, 913 were identified as being carried out on patients with Parkinson's disease. The control group was created using propensity score matching at a ratio of 1:2, thus bringing the total number of implants considered to 2,739. No differences in age or gender were observed between the two groups, with females being more represented (59.6%). There were no differences between the groups regarding the type of fixation (cemented, uncemented, hybrid) (p=1.000). No differences were found (p=0.998) in the implants used (standard vs dual mobility). The difference in joint pairing was not statistically significant between the two groups (p=0.275). The most commonly used pairing in both the Parkinson's group and the control group was ceramic-on-ceramic, with 26.5% (242) and 31.5% (576) respectively. However, a difference was found in the diagnosis leading to hip replacement between the two groups (p<0.001). In both groups, primary coxarthrosis and fracture were the most common diagnoses, with 45.5% (414) and 43.9% (399) in the Parkinson's group, and 68.5% (1,247) and 19.7% (358) in the control group (Table 6).

	PD group, N = 913	Control group, N = 1,826	p-value
Age			0.789
Median (Iqr)	73 (68, 78)	73 (68, 78)	
Mean (Range)	72 (24, 92)	72 (26, 92)	
Age Groups			0.969
<40	6 (0.7)	10 (0.5)	
40-49	15 (1.6)	29 (1.6)	
50-59	61 (6.7)	119 (6.5)	
60-69	206 (22.6)	414 (22.7)	
70-79	474 (51.9)	928 (50.8)	
80+	151 (16.5)	326 (17.9)	
Age Groups			0.765
≤65	161 (17.6)	332 (18.2)	
>65	752 (82.4)	1,494 (81.8)	
Sex			>0.999
F	544 (59.6)	1,088 (59.6)	
M	369 (40.4)	738 (40.4)	
BMI			<0.001
Underweight	19 (2.5)	13 (0.9)	
Normal Weight	298 (38.9)	467 (30.7)	
Overweight	330 (43.0)	710 (46.6)	
Obese	120 (15.6)	333 (21.9)	
Unknown	146	303	
Prosthesis Fixation			>0.999
Uncemented	788 (86.3)	1,576 (86.3)	
Cemented/Hybrid	125 (13.7)	250 (13.7)	
Implant Component			0.998
DM	140 (15.3)	275 (15.1)	
Sc-≤28	228 (25.0)	456 (25.0)	
Sc-32	257 (28.1)	514 (28.1)	
Sc-≥36	288 (31.5)	581 (31.8)	
Articular Coupling			0.275
Ceramic Composite-Ceramic Composite	242 (26.5)	576 (31.5)	
Dual Mobility	140 (15.3)	275 (15.1)	
Composite Ceramic-Xlpe	140 (15.3)	263 (14.4)	
Metal-Polyethylene Standard	89 (9.7)	171 (9.4)	
Metal-Xlpe	93 (10.2)	131 (7.2)	
Alumina-Polyethylene Standard	41 (4.5)	94 (5.1)	
Alumina-Alumina	44 (4.8)	69 (3.8)	
Composite Ceramic-Xlpe + Vitamin E	35 (3.8)	71 (3.9)	
Metal-Metal	29 (3.2)	47 (2.6)	
Metal-Ceramic-Xlpe	19 (2.1)	38 (2.1)	
Composite Ceramic-Standard Polyethylene	14 (1.5)	30 (1.6)	
Other	10 (1.1)	27 (1.5)	
Alumina-Xlpe	9 (1.0)	15 (0.8)	
Alumina-Ceramic Composite	7 (0.8)	15 (0.8)	
Missing	1 (0.1)	4 (0.2)	
Diagnosis			<0.001
Primary Coxarthrosis	414 (45.5)	1,247 (68.5)	
Fractures And Their Outcomes	399 (43.9)	358 (19.7)	
Idiopathic Femoral Head Necrosis	45 (5.0)	93 (5.1)	
Outcomes Of Congenital Pathologies	33 (3.6)	98 (5.4)	
Other	10 (1.1)	17 (0.9)	

Rheumatic Arthritis	8 (0.9)	7 (0.4)	
Unknown	4	6	

Table 6: Descriptive analysis of the two study groups

At 5 years of follow-up, survival was 96.0% in the control group and 95.0% in the group with Parkinson's disease. At 10 years, the survival rates were 91.8% and 93.4%, respectively. At 15 years, survival was 89.8% in the control group and 92.5% in the Parkinson's group. The log-rank test comparing the two survival curves did not show any statistically significant differences between the groups (p = 0.744) (Figure 5).

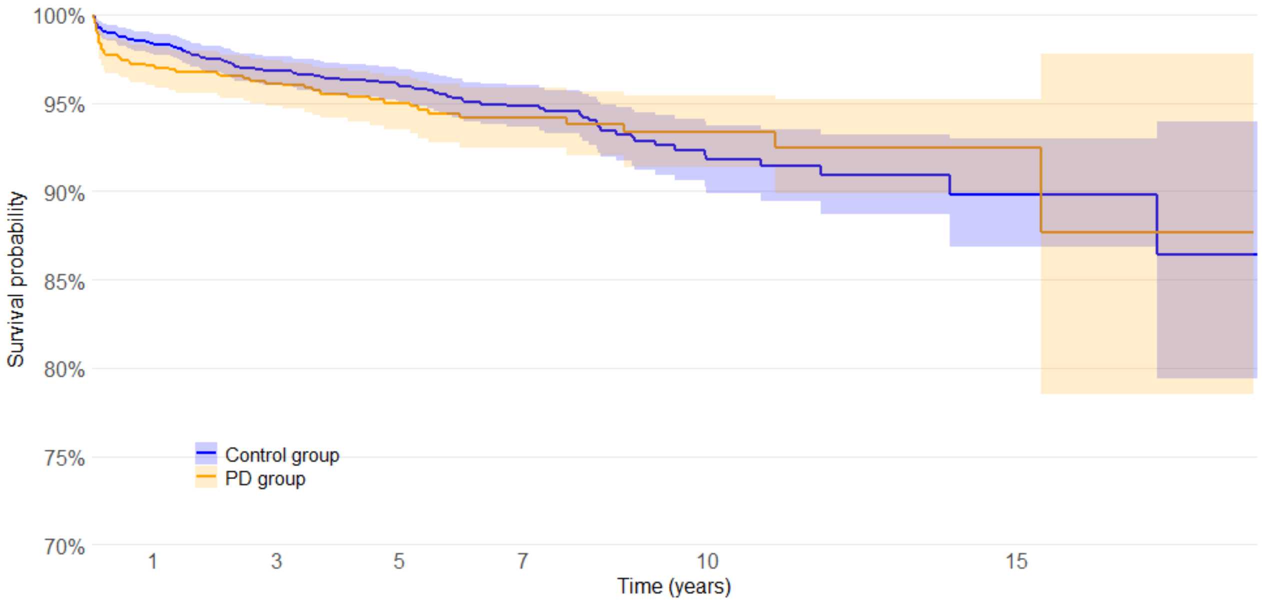

Figure 5: The Kaplan-Meier curves did not show any significant differences between the group with Parkinson's disease (yellow line) and the control group (blue line).

All causes leading to prosthetic failure were evaluated, and the overall incidence of prosthetic failure requiring revision surgery (removal or replacement of components) for any reason was found to be comparable between the groups: 5.3% (97 cases) in the control group versus 5.4% (49 cases) in the Parkinson's group.

When analyzing the individual causes of failure, we observed that in the control group, aseptic loosening accounted for 28 cases (1.5% of the population; 28.9% of all failures), whereas in the Parkinson's group there were 12 cases (1.3%; 24.5%). Instability or dislocation was seen in 17 patients (0.9%; 17.5%) in the control group and in 10 patients (1.1%; 20.4%) in the Parkinson's group. Periprosthetic fractures occurred in 19 patients in the control group (1.0%; 19.6%) and in 12 patients with Parkinson's (1.3%; 24.5%). Other less frequent causes included prosthesis breakage (0.4% vs 0.1%), septic loosening (0.4% vs 0.4%), and polyethylene wear

(0.1% vs 0.1%). The Parkinson's and control groups were analyzed and compared, without showing significant differences in terms of aseptic loosening (log-rank p=0.761), instability (log-rank p=0.634), and periprosthetic fracture (log-rank p=0.431) (Table 7).

Cause of Failure	**Control Group (N = 1,826)**			**PD Group (N = 913)**		
	N	Incidence (%)	% of Failures	N	Incidence (%)	% of Failures
Aseptic loosening	28	1.5	28.9	12	1.3	24.5
Instability/Dislocation	17	0.9	17.5	10	1.1	20.4
Periprosthetic fracture	19	1.0	19.6	12	1.3	24.5
Unknown	9	0.5	9.3	4	0.4	8.2
Prosthesis breakage	8	0.4	8.2	1	0.1	2.0
Septic loosening	7	0.4	7.2	4	0.4	8.2
Other	6	0.3	6.2	5	0.5	10.2
Polyethylene wear	2	0.1	2.1	1	0.1	2.0
Pain without loosening	1	0.1	1.0	–	0.0	0.0
Total	97	5.3	100.0	49	5.4	100.0

Table 7: Causes of failure in the control group and the Parkinson's group

The two groups were comparable in terms of age, sex, type of fixation, and implant model. The BMI distribution showed significant differences, with a higher prevalence of obesity in the control group (21.9% vs 15.6%) and a higher prevalence of underweight in the PD group (2.5% vs 0.9%). Within 24 months, survival was slightly lower in PD patients (95.0%) compared to controls (97.8%), with a statistically significant difference (p = 0.034). During this period, failures were more frequently due to periprosthetic fractures (2.0% in PD vs 0.8% in controls). Finally, the overall 5-year survival of patients was lower in PD (71.2%) compared to controls (84.7%), with a significant difference (log-rank p < 0.001).

Biomechanical Analysis[15–18]

The biomechanical analysis carried out using the parameters described in the Materials and Methods section did not reveal any significant differences in joint reaction forces between a patient with Parkinson's disease and a control patient undergoing knee prosthesis replacement. The results obtained from computer simulation, based on a validated biomechanical model, showed trends that were almost identical to those observed in the control subject, suggesting a substantial similarity between the two joint load profiles.

It is, however, important to emphasize that these outcomes may be influenced by numerous factors, foremost among which is the biomechanical model used for the simulation. As reported by Curreli et al., although the various models described in the literature tend to provide a fairly consistent representation of joint reaction forces, discrepancies remain both in terms of the magnitude of the forces and their spatial distribution (Figures 6–7). To date, there are no unequivocal indications in the literature regarding the superiority of one model over another, and this constitutes a potential source of bias in the interpretation of results.

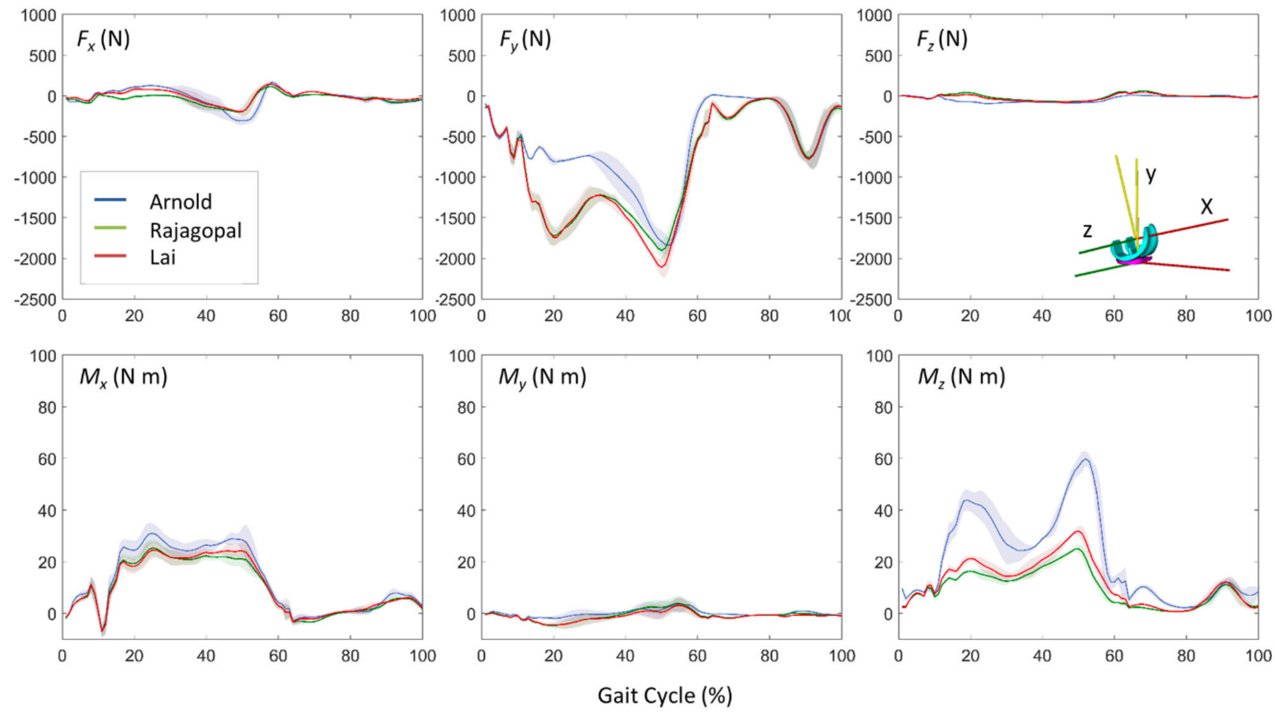

Figure 6: Graphs taken from Curreli et al. Representation of the forces and moments acting on the tibial insert. The three distinct lines highlight three different biomechanical models (Arnold, Rajagopal, and Lai): among the new generation models, there are few differences that can be identified.

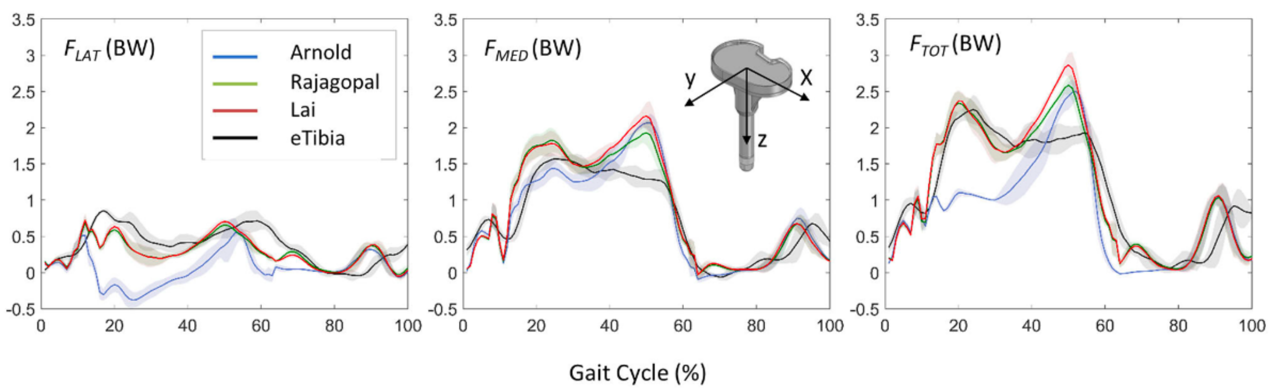

Figure 7: Graphs taken from Curreli et al. The forces predicted by the models do not differ significantly from those measured in vivo using the eTibia device.

An additional critical aspect concerns the representation of the patient with Parkinson's disease. This pathological condition, in fact, is characterized by considerable clinical heterogeneity, both in terms of the types of symptoms (tremor, rigidity, bradykinesia, postural instability) and in terms of severity and progression. Even within the same patient, symptoms may show marked variability depending on the context and the level of attention devoted to performing a particular action. The literature has demonstrated that the simultaneous execution of a cognitive and a motor task—known as dual tasking—leads to a significant worsening of motor performance in Parkinson's patients. In such circumstances, walking tends to become slower, with shorter steps and greater variability in the locomotor pattern, resulting in increased energy expenditure. Furthermore, the real impact of Parkinson's disease on the forces generated at the joints remains to be quantified. The work of Viceconti et al. in 2021 used biomechanical models to highlight how suboptimal neuromuscular control may be associated with increased polyethylene wear in knee prostheses. To simulate the suboptimal control typical of neuromuscular conditions, an uncontrolled manifold of 10% was used: using these parameters, Viceconti et al. showed that reducing neuromuscular control leads to increased polyethylene wear (Figures 8–9).

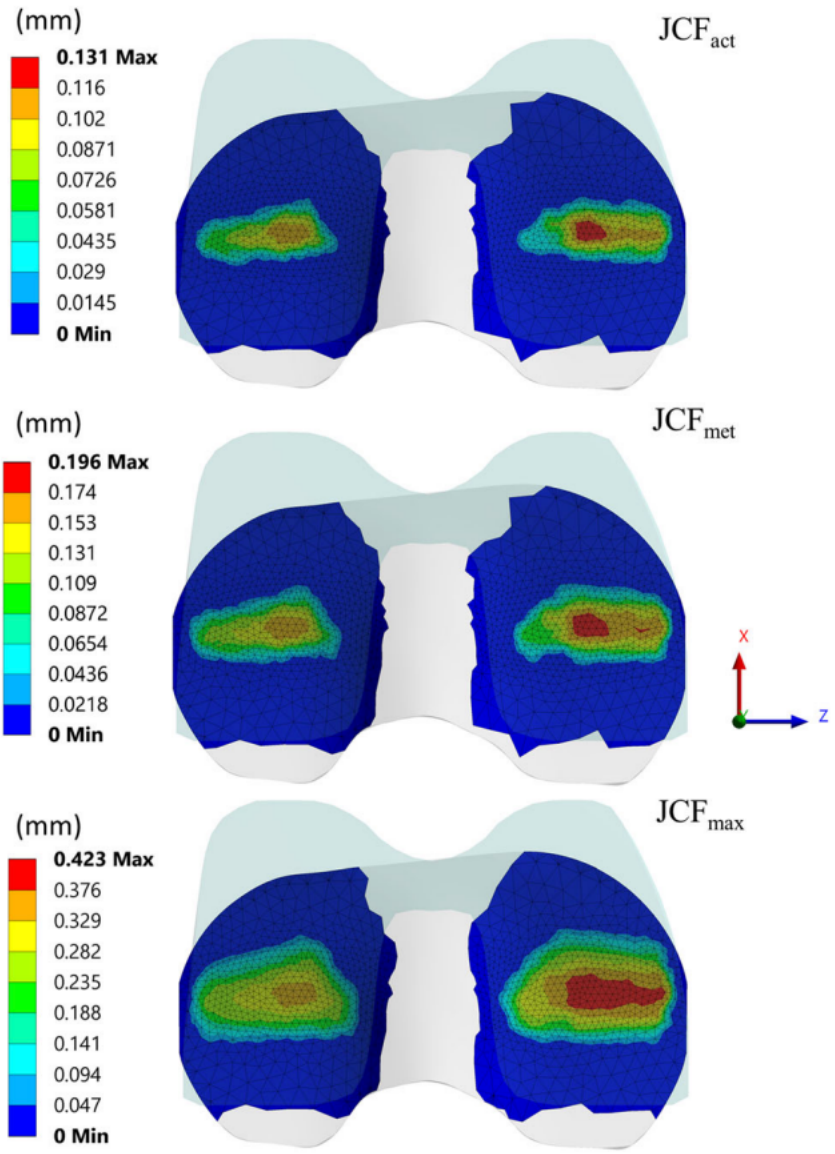

Figure 8: Figures taken from Viceconti et al. Maps of polyethylene wear after 3 million loading cycles. JCFact represents the simulation with optimal neuromuscular control, JCFmet represents the simulation with suboptimal neuromuscular control, while JCFmax represents the maximum workload (worst case scenario).

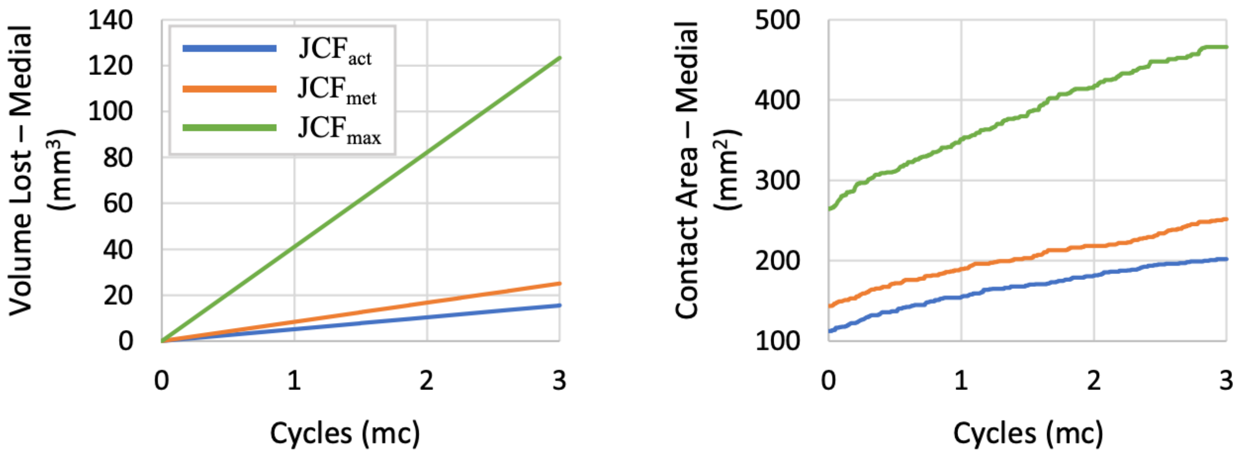

Figure 9: Figures taken from Viceconti et al. On the right, a depiction of the volume of

polyethylene lost at the medial tibial plateau, while on the left, an illustration of the lost contact area.

Although these results suggest that suboptimal neuromuscular control may play a role in increased polyethylene wear and therefore prosthetic failure, it is not clearly defined whether this simulation can be considered representative of a patient with Parkinson's disease. In fact, although it is established that suboptimal muscular control causes increased energy expenditure for a Parkinson's patient, muscle strength appears to be symmetrically reduced in both flexors and extensors of the lower limb. In particular, the study by Romanato et al. highlighted that there are no significant differences between the moments of force generated in a normal patient and those in a patient with Parkinson's disease (Figure 10).

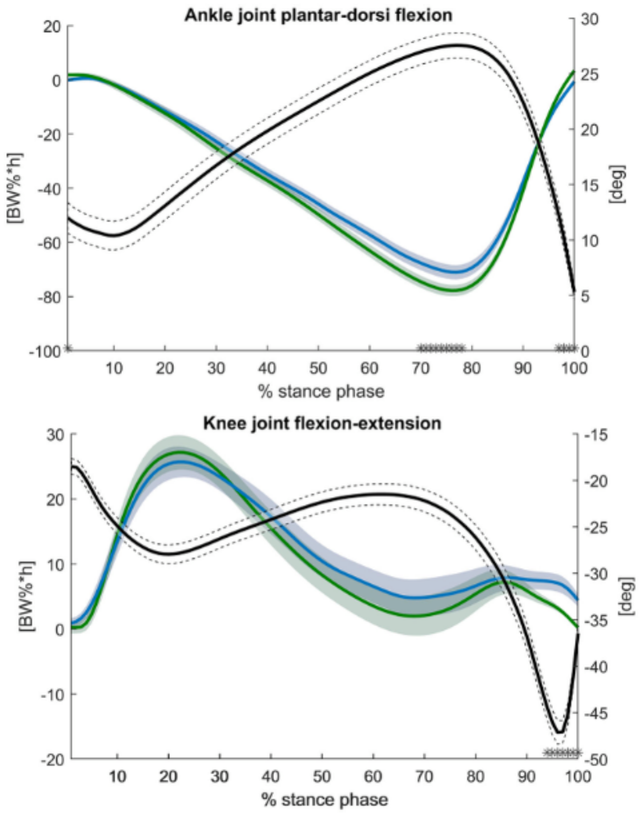

Figure 10: Graphs taken from Romanato et al. The green lines represent the moments of force generated in normal patients, while the blue lines represent Parkinson’s patients.

The authors of the study delved further into the details, analyzing how this difference is reflected in each individual muscle group (Figure 11). In doing so, differences between the two groups become apparent; however, overall, a reduction in the moments of force in Parkinson's patients is observed (which translates into a decrease in the forces developed at the prosthetic level).

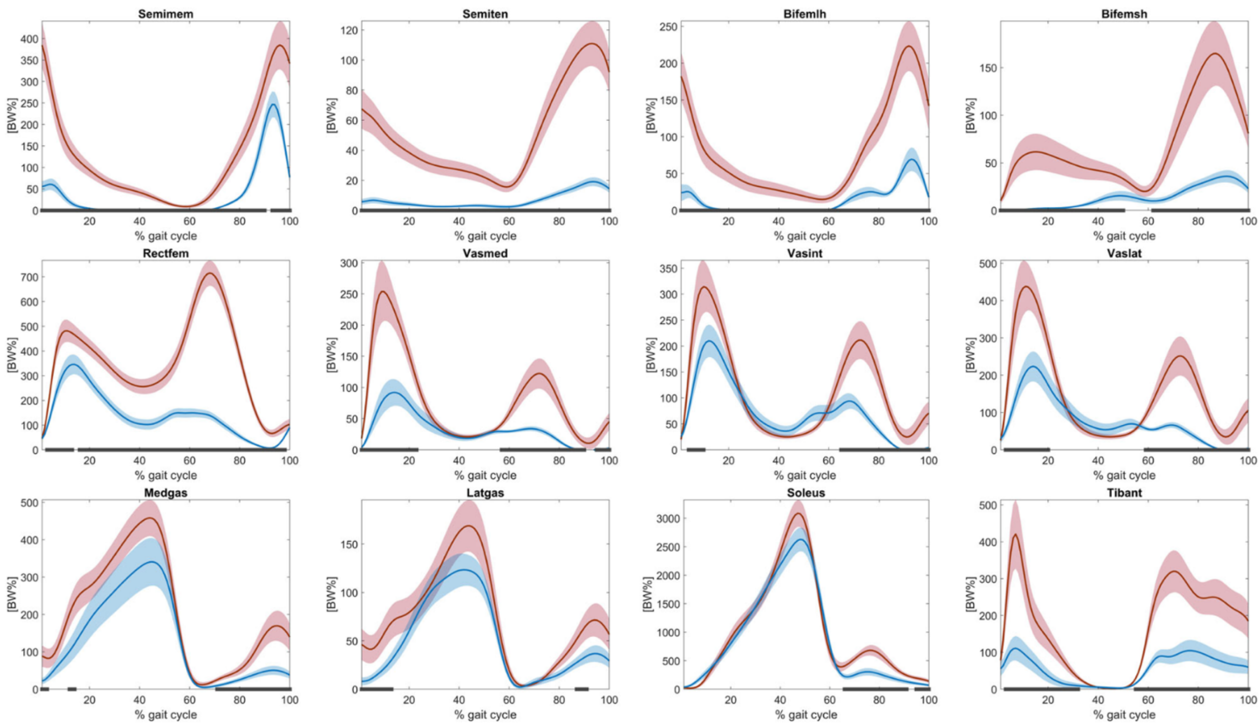

Figure 11: Graphs taken from Romanato et al. The blue lines represent modelled Parkinson's patients, for whom a widespread reduction in the moments of force across all muscle groups of the lower limb is evident.

Furthermore, quantifying the impact of dual tasking on joint function represents a complex challenge, especially within the field of computational modelling. Every simulation should, in fact, be considered not only as the representation of a single individual but as a new experimental scenario, comparable to modelling a different patient. As a result, a simplified model is unable to capture the complexity and variability that characterize Parkinson's disease in its entirety. This methodological limitation highlights the need to develop more sophisticated models, capable of integrating not only static biomechanical parameters but also dynamic factors related to attention, intra-individual symptom variability, and the interference of concurrent tasks.

Patients suffering from Parkinson's disease also present another important variable: pharmacological therapy. The pharmacological management of Parkinson's disease aims to correct dopamine deficiency at the striatal level, in order to improve motor symptoms and the patient's quality of life. The gold standard therapy is levodopa, a precursor of dopamine which, when administered in combination with peripheral decarboxylase inhibitors (such as carbidopa or benserazide), is able to cross the blood-brain barrier and restore neurotransmitter levels. Alongside levodopa, the therapeutic arsenal includes other classes of drugs, such as dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, and catechol-Omethyltransferase (COMT) inhibitors, each with specific mechanisms of action and efficacy profiles. However, the crucial aspect that dominates therapeutic strategy is extreme interindividual variability, manifesting both in the choice of initial treatment and in the long-term clinical response. In fact, there is no universally valid therapy; the decision regarding which drug to use and at what dosage depends on a careful assessment of factors such as the patient's age, the stage and severity of the disease, the prevailing symptom profile (tremor-dominant versus akinetic-rigid), and the presence of comorbidities. Consequently, individual responses are equally variable: while some patients achieve excellent and prolonged symptom control with monotherapy, others experience a suboptimal response or develop disabling motor complications early, such as "on-off" fluctuations and levodopa-induced dyskinesias. Such heterogeneity demands a "tailored" therapeutic approach, dynamic and constantly adapted according to the individual patient's clinical evolution. However, the variability in therapy and response makes it even more challenging to accurately model a patient. As highlighted by the study by Shida et al. (Figure 12), the variability of ground reaction forces between Parkinson's patients on therapy and those not on therapy is evident across all planes of space.

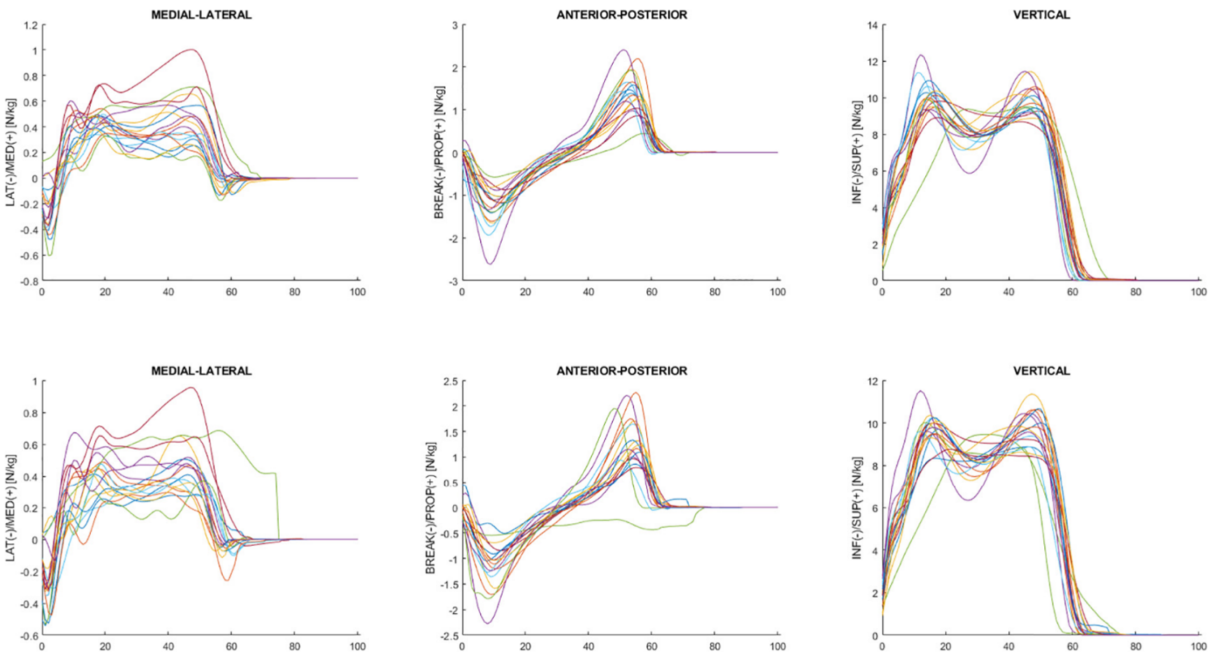

Figure 12: Graphs taken from Shida et al. There is evident inter-individual variability between subjects who are on therapy (upper graphs) and those who are not (lower graphs).

The simulation using computerized models of the bone–prosthesis interface and the ways in which micromovements can influence it remains an ever-evolving field of research, rich in ideas and developmental prospects. In the specific context of knee prosthetics, this issue becomes even more pronounced due to the widespread use of bone cement in most implants. The thickness, quality, and intrinsic properties of the cement are factors that significantly affect the behaviour of the prosthetic interface, especially in response to altered or repetitive mechanical stimuli. Thus, it is essential to consider how the different characteristics of the cement, together with the patterns of joint loading and the patient's clinical conditions, can lead to varied outcomes in terms of implant stability and longevity.

Finally, and probably representing a significant weakness of computerized biomechanical models, these models are not designed to account for abnormal lower limb alignments and/or different types of prosthetic component alignment. The alignment of the lower limb crucially determines the position of the load axis of the lower limb, and even minimal variations can be responsible for important changes in loading profiles and, consequently, the ground reaction forces of prosthetic implants. To date, much of the literature discusses the potential advantages and disadvantages of particular prosthetic and overall limb alignments, as well as their role in clinical and functional outcomes following knee replacement. However, from a biomechanical perspective, there are no studies that consider how such variations may affect the biomechanics of the joint.

Despite these limitations, this biomechanical analysis allows for a critical review of the results obtained from registry studies. In particular, the similarity of outcomes between a normal subject and a patient with Parkinson's disease may justify why there is no observed increase in aseptic loosening within the Parkinson's population—a finding that could be interpreted as surprising.

Discussion[6,8,19–27]

The results of the retrospective study conducted on the population of the Emilia-Romagna Region represent a relevant and original contribution to the understanding of the impact of neurodegenerative comorbidities, particularly Parkinson's disease (PD), on the survival of knee and hip prosthetic implants.

Interpretation of the Results

The epidemiological analysis highlighted that PD patients undergoing knee replacement present a significantly higher risk of revision compared to the control population, with a hazard ratio of 2.7 (95% CI 2.1–3.7). This finding, in line with some evidence from the international literature, underlines the need for more careful preoperative assessment and personalized postoperative management for this category of patients.

Examining the details of the causes of failure reveals a peculiar picture. The increased risk is not due, as might be assumed, to early mechanical failure of the implant (aseptic loosening), whose incidence was found to be similar in both groups. The computerized biomechanical analysis supports this observation, showing no substantial differences in joint loading between the model of a healthy patient and that of a patient with PD. This suggests that, in simulated conditions, the disease does not alter knee kinematics in a way that would overload the implant. The true driver of the higher revision rate seems to reside in two specific causes: septic loosening (periprosthetic infections) and implant dislocations. PD patients present greater systemic fragility, sarcopenia, and reduced ability to counteract infections—factors which can explain the increased risk of infection. Postural instability, rigidity, and bradykinesia, key symptoms of PD, instead increase the risk of falls and uncoordinated movements, which can lead to implant dislocations, especially in a biomechanically complex joint such as the prosthetic knee.

Extending the study to hip prosthetics showed partially different results: no significant differences in the revision rate emerged between PD patients and controls, although the former showed a higher incidence of early complications (periprosthetic fractures) within 24 months. This finding can be interpreted in light of the different biomechanics of the hip compared to the knee and the greater vulnerability of Parkinson's patients to falls, which are a known risk factor for femoral neck fractures.

Study Limitations

Despite the robustness of the cohort design and the large sample analyzed, the study presents some methodological limitations worth discussing:

- Retrospective nature and sources of bias: The use of registry data and administrative databases, although allowing analysis of large populations, exposes the study to possible selection bias and classification errors. For example, the diagnosis of PD was identified through ICD-9 codes and pharmaceutical prescriptions, criteria that may not capture all the clinical nuances of the disease or may exclude patients with late diagnoses.

- Lack of detailed clinical data: The RIPO registry does not provide detailed information on the stage of Parkinson’s disease, the severity of motor symptoms, the presence of other comorbidities (e.g., dementia, cardiovascular disorders), or the patient’s level of functional independence. These factors can significantly influence the risk of complications and revision but were not included in the multivariate analysis.
- Limited follow-up and data loss: Although the average follow-up is around five years for both knee and hip, patient loss to follow-up (e.g., due to transfers out of the region) may have influenced the estimate of implant survival. Furthermore, high mortality rates in elderly PD patients may have masked the actual rate of prosthetic failure.
- Limited follow-up and data loss: Although the average follow-up is around five years for both knee and hip, patient loss to follow-up (e.g., due to transfers out of the region) may have influenced the estimate of implant survival. Furthermore, high mortality rates in elderly PD patients may have masked the actual rate of prosthetic failure.
- Generalization of the results: The study was conducted on an Italian regional population with specific demographic characteristics and access to care. The generalizability of the results to other populations, with different health systems or different prevalences of comorbidities, may be limited.

Future Perspectives for Treatment

In light of the results obtained and the limitations highlighted, some future research and treatment perspectives emerge that could improve the management of patients with neurodegenerative comorbidities undergoing prosthetic replacement:

- Multidisciplinary approach: The management of a Parkinson’s patient candidate for joint prosthesis should involve a multidisciplinary team comprising orthopaedic surgeons, neurologists, physiatrists, and physiotherapists. Optimizing pharmacological therapy, assessing postural stability, and planning a personalized rehabilitation pathway can reduce the risk of complications and improve functional outcomes.
- Selection and customization of the implant: The study’s results suggest that implant design (constrained vs unconstrained) affects the risk of revision. Greater attention to the choice of prosthesis type, considering residual joint stability and the patient’s muscular conditions, could reduce the risk of dislocations and loosening.

- Prevention of infections and falls: The increased risk of septic loosening in PD patients requires strict antibiotic prophylaxis and intensive postoperative monitoring. In addition, targeted interventions for fall prevention (e.g., exercise programs, environmental adaptations, monitoring of osteoporosis risk) are fundamental to reducing traumatic complications.
- Development of advanced predictive models: The creation of more sophisticated biomechanical and statistical models, capable of integrating clinical data, imaging, functional parameters, and cognitive variables, could allow for more accurate prediction of prosthetic failure risk in patients with neurodegenerative comorbidities. The use of artificial intelligence and machine learning technologies is a promising prospect in this field.
- Extension of research to other conditions and joints: The study highlighted the need to analyze the impact of other neurodegenerative conditions (e.g., Alzheimer's dementia, multiple sclerosis) and to extend research to other joints (shoulder, ankle), in order to outline specific treatment strategies for each patient subgroup.
- Assessment of quality of life and functional outcomes: Beyond implant survival, it is essential to evaluate the impact of prosthetic replacement on quality of life, autonomy, and social participation of the patient. Prospective studies integrating measures of functional outcome and patient satisfaction could provide more complete information for personalizing treatment.

Conclusions

In conclusion, this study clearly demonstrates that Parkinson's disease is an independent and significant risk factor for knee prosthesis revision, with an incidence nearly tripled compared to the general population. This risk is not primarily linked to mechanical failure due to overload, but rather to increased vulnerability to periprosthetic infections and dislocations—complications directly related to systemic fragility and neuromuscular deficits induced by the disease.

Conversely, the impact of Parkinson's disease on long-term hip prosthesis survival appears less marked, although a higher risk of periprosthetic fractures emerges in the short postoperative period, highlighting how postural instability and fall risk are the main threat to this joint.

These results emphasize the need to move beyond a “one-size-fits-all” approach. The patient with Parkinson’s disease who is a candidate for arthroplasty should be considered high-risk and require thorough preoperative assessment, personalized surgical planning (also considering higher constraint implants for the knee), and a rehabilitation pathway aimed at minimizing the specific risks of the disease. The future of prosthetics in these complex patients lies in an integrated and multidisciplinary approach, aimed at improving not only implant survival but also overall quality of life.

References

1. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. the framingham osteoarthritis study. *Arthritis & Rheumatism*. 1987;30(8):914-918. doi:10.1002/art.1780300811

2. MacDessi SJ, Griffiths-Jones W, Harris IA, Bellemans J, Chen DB. Coronal Plane Alignment of the Knee (CPAK) classification. *Bone Joint J*. 2021;103-B(2):329-337. doi:10.1302/0301-620X.103B2.BJJ-2020-1050.R1

3. Dubin JA, Bains SS, Hameed D, et al. Projected volume of primary total joint arthroplasty in the USA from 2019 to 2060. *Eur J Orthop Surg Traumatol*. 2024;34(5):2663-2670. doi:10.1007/s00590-024-03953-3

4. Yoon JR, Yoon TH, Lee SH. The effect of Parkinson's disease on total knee arthroplasty: a systematic review and meta-analysis. *Knee Surg Relat Res*. 2023;35(1):6. doi:10.1186/s43019-023-00179-1

5. Wong EH, Oh LJ, Parker DA. Outcomes of Primary Total Knee Arthroplasty in Patients With Parkinson's Disease. *J Arthroplasty*. 2018;33(6):1745-1748. doi:10.1016/j.arth.2018.02.028

6. Rondon AJ, Tan TL, Schlitt PK, Greenky MR, Phillips JL, Purtill JJ. Total Joint Arthroplasty in Patients With Parkinson's Disease: Survivorship, Outcomes, and Reasons for Failure. *The Journal of Arthroplasty*. 2018;33(4):1028-1032. doi:10.1016/j.arth.2017.11.017

7. Ashraf M, Priyavadhana S, Sambandam SN, Mounasamy V, Sharma OP. Total Knee Arthroplasty In Patients With Parkinson's Disease- A Critical Analysis of Available Evidence. *Open Orthop J*. 2017;11:1087-1093. doi:10.2174/1874325001711011087

8. Jämsen E, Puolakka T, Peltola M, Eskelinen A, Lehto MUK. Surgical outcomes of primary hip and knee replacements in patients with Parkinson's disease: a nationwide registry-based case-controlled study. *The Bone & Joint Journal*. 2014;96-B(4):486-491. doi:10.1302/0301-620X.96B4.33422

9. Macaulay W, Geller JA, Brown AR, Cote LJ, Kiernan HA. Total knee arthroplasty and Parkinson disease: enhancing outcomes and avoiding complications. *J Am Acad Orthop Surg*. 2010;18(11):687-694. doi:10.5435/00124635-201011000-00006

10. Bordelon YM, Fahn S. Gender differences in movement disorders. *Neurologic disease in women New York: Demos*. Published online 2006.

11. Dluzen DE, McDermott JL. Gender differences in neurotoxicity of the nigrostriatal dopaminergic system: implications for Parkinson's disease. *J Gend Specif Med*. 2000;3(6):36-42.

12. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity. *American Journal of Epidemiology*. 2003;157(11):1015-1022. doi:10.1093/aje/kwg068

13. Haaxma CA, Bloem BR, Borm GF, et al. Gender differences in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2007;78(8):819-824. doi:10.1136/jnnp.2006.103788

14. Taylor KSM, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2007;78(8):905-906. doi:10.1136/jnnp.2006.104695

15. Curreli C, Di Puccio F, Davico G, Modenese L, Viceconti M. Using Musculoskeletal Models to Estimate in vivo Total Knee Replacement Kinematics and Loads: Effect of Differences Between Models. *Front Bioeng Biotechnol*. 2021;9. doi:10.3389/fbioe.2021.703508

16. Viceconti M, Curreli C, Bottin F, Davico G. Effect of Suboptimal Neuromuscular Control on the Risk of Massive Wear in Total Knee Replacement. *Ann Biomed Eng*. 2021;49(12):3349-3355. doi:10.1007/s10439-021-02795-y

17. Romanato M, Volpe D, Guiotto A, Spolaor F, Sartori M, Sawacha Z. Electromyography-informed modeling for estimating muscle activation and force alterations in Parkinson's disease. *Computer Methods in Biomechanics and Biomedical Engineering*. 2022;25(1):14-26. doi:10.1080/10255842.2021.1925887

18. Shida TKF, Costa TM, de Oliveira CEN, et al. A public data set of walking full-body kinematics and kinetics in individuals with Parkinson's disease. *Front Neurosci*. 2023;17. doi:10.3389/fnins.2023.992585

19. Rong X, Dahal S, Luo ZY, Zhou K, Yao SY, Zhou ZK. Functional outcomes after total joint arthroplasty are related to the severity of Parkinson's disease: a mid-term follow-up. *J Orthop Surg Res*. 2019;14(1):396. doi:10.1186/s13018-019-1447-8

20. Montiel Terrón V, Vitoria M, Lamo de Espinosa Vázquez de Sola JM, Valentí Nin JR, Valentí Azcárate A. Do we really improve life quality after total knee arthroplasty in patients with Parkinson's disease? *Arch Orthop Trauma Surg*. 2021;141(2):313-319. doi:10.1007/s00402-020-03644-8

21. Ergin ÖN, Karademir G, Şahin K, Meriç E, Akgül T, Öztürk İ. Functional outcomes of total knee arthroplasty in patients with Parkinson's disease: A case control study. *J Orthop Sci*. 2020;25(3):487-491. doi:10.1016/j.jos.2019.06.003

22. Newman JM, Sodhi N, Wilhelm AB, et al. Parkinson's disease increases the risk of perioperative complications after total knee arthroplasty: a nationwide database study. *Knee Surg Sports Traumatol Arthrosc*. 2019;27(7):2189-2195. doi:10.1007/s00167-018-4970-y

23. Goh GS, Zeng GJ, Thever Y, et al. Unicompartmental knee arthroplasty in patients with Parkinson's disease. *Knee*. 2020;27(5):1325-1331. doi:10.1016/j.knee.2020.06.017

24. Marchand KB, Vakharia R, Sodhi N, et al. Impact of Parkinson's Disease on Complications, Readmission Rates, and Costs of Care following Primary Total Knee Arthroplasty. *J Knee Surg*. 2022;35(1):21-25. doi:10.1055/s-0040-1710546

25. Cheppalli NS, Senthil T, Sakthivelnathan V, Menedal A, Mounasamy V, Sambandam S. Complications During the Hospital Stay, Length of Stay, and Cost of Care in Parkinson Patients Undergoing Total Knee Arthroplasty: A Propensity Matched Database Study. *J Am Acad Orthop Surg Glob Res Rev*. 2022;6(7):e22.00121. doi:10.5435/JAAOSGlobal-D-22-00121

26. Kleiner JE, Gil JA, Eltorai AEM, Rubin LE, Daniels AH. Matched cohort analysis of peri-operative outcomes following total knee arthroplasty in patients with and without Parkinson's disease. *Knee*. 2019;26(4):876-880. doi:10.1016/j.knee.2019.05.003

27. Stefanini N, Di Martino A, Brunello M, et al. Sarcopenia: current state of knowledge and its implications in orthopaedics and traumatology for enhanced clinical strategies and patient outcomes. *Musculoskelet Surg*. Published online September 8, 2025. doi:10.1007/s12306-025-00923-8