THE UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL FIELD OF MEDICINE

THE OPTIMIZATION OF TIBIAL STEM EXTENSION USAGE IN TOTAL KNEE ARTHROPLASTY

PhD Thesis Summary

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Introduction

Total knee arthroplasty (TKA) is considered a last-resort solution for advanced knee osteoarthritis, and since the mid-19th century, the first prototypes of knee implants have appeared, and surgeons and scientists have constantly experimented various prosthetic designs and materials, with more or less success. Only after 1970, however, the phenomenon of total knee arthroplasty took off and prosthetic models similar to those still used today were finalized and used on an increasingly large scale.

Numerous practical protocols related to knee arthroplasty are developed and proposed annually by Orthopedic Societies. However, at the time of initiating this research study, there were controversies and no consensus had been reached regarding the addition of modular tibial extension stems in complex primary total knee prostheses. Moreover, there was no consensus regarding the specific primary difficult cases in which this extension rod would be indicated, as well as the choice of its appropriate dimensions. Meanwhile, in recent years, some generally applicable principles are beginning to take shape, but still a standardized protocol for their use could not be established.

The doctoral thesis is structured in two main parts, a general part and a personal contribution part.

The general part includes current concepts about the anatomy of the knee joint (Chapter 1), native knee axes, dislocations, imaging evaluation and surgical strategies for their reproduction (Chapter 2), current concepts about the types of knee prostheses used, but also the existing alternatives to primary total knee arthroplasty (Chapter 3). The last part deals in detail with knee arthroplasty surgery, with current surgical approaches, surgical techniques for complex primary cases, but also the complications of knee arthroplasty (Chapter 4).

The original part contains a chapter of personal contributions in which we conducted a clinical study on the medium-term evolution of cases of primary complex knee arthroplasty operated in the Orthopedic Clinic of the "Saint Pantelimon" Hospital (Chapter 5), a chapter in which we analyzed based on the finite element technique the behavior of the three-dimensional (3D) knee prosthesis model with and without tibial extension by the finite element technique (Chapter 6). This chapter contains the following important study directions: a subchapter in which we analyzed the behavior of the 3D model of the knee prosthesis without tibial extension

(6.3.1), another one in which the behavior of the 3D model with tibial extension is analyzed (6.3.2), then two subchapters in which the 3D model was analyzed subjected to varus and valgus loading forces at different angles with and without tibial extension (6.3.3 and 6.3.4), another subchapter in which we tested the fatigue resistance of the 3D model in the configuration with and without tibial extension (6.3.5), then the final conclusions and personal contributions chapter (Chapter 7).

The research project incorporates the interdisciplinarity between orthopedics, anatomy, statistics, data analysis, informatics, materials science and engineering, but also computer-aided design.

I. GENERAL PART

CHAPTER 1. General concepts of knee anatomy

The complex kinematics of the knee is dictated by the distinct regimes of motion that the CFM and CFL have relative to the tibia due to their different architecture. The CFL moves posteriorly on the tibia (posterior sliding) as a result of the change in radius of curvature, but the CFM remains mainly immobile during knee flexion due to its relatively uniform radius of curvature [17]. The distal femur externally rotates due to this more pronounced "posterior slip" of the CFL relative to the CFM (which remains mostly in place). During the first 15° of knee flexion, most of this external rotation occurs. This helps guide the trajectory of the patella as it engages in the trochlear groove of the femur at 15° of knee flexion, which is the critical point where the patella must be centrally positioned to avoid lateral dislocation or subluxation [15].

There is another reason why the posterior sliding of the femur relative to the tibia is important. This increases the final or maximum flexion angle of the knee. To achieve deep flexion (e.g. in squatting or kneeling movements), posterior sliding of the distal femur relative to the tibia is required to increase its posterior clearance prior to impact with the tibia. Without the posterior gliding motion, the posterior cortex of the femoral shaft will contact the tibia at an angle of 90° and this will be the maximum flexion angle [18].

CHAPTER 2. Imaging evaluation of the knee joint and its axes

Radiological evaluation

For an effective radiological evaluation of the knee for total knee arthroplasty, four types of radiographs are required:

- Antero-posterior X-ray while loading;
- Lateral X-ray;
- Axial tangential radiography of the patella;
- Long-leg standing X-ray.

Essential angles in the assessment of the knee joint

An essential angle is the one formed by the mechanical axes of the femur and the tibia, for the calculation of its value a special radiograph called a long-leg standing X-ray is required, which includes the entire lower limb in a single image taken in orthostatism. This is considered to be the gold standard in assessing knee alignment in the frontal plane and is called the "hip knee angle", also in Anglo-Saxon literature, or abbreviated HKA, and provides information on how the load is distributed at the knee joint [38][48][49].

The lateral distal femoral angle (LDFA) is formed between the mechanical axis of the femur and the distal femoral joint line (tangent at the lateral femoral condyle) and normally measures 87°±3°. Lower values may indicate a valgus deformity of femoral origin, while higher values, over 87°±3°, may suggest a femoral varus deformity.

The medial proximal tibial angle (MPTA) is formed between the tibial mechanical axis and the proximal tibial joint line. Contrary to LDFA, its values <87°±3° indicate varus of tibial origin, and >87°±3° tibial valgus.

In the degenerative joint disease, there are sometimes consistent changes in the thickness of the joint cartilage, changes in the bone structure and ligament balance so that all these axes will be modified in one way or another. From this situation were born several different philosophies that are still debated in total knee replacement surgery and to which we will refer next, two of which are the most popular, namely mechanical and kinematic alignment [51][52][53][48].

Surgical strategies for reproduction of knee axes in the frontal plane

Mechanical alignment

Freeman and Insall promoted mechanical alignment (MA) and established it as the standard of reference in knee arthroplasty [53]. The basic principle of mechanical alignment is to restore the normal mechanical axis of the knee [58]. Both the distal femur and proximal tibia are cut to be perpendicular (0°) to the mechanical axis. The goals were the following: the biomechanical advantage of equalizing the forces borne by the medial and lateral tibial condyle, but also the standardization of the surgical technique to be easily reproducible for all orthopedic surgeons, so that in the long term good clinical results and high durability of the implant [59]. However, this does not imply exact replication of the joint line between the tibia and femur, which ideally would be 3° tibial varus and 3° femoral valgus in the native knee.

Anatomical alignment

The anatomical alignment (AA) initiated by the pioneers Hungerford, Kenna, and Krackow [62] tries to restore the joint in its physiological inclination by making bone slices strictly respecting the slope of 3° of the tibia and 9° of the femur (3° of the inclination of the anterior joint of the mechanical axis and another 6° added from the inclination of the anatomical axis) [63]. Nowadays this angle can be deliberately incorporated into the design of the prosthesis.

Adjusted mechanical alignment

Adjusted mechanical alignment (AMA) which still does not have many followers, is based on the fact that some patients constitutionally present a varus knee deformity and proposes a limited correction through bone trenches of this deformity with a maximum value of 3°, leaving residual a misalignment of the knee. The promoters of this technique claim that it reduces the need for soft tissue intervention, increasing patient satisfaction [64][65].

Kinematic alignment

A newly emerging philosophy is kinematic alignment (CA), propagated by Howell and Hull [66], in which emphasis was placed on individualized surgical treatment of the patient. Practically, a very thorough assessment of the state of the articular cartilage imaging, by means of nuclear magnetic resonance (NMR), is necessary. In this way, the current wear of the cartilage due to the disease is determined and its thickness before the disease is estimated, thus planning the thickness of the bone slices that will be made intraoperatively. During the surgical intervention, it is checked by measuring the resected parts with a caliper whether the preoperative plan corresponds to the reality and adjustments of the slices can be made if necessary. Thus, an alignment identical to that before the condition is obtained, but also a ligament balance and joint biomechanics [52].

CHAPTER 3. General concepts regarding knee prostheses

Types of knee prostheses

Primary prostheses

A typical primary total knee arthroplasty (TKA) involves a cemented femoral component made of chromium-cobalt or other low-wear materials, a cemented tibial titanium component with a polyethylene insert and a polyethylene patella button (if which knee replacement is performed) [90].

In the development of total knee prostheses, two main design approaches have emerged, cruciate ligament-sacrificing prostheses and posterior cruciate ligament-preserving prostheses. Despite the fact that many researchers have compared the 2 designs, there is no consensus regarding the optimal prosthesis regarding patient satisfaction, function, pain relief, or complication rates [91][92][93][94].

Posteriorly stabilized total knee prosthesis

The objective achieved by posterior stabilized PTG (PS) is mechanical alignment, where the corresponding tibial and femoral segments are perpendicular to the mechanical axis [97]. It uses a guide cutout on the center of the femoral component and a polyethylene protrusion as a pivot on the back of the tibial component that provides guidance and stability, the two meshing with the movements of the knee for fluid movement. This pivot generally has a cylindrical or slightly conical shape, and during knee flexion it recreates the natural phenomenon of posterior sliding of the femur. This mechanism helps achieve deeper flexion unlike knee implants that only allow 90° of flexion [96].

Cruciate retaining total knee prosthesis

The posterior cruciate ligament-preserving knee prosthesis has a different structure than the previous one, without the central tibial pivot, using the posterior cruciate ligament as a stabilizer in flexion movements, but also a medial femoral condyle with a greater radius of curvature, just like the native femur.

This prosthetic model has the advantages of preserving a larger part of the femur, not requiring the central slice, but also preserving proprioception through the receptors that are at the level of the LIP [100]. Its disadvantages consist in the difficulty of swinging the knee in flexion-extension, but also the fact that over time the soft structures can lose their function and thus lead to instability [101].

Ultra congruent total knee prosthesis

It is a system sometimes known as "medially stabilized" TKA or "highly congruent". The stability in this case is not provided by the central polyethylene pivot, but is achieved by a recessed polyethylene insert, especially in the medial part, with high edges, called the medial pivot, which controls the kinematics and stability of the joint using its extremely articular shape conforms to the medial compartment of the tibia. The lateral part is groove-like in shape and allows the lateral femoral condyle to slide posteriorly during flexion. This implant model has been associated with satisfactory patient outcomes, particularly in the short and medium term [102].

Revision prostheses

Overstabilized total knee prosthesis

This type of prosthesis is used especially in revision surgeries of total knee arthroplasty but sometimes, rarely, also in primary arthroplasty [103]. It is known in the English literature as "Constrained Condylar Knee" (CCK) [104]. It addresses the lack of stability, especially in the frontal plane, but also rotationally, when the anatomical structures that should provide support to the knee no longer function effectively. The over stabilized PTG aims to solve this problem with a simple structural concept: it features a central pivot at the level of the tibial component, made of polyethylene, similar to that of the postero-stabilized prosthesis, but with some distinct changes

Hinge-type knee prosthesis

This type of prosthesis has the highest degree of constraint, so its two component parts, the femoral and the tibial, are connected to each other and allow movements only in the front plane of flexion and extension. Knowing that with the increase in the degree of constraint, the stress at the interface between bone and cement also increases, and taking into account the failure of the first prototypes of hinge-type prostheses, which date back to the 19th century [84], prostheses manufacturers contemporaries adapted the tibial component, excessively finishing its upper surface, on it allowing the polyethylene insert a slight rotation of a few degrees, a concept called rotating platform.

CHAPTER 4. Knee arthroplasty surgery

Surgical techniques for complex cases of primary knee arthroplasty

Genu Varus

The goal of the surgeon in this situation is to achieve a neutral mechanical axis of the knee ensuring that the total knee prosthesis (TKT) will function effectively and for a long period of time [169]. Patients affected by genu varum may experience asymmetric wear of the prosthesis due to changes in loading patterns.

For moderate varus deformities (10° - 20°), posteromedial corner or semimembranosus tendon release can be performed (especially if there is an associated flexion contracture). Finally, for very severe varus deformities (>20°), posterior cruciate ligament release, superficial LCM release, or pes anserinus [170] or even soleus muscle release can be performed. Some authors have proposed lengthening by the "pie-crust" technique, or serial incisions of the LCM [171].

Genu Valgus

Initially, the arcuate ligament and the posterolateral capsule are released with the scalpel, followed by sectioning with the scalpel following the "pie-crust" technique of the iliotibial tract, the lateral retinaculum, and the LCL, to a maximum depth of 1 cm in order not to injure the peroneal nerve [172]. The ligament balance is checked and the technique is continued until it becomes satisfactory. In the case of a severe, irreducible deformity, an extreme solution such as complete release of the medial structures may be necessary, either by dissection of them from the lateral femoral epicondyle, or by osteotomy of the lateral femoral epicondyle together with its attachments, solutions that may cause further rotational instability [170].

Genu Flexum

For mild deformities (<10°), hamstring tendon release and osteophyte removal are performed. For moderate deformities (10° - 20°), release of the gastrocnemius muscle (especially the medial head, only if it is contributing to the contracture) and posterior capsular release are performed. For severe deformities (>20°), in addition to the releases mentioned above, posterior cruciate ligament release or quadriceps release can be performed if they contribute to the flexion deformity [78][80].

Genu Recurvatum

The distal portion of the femur is minimal to achieve reduced extension space, and the femoral component should be chosen with a smaller anteroposterior dimension to increase flexion space. In addition, the posterior cruciate ligament should be thoroughly evaluated; if it is excessively loose, it will have to be sacrificed. Instead, a PS implant will be added to maintain balance and stability [177].

II. PERSONAL CONTRIBUTIONS

CHAPTER 5. Contributions regarding the mid-term clinical evolution of patients operated with knee prosthesis and tibial extension rod

Introduction

The objective of this study was to research the experience of the Orthopedic Clinic of the "Saint Pantelimon" Hospital in Bucharest in the use of tibial extension rods in difficult primary PTG and the mid-term analysis of the results from a clinical, statistical and radiological point of view. The evaluation included primary arthroplasties performed between 2013 and 2021, with the particularity of using modular tibial components with an attached intramedullary rod.

Therefore, we asked what is the benefit and survival rate of these primary PTGs with an extension rod and what are the causes leading to implant failure, but also the search for solutions for the clinical optimization of the use of these rods.

Materials and methods

Our indications for using a tibial stem extension in these difficult primary knee arthroplasty cases are: varus (>10° deviation from normal), valgus deformities (>10° deviation from normal), or Grade II according to the Ranawat classification [76], severe osteoporotic bone structure, autoimmune conditions such as rheumatoid arthritis with severely affected bone structure, severe osteoporosis, large bone defects of the tibial plateau, equivalent to AORI type T1 defect [211], osteonecrosis of the proximal tibia, corrective osteotomy proximal tibial deformity in the antecedents or tibial deformity with callus after a viciously consolidated fracture, or some cases of morbid obesity [212].

Patients were assessed using the 2012 update of the Knee Society Score (KSS) [216], downloaded from the organization's website [217]. This is a score with information from both the knee surgeon and the patient. It consists of a preoperative and a postoperative assessment version, as well as an optional short form, which we did not use [218][219][220][221][222].

Our usual standard has been to evaluate each patient preoperatively, and then postoperatively at one month, three months, six months, 12 months, and then at 1-2 years

The greatest improvement in the KSS Knee score occurred between its preoperative and 3-month values for both male and female patients, with a slightly higher value for females at all three assessments.

Similarly, the "Functional KSS" score improved significantly at 3 months and at the last assessment for both the operated left and right sides, although it was slightly higher on the right side. In addition, this score maintained the increasing trend relative to the diagnosis of Ostheoarthritis secondary to trauma, Rheumatoid Arthritis and Primary Ostheoarthritis, however with a slightly higher value for the diagnosis of Ostheoarthritis secondary to trauma.

Another component of the evaluation consisted of analyzing the patients' radiographs. We obtained anteroposterior and lateral radiographs with the patient supine, as well as standing axial radiographs with the limbs extended according to current practice, when possible, at each follow-up [223][224][225].

Conclusions

The most important conclusion from our study was that the primary prosthesis with tibial extension was able to successfully correct the deformities present preoperatively, as evidenced by the increase of the HKA angle from 171.1°±9.9° to 178.7°±2.6°, very close to the ideal of 180°[249], and in addition managed to restore the functional parameters of the knee, increasing knee flexion from a preoperative mean of 99.4°±15.7°, to a postoperative mean of 117.7°±16.4°.

The greatest increase in KSS scores, both knee and functional, was at the 3-month assessment compared to the last assessment, regardless of gender or pre-existing pathology.

According to this study we can support the idea that the use of an intramedullary extension in complicated primary PTGs can be beneficial in the medium term, with the possibility to study the effect in the longer term.

The limitations of this study were the following: a select patient population, a small number of patients that could have caused a sample interference, and the relatively short follow-up period. We did not compare the group with tibial extension in complicated primary PTG with those without tibial extension. We did not divide into different categories the patients with extensions of different sizes, this would require a very large number of patients, which was not available.

CHAPTER 6. Analysis of the behavior of the 3D knee prosthesis model with and without tibial extension by finite element technique

To support medical decision-making, we considered that a finite element analysis of the knee with knee prosthesis model in various situations found in medical practice would bring additional useful information.

We hypothesized that creating a virtual model and testing the behavior of the bone-implant assembly both in the version with attached tibial extension and in the version without extension can highlight the improvement of its stability in certain situations and a better distribution of stresses in critical points, thus increasing the duration of implant life.

In collaboration with members of the Materials Engineering Faculty of Valahia Târgoviște University, the real tibial bone was scanned and modeled in the Solidworks program (Dassault Systèmes Solidworks Corp., Vélizy, France), creating an external cortical bone layer with an increasing thickness of at 0.8 mm in the proximal area at 4 mm in the diaphyseal region, then an internal layer of cancellous bone with different mechanical properties.

The virtual model was studied in two concepts (study models): without tibial extension and with tibial extension to obtain results that highlight the mechanical stress behavior of the two models.

Several types of mechanicals analyze were performed for both virtual study models. Mechanical analyzes were differentiated according to the direction of force application and the number of force applications.

The analyzes performed were:

1. Axial force application (on the natural axis of the tibia) for both study models without and with tibial extension, coded A and B:

- A.a – model without tibial extension with ideal connection (considered without movements) between the assembly elements (tibial implant – polyethylene insert – femoral implant);

- A.b – model without tibial extension with real contact (considered with movements) between the assembly elements (tibial implant – polyethylene insert – femoral implant);

- B.a – model with tibial extension with ideal connection (considered without movements) between the assembly elements (tibial implant – polyethylene insert – femoral implant);

- B.b – tibial extension model with real contact (considered with movements) between the assembly elements (tibial implant – polyethylene insert – femoral implant).

The stresses developed between the tibia and the implant σvon Mises, the equivalent strains δech (mm), the strains on the vertical axis δy (mm), the safety factor FOS and the contact pressure were monitored.

2. The misaligned application of the force, in relation to the natural axis of the tibia, to simulate the varus and valgus position, respectively the situations in which a degree of misalignment remains, unresolved by the surgical intervention, or a degree of ligamentous instability which makes when walking, the weight of the body should be applied misaligned in varus or valgus.

This force was applied to both study models, without and with tibial extension, coded C and D:

- C.a – model without tibial extension, simulation of varus angular forces;
- C.b – model with tibial extension, simulation of varus angular forces;
- D.a – model without tibial extension, simulation of angular valgus forces;
- D.b – model with tibial extension, simulation of valgus angular forces.

The stresses developed between the tibia and the implant σvon Mises, the equivalent strains δech (mm), the strains on the vertical axis δy (mm), the safety factor FOS and the contact pressure were monitored.

3. Simulation of the phenomenon of fatigue at repeated demands, virtual model E.

The problem of prosthesis damage after a certain period of use was analyzed by virtual fatigue stress. The use of the prosthesis was simulated over a period of 2 years with an average number of 500 steps per day, leading to 360000 steps, i.e. 360000 stress cycles.

Models E.a without tibial extension and E.b with tibial extension were analyzed.

Conclusions of the finite element study

In the case of analyzes A.a and A.b, the following conclusions can be listed:

- for model A.a, maximum local stresses occur due to the very small contact between the cortical edge of the tibia and the tibial implant, these stresses, if there is an error in surgical technique and the tibial plateau is not positioned in contact with the cortical edge, then they will be transferred to the cancellous bone, a much less resistant bone, and failure of the arthroplasty will be inevitable

- the FOS safety factor, for model A.a, shows that, when the axial force is applied, the base and foot of the tibial implant cause dangerous tensions at the cancellous bone level;

- the safety factor shows better values on the leg of the tibial implant, but small at the level of the tibial extension, which confirms that the cortical bone, at the level of the medullary canal, is strongly stressed and confirms the pains reported by patients who have implants with long tibial extension, known in specialized literature under the name pain at the tip of the implant or "end of stem pain".

In the case of analyzes C and D, the following conclusions can be expressed:

- the off-center application of the force of 2500 N, the model without tibial extension (model C), under varus and valgus angles, caused higher stresses between the tibial implant plateau and the sectioned surface of the tibial bone, in the side where the force is applied and a relaxation in the side opposite to the application of force, a fact that can lead in practice to the phenomenon of "tibial liftoff" or "tibial liftoff" as it is known in the specialized literature and which means the detachment of the prosthesis from the underlying bone;

- also in model C, the leg of the tibial implant is subjected to higher stresses on the side opposite to the application of force and on the front side in both cases (varus/valgus). This shows that it is possible to degrade cancellous bone in contact with cement;

- in the case of the model with tibial extension (D), the lateral stresses given by the varus/valgus misalignment are taken over by the tibial extension, the stresses on the leg of the tibial implant decrease and are found at the contact between the tibial extension and the medullary canal;

The study of the virtual model E presents the following conclusions:

The problem of prosthesis damage after a certain period of use was analyzed by virtual fatigue stress. The use of the prosthesis was simulated over a period of 2 years with an average number of 500 steps per day, leading to 360000 steps, i.e. 360000 stress cycles.

Models E.a without tibial extension and E.b with tibial extension were analyzed:

- in the case of the model without tibial extension E.a, the damage appears from the first 360 steps and is local, so it can be attributed to the local breaks of the extremities of the sectioned surface of the tibial plateau;

- the percentage of destruction increases with the increase in the number of stresses (steps taken) and propagates to the tibial implant leg and to the polyethylene insert;

- the application of the tibial extension, model E.b, shows that the presence of the extension helps the tibial implant, the damage first appears at the level of the tibial extension and propagates, with the increase in the number of stress cycles, towards the foot of the tibial implant;

- in both analyzes (E.a and E.b), the analysis of the life cycles confirms the determinations of the destruction percentages.

CHAPTER 7. Final conclusions and personal contributions

In this thesis, a topic of current interest, still debated by the international orthopedic community, regarding the use of modular tibial extension rods in the primary knee prosthesis was addressed. Very often used in revision arthroplasty, intramedullary extension rods are not usually used in primary arthroplasty, and in most cases, there is no need for it. However, there are some cases where it can be useful. We tried to accept this challenge to study and find answers and solutions to optimize the use of this tibial extension, and automatically total knee arthroplasty. In this sense, the goal was both to find the right surgical cases in which this type of implant would be useful, but also some practical details that could lead to increasing the success rate of surgical interventions and thus increasing the life of the implants without the need for further interventions.

According to the results obtained in the clinical study, we can support the idea that in difficult cases of severe gonarthrosis of the knee, the use of a tibial extension can be beneficial.

Our results were consistent with similar studies in the international literature, suggesting that it is a favorable practice for good patient outcomes.

In order to facilitate the medical decision-making act, we carried out a study with finite elements in which we tried to look at the behavior of knee prostheses and the prosthetic knee joint from a different perspective, starting from some real but also hypothetical situations that we can face during and after knee replacement surgery. The goal was to find optimal solutions for the use of knee implants, but also to find practical methods for perfecting the surgical technique. In this endeavor, I found support at the Department of Anatomy of the Carol Davila University of Medicine and Pharmacy, Bucharest, but especially at the Valahia University in Târgoviște, Faculty of Materials Engineering.

An unachieved objective of finite element research was to find an optimal size of the tibial extension rod, thickness and length, adapted to the individual anatomy of the patients, or to find practical solutions for the optimal choice of the size of this rod. This study, consuming considerable resources, may be the object of future postdoctoral research directions, involving orthopedic surgery and mechanical engineering applied in the future context of the development of digital technologies and environments.

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LIST OF PUBLISHED SCIENTIFIC ARTICLES

1. Filip A.C., **Cuculici S.A.**, Cristea S., Filip V., Negrea A. D., Mihai S., and Pantu C. Tibial Stem Extension versus Standard Configuration in Total Knee Arthroplasty: A Biomechanical Assessment According to Bone Properties. *Medicina (Kaunas)*. 2022;58(5):634. Published 2022 May 2.

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2. **Cuculici S.A.**, Groșeanu F., and Cristea S. Tibial Stems in Primary Total Knee Arthroplasty: A literature Review. *Balneo and PRM Research Journal*. 2022;13(4):523 Published 2022 December 15.

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