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ASSESSMENT OF BONE MINERAL DENSITY AT THE BONE-IMPLANT INTERFACE AND JOINT TEMPERATURE IN PATIENTS UNDERGOING TOTAL KNEE ARTHROPLASTY

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ABSTRACT

The field of knee prosthetic surgery is constantly evolving, with the aim of improving patient satisfaction and increasing implant survival. Several innovations have been introduced in recent years regarding designs, alignments, soft tissue balancing and fixation techniques. However, in the field of materials, many aspects still must be evaluated. Indeed, common cobalt-chrome (CoCr) prostheses have tribological properties that differ widely from those of human bone, mainly in terms of stiffness and thermal conductivity. The high stiffness leads to an alteration in the transmission of loads on the bone, a phenomenon known as 'stress shielding', which in the long-term leads to slow and relentless periprosthetic bone resorption and eventually to implant loosening or periprosthetic fractures. The high thermal conductivity of metal, on the other hand, could cause discomfort perceived by the patients, who often report a feeling of increased heat at the operated knee or a different adaptation to the external temperature compared to the non-operated knee.

The need for innovations and alternatives is even more required due to the ageing of population undergoing total joint replacement and, at the same time, to the always earlier onset of Osteoarthritis, which requires end-stage procedures in relatively young patients.

The present PhD thesis aimed at investigating the impact of joint prostheses on periprosthetic bone remodeling and joint temperature trends, focusing on Total Knee Arthroplasty (TKA). The objectives of the thesis were developed in 4 aims: (I) Literature review about migration of the femoral component and clinical outcomes after TKA; (II) Systematic review about variations in periprosthetic Bone Mineral Density (BMD) after joint replacement examining different anatomical regions, fixation techniques, and implant design; (III) clinical study on the evaluation of bone mineral density at the interface with the femoral and tibial component in patients undergoing TKA; (IV) clinical study on the evaluation of knee surface temperature before and after TKA.

The first literature review focusing on the femoral component showed how an annual migration of 0.10 mm seems compatible with good long-term performance and good clinical and functional outcomes after TKA, whereas higher values leading to implant failure could be due to inadequate primary fixation and low mineral density.
The systematic review on periprosthetic BMD variation showed how it progressively decreases after total joint replacement. Moreover, the fixation technique and implant design influence the extent and pattern of this decline.
Considering this background, a clinical study using Dual X-ray Absorptiometry (DXA) to evaluate BMD after TKA was then initiated, setting up this technique for the first time at the Rizzoli Orthopedic Institute. The preliminary results from the first patients implanted with CoCr prostheses seem promising and will be presented in this thesis.
Lastly, the analysis of surface knee temperature in patients underwent TKA confirmed their subjective feeling. Indeed, temperature after surgery was higher than pre-op and correlated with clinical outcomes.
The findings of the present thesis provide insights into the evaluation of innovative and more biocompatible materials, with the aim of improving the durability and tolerability of joint prostheses.

INTRODUCTION

Total Knee Arthroplasty (TKA) represents a crucial solution for patients suffering from end-stage osteoarthritis and other debilitating joint conditions. As the global population ages and the prevalence of osteoarthritis increases, TKA has become a widely performed procedure, offering patients a significant improvement in terms of pain relief, functional recovery, and quality of life. However, despite the growing success of TKA, significant challenges remain in achieving long-term implant survival and ensuring patient satisfaction [1].

Over the years, the evolution in the development of new designs, alignment strategies, soft tissue balancing, and fixation techniques has made it possible to perfect kinematics and improve the satisfaction of patients undergoing this type of surgery. However, one critical area that requires further investigation is the tribology of knee prostheses. Most knee implants are made of cobalt-chrome (CoCr) alloys, which present mechanical and thermal properties vastly different from human bone. While CoCr provides high durability and strength, its inherent stiffness, the release of metal particles and high thermal conductivity can lead to complications such as stress shielding, periprosthetic bone resorption, and patient discomfort due to thermal sensitivity [2,3]. These issues are particularly concerning given the increasing number of younger patients undergoing TKA, who are more likely to experience the long-term effects of implant wear and failure, placing a great burden on the economies of health care systems to face the higher rates of revisions or osteosynthesis of periprosthetic fractures expected in the future.

In the next two paragraphs, the phenomenon of stress shielding, and the thermal properties of CoCr knee implants will be discussed in more detail.

Stress shielding: focus on

Stress shielding is a well-documented phenomenon in total knee arthroplasty (TKA), where the mechanical loading of the prosthetic implant alters the stress distribution in the surrounding bone, often leading to a decrease in bone mineral density (BMD) and potential complications such as implant loosening or failure. This response is particularly significant in the context of the materials and design of the femoral components used in TKA. Studies have shown that the use of high-stiffness materials, such as CoCr and titanium alloys, can exacerbate stress shielding effects. For instance, Galas et al. demonstrated through finite element analysis that different femoral component materials significantly influence periprosthetic bone stresses, with high-stiffness materials leading to decreased BMD and increased bone resorption around the implant [4]. Similarly, Zhang et al. highlighted that the design and alignment of the implant also play critical roles in the extent of stress shielding observed in periprosthetic bone [5]. The implications of stress shielding are profound, as it can lead to a reduction in BMD of 16-36% in the distal femur within the first year post-surgery, as reported by Jonbergen et al. [6]. This decrease in bone density not only compromises the structural integrity of the bone but also increases the risk of complications such as periprosthetic fractures and implant migration [7]. Minoda et al. further emphasized that specific designs, such as cemented mobile-bearing components, may mitigate the loss of BMD compared to fixed-bearing designs, suggesting that the choice of implant can influence the degree of stress shielding [8]. Moreover, the method of fixation, e.g. cemented versus uncemented, has been shown to affect the extent of stress shielding. Small et al. found that cemented implants exhibited different patterns of bone density changes compared to uncemented ones, indicating that fixation methods can influence the biomechanical environment around the implant [7]. This is crucial as stress shielding can lead to complications that necessitate revision surgeries, which are costly and can adversely affect patient outcomes [9]. In conclusion, stress shielding in TKA is a multifaceted issue influenced by implant material, design, and fixation method. Understanding these factors is essential for optimizing surgical outcomes and minimizing the risk of complications associated with decreased periprosthetic bone density.

Thermal properties of CoCr Total Knee Prostheses

The choice of materials used in TKA components, particularly cobalt-chromium (CoCr) alloys, plays a critical role in the performance and longevity of the implant. CoCr is favored for its mechanical properties and resistance to wear; however, it is not without complications, particularly concerning heat generation and wear debris. Heat generation during TKA can be attributed to several factors, including the friction between the bearing surfaces and the mechanical properties of the materials used. Studies have shown that CoCr components can produce significant wear debris, which may lead to inflammatory responses in the surrounding tissues. This wear debris can consist of metal ions and particles that contribute to osteolysis and implant failure [10,11]. The wear mechanisms in CoCr implants are influenced by the material's surface characteristics and the presence of third-body particles, which can exacerbate wear and heat generation [12,13].

Moreover, the biotribological properties of CoCr have been extensively studied, revealing that the friction and wear rates can vary significantly depending on the lubrication conditions and the presence of contaminants [14]. For instance, the interaction between CoCr and polyethylene components can lead to increased wear rates, which in turn can elevate the temperature at the implant interface [12,13]. This is particularly concerning in long-term scenarios where excessive heat can compromise the integrity of the surrounding bone and soft tissues, potentially leading to adverse outcomes such as implant loosening and increased pain [10,15].

In contrast, alternative materials such as polyetheretherketone (PEEK) have been proposed as potential substitutes for CoCr in TKA applications. Preliminary studies indicate that PEEK may generate less heat and wear debris compared to CoCr, thereby reducing the risk of inflammatory responses and improving the longevity of the implant [16,17]. The mechanical properties of PEEK allow for a more favorable strain distribution in the surrounding bone, which can mitigate stress shielding, a common issue associated with CoCr implants [17].

Furthermore, the corrosion resistance of CoCr alloys is vital in preventing degradation and subsequent wear. The formation of a passive oxide layer on CoCr surfaces is crucial for maintaining its integrity; however, this layer can be compromised under certain conditions, leading to increased wear and heat generation [10,18]. Studies have shown that the long-term performance of CoCr components can be significantly affected by corrosion and wear mechanisms, necessitating ongoing research into alternative materials and coatings that can enhance performance and reduce complications [15,19].

In conclusion, while CoCr remains a standard material in TKA due to its favorable mechanical properties, concerns regarding heat generation and wear debris necessitate further exploration of alternative materials such as PEEK. Understanding the biotribological behavior of these materials and their impact on implant longevity and patient outcomes is essential for advancing TKA practices.

JUSTIFICATION AND AIMS

It is evident from the previous introduction that modern joint replacements require further advancements to enhance their biocompatibility, durability, and patient satisfaction. While there is a wealth of literature on these topics, it appears to be fragmented and would benefit from greater systematization. Additionally, the assessment of changes in periprosthetic bone mineral density (BMD) and joint temperature after knee replacements requires further investigation, with a potential need to correlate these factors with clinical outcomes.

This PhD thesis aims to address these concerns by investigating the effects of joint replacements on periprosthetic bone resorption and joint temperature dynamics. Specifically, the research focuses on assessing bone mineral density (BMD) changes and knee surface temperature variations in patients receiving CoCr knee prostheses.

The objectives are organized into four key aims:

- **Aim I** ***"Is it possible to predict the loosening of a knee replacement and correlate it with clinical outcomes?"***: to assess in a literature review the femoral component migration and clinical outcomes following TKA;

- **Aim II** ***"What factors influence BMD changes after joint replacement?"***: to assess in a systematic review the periprosthetic BMD variations across different anatomical regions, implant designs and fixation techniques;

- **Aim III** ***"Is it feasible to analyze BMD changes after TKA in clinical setting?"***: starting of a clinical study to measure BMD changes in patients using Dual Energy X-ray Absorptiometry (DEXA);

- **Aim IV** ***"Does heat generation influence the perception of the knee after TKA?"***: to assess in a clinical study the post-operative knee surface temperature before and after TKA correlating it with the clinical outcomes.

AIM I: ***"Is it possible to predict the loosening of a knee replacement and correlate it with clinical outcomes?"***

Migration of the femoral component and clinical outcomes after total knee replacement: a narrative review

Abstract: Loosening is considered as a main cause of implant failure in total knee replacement (TKR). Among the predictive signs of loosening, migration is the most investigated quantitative parameter. Several studies focused on the migration of the tibial component in TKR, while no reviews have been focused on the migration of the femoral component and its influence on patients' clinical outcomes. The aim of this narrative review was (1) to provide information about of the influence of migration in femoral component of TKR prostheses, (2) to assess how migration may affect patient clinical outcomes and (3) to present alternative solution to the standard cobalt-chrome prostheses. A database search was performed on PubMed Central® according to the PRISMA guidelines for studies about Cobalt-Chrome femoral component migration in people that under- went primary TKR published until May 2020. Overall, 18 articles matched the selection criteria and were included in the study. Few studies investigated the femoral component through the migration, and no clear migration causes emerged. The Roentgen Stereophotogrammetric Analysis has been mostly used to assess the migration for prognostic predictions. An annual migration of 0.10 mm seems compatible with good long-term performance and good clinical and functional outcomes. An alternative solution to cobalt-chrome prostheses is represented by femoral component in PEEK material, although no clinical evaluations have been carried out on humans yet. Further studies are needed to investigate the migration of the femoral component in relation to clinical outcomes and material used.

Keywords: TKR; Migration; Clinical outcome; RSA; Femoral component; Cobalt-chrome

Introduction

Total knee replacement (TKR) represents a valid solution for the treatment of end-stage knee osteoarthritis. With the right indications and a reliable and reproducible surgical technique, TKR has an average lifetime of nearly 20 years with in vivo use before revision surgery becomes a necessity [1]. A recent systematic review suggests that the rate of survival at 25 years of TKR is 82% [2]. Anyway, there is still a considerable percentage of TKR failure whose consequent revision surgery might occur earlier than 20–25 years.

There are the causes that can lead to TKR failure: the most frequent is aseptic loosening, followed by infection, unexplained pain, wear, instability, and periprosthetic bone fractures [3–6]. Some of these causes seem to be favored by stress shielding. Indeed, stress shielding is an inevitable phenomenon occurring mainly in the first year after TKR [7]. It is caused by the different stiffness of bone and prosthetic implant, with the latter being nearly one order of magnitude stiffer than the former. It has been demonstrated that stress shielding reduces the load at the bone–prosthesis interface and leads to a gradual bone remodeling and osteolysis which, in turn, can lead to aseptic loosening of the implant or, to a lesser extent, can weaken the bone such that it will fracture [8]. According to Parchi et al. [7] stress shielding causes a constant decrease of periprosthetic bone mineral density (BMD), especially at femoral level, mainly during the first 3–6 months following surgery.

However, aseptic loosening can also be caused by wear, fixation and/or migration of implant components.

As far as clinical symptoms are concerned, patients presenting with loosening of TKR components and requiring surgery might be completely asymptomatic or present the insidious onset of knee pain, most commonly following a prolonged pain-free interval after the index procedure [9]. Considering the variability in clinical presentation and the need for a prompt diagnosis, migration was deemed a useful predictor for late-term risk for revision of TKR [10]. Indeed, migration has been revealed to be able to predict implant failure, even before clinical symptoms appear. Therefore, migration is advised as a key marker for the quality of a TKR.

Understanding the biological behavior of the bone in contact with the prosthetic surface and how it can affect implant survival and clinical outcomes, might lead to the development of newer designs and materials (e.g., with stiffness closer to the one of the bones) that could provide significant benefits to improve function and survival rate after TKR.

Several studies focused on the migration of the tibial component in TKR, and reviews have already been performed on this topic [10]. No literature reviews have been focused on migration of the femoral component and its influence on patients' clinical outcomes.

Therefore, the purpose of this narrative review was to provide (1) information about the influence of migration in the femoral cobalt-chrome (CoCr) alloy components routinely used in TKR, (2) to assess how this migration may affect patient clinical outcomes, and (3) to present alternative solutions that could replace materials traditionally used in joint prostheses, overcoming the issues related to the mechanical properties.

Material and methods

Data sources

An electronic database search was performed on August 1, 2020, using PubMed Central® to identify articles concerning general CoCr femoral component micromotion in people that underwent primary TKR and how it affected the patients' clinical outcomes.

Search terms

The terms and keywords used for the literature research were ('femoral') OR ('femur') AND ('micromotion') OR ('migrat*') OR ('sink*') OR ('loss') OR ('loos*') AND ('total knee arthroplasty') OR ('TKA') OR ('total knee replacement') OR ('TKR') located within the title and/or abstract.

Study selection process

All articles published until August 2020 were included in this review. During the screening procedure, only full-text available items, written in English language, were considered; pre-clinical and 'other animal' studies were included; moreover, reviews were added to the list. Subsequently, the authors further screened title and abstract of the papers, in order to exclude the irrelevant ones for this review. Then, the authors full-screened the remaining papers to leave out those not concerning femoral micromotion analysis, while papers concerning femoral components materials alternative to most used CoCr were included. In the end, 21 papers were included in the review. Furthermore, 17 papers (gray) mentioned in the selected works were added, since they did not appear in the first screening (Figure 1).

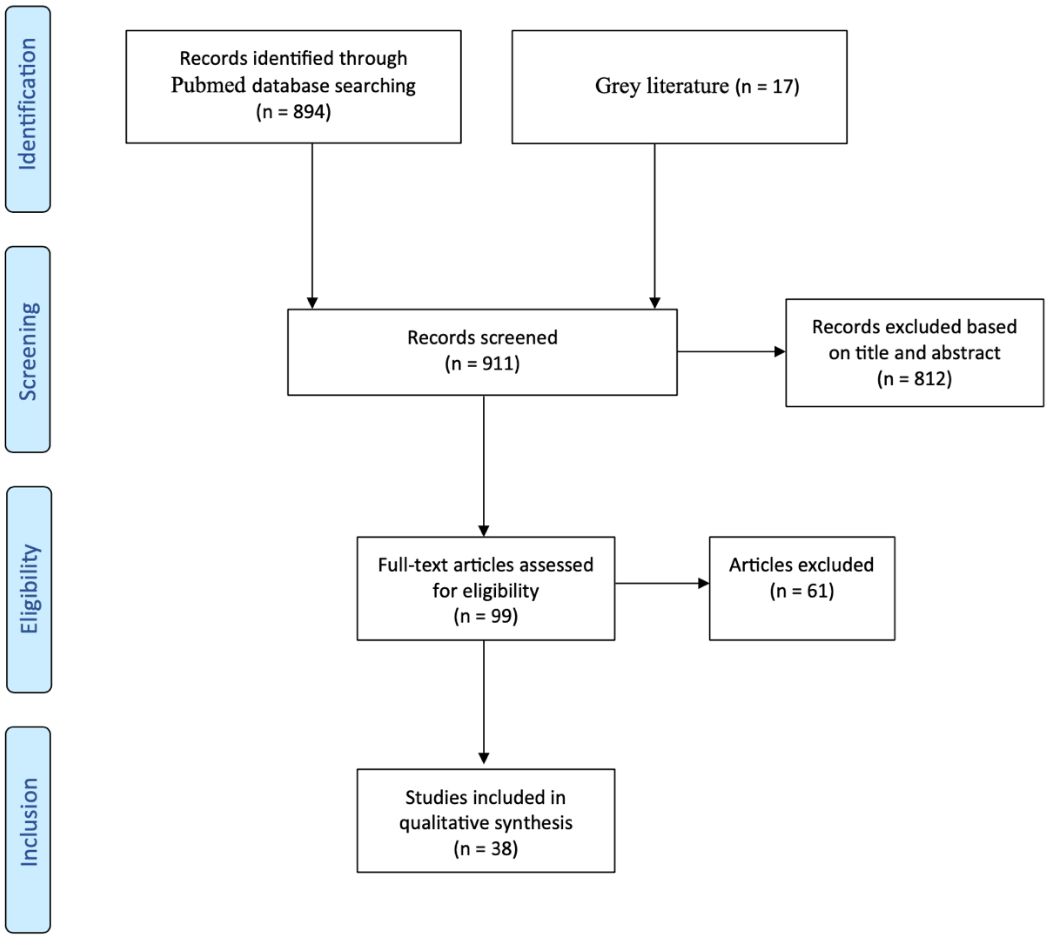

Figure 1. Flow chart of the narrative review according to the PRISMA guidelines

Results

Causes and evaluation methods of migration

Only few studies assessing migration of the femoral component were retrieved, in contrast to the numerous studies assessing the migration of the tibial component (Table 1). No clear evidence of migration causes emerged from the analysis. However, a possible cause of migration could be related to bony fixation. Indeed, the lack of bony fixation may cause the implant to become unstable and migrate [1]. Moreover, factors such as low mineral density, bone remodeling, and reabsorption might lead to implant migration [11].

The quantity of migration has been mostly assessed through the maximal total point motion (MPTM). The MTPM is the unit of measure for the largest 3D migration of any point on the prosthesis surface [12]. The calculation of MTPM is mainly performed through Roentgen Stereophotogrammetric Analysis (RSA). There are two different methods: on the one hand, the manual marker-based; on the other hand, the semi-automatic CAD model-based [10]. Both methods are suitable for in vivo measurement of implant migration in clinical research studies concerning the TKR [13]. Indeed, RSA measurements are claimed to have a high prognostic precision in early detection of potential late occurring aseptic loosening [14, 15]. Moreover, RSA allows the calculation of the "inter-marker distance" parameter, which can be seen as an index of material deformation within the different districts of a prosthetic implant (e.g., for the TKR, condyles and shield) [16]. RSA technique has been successfully used also in other joint surgery contexts and in presence alternative material solutions, e.g., in hip prosthesis to assess migration and material deformation of less stiff stems [17] and in spinal arthrodesis to predict lumbosacral stability of carbon fiber-reinforced cages [18].

Since the migration is linked to bone remodeling, measurement of bone density is crucial. Therefore, the use of dual-energy X-ray absorptiometry (DEXA), evaluating the bone density, could be a useful tool. Indeed, DEXA analysis could be used also in the assessment of bone remodeling of the femoral condyles after TKR [7]. Three studies show a dominating tendency toward decrease in tibia and femur bone mineral density (BMD) after the implantation of TKR [7–19]. However, BMD was shown to be an effective tool only in some specific loading conditions, as stated in a pre-clinical cadaveric study [20].

Quantification of migration and patients' outcomes

Due to the lack of studies regarding the femoral component, no migration thresholds suggesting short- and long-term survival of the femoral component prosthetic implants were retrieved.

Migration patterns must be evaluated through at least three-times assessments, one at baseline and two follow-ups within the first 2 years. For the tibial component, the most frequently reported follow-up time for MTPM evaluation was 1 year [10]. Nevertheless, the literature reported other time intervals, as well: 6 weeks, 3 months, 6 months, 2 years, 5 years, and 10 years [10, 14].

Three RSA studies have shown that loosening can be concretely assessed in the early postoperative period [12–22]. Henricson et al.[11] reported a displacement of the femoral component MTPM of 0.10 mm per year for cemented implant and 0.09 mm per year for the cementless implant, throughout a 10-year follow-up evaluation. Few studies correlated the amount of migration with the patients' outcomes. Henricson et al.[11] suggested that an annual migration of 0.10 mm seems compatible with good long-term performance and good clinical and functional outcomes at 10-year follow-up [11]. Gao et al [14] found the same clinical and radiological results with patients younger than 60 years old.

These results are in accordance with Park et al.[23], who evaluated the clinical and radiological results comparing the identical cemented or cementless TKR design, implanted bilaterally in the same patient. They showed that after 14 years from surgery, the survival rate was 100% for both femoral components. Moreover, no differences were found in the outcomes like KSS, Western Ontario and McMaster Universities Arthritis Index (WOMAC), Visual Analogue Scale (VAS), range of movement (ROM), and radiological results.

On the contrary, Wang et al.[24] reported that the cementless group had better KSS-function and KSS-pain, better ROM recovery, and fewer radiolucent lines (<1mm) than the cemented one, in a systematic review with >500 knees comparing postoperative outcomes of fixation in primary TKR for young patients (<65 years). Hence, they suggested that cementless TKR was substantially superior to cemented TKR in young patients [24].

A further study showed that the migration strongly affects TKR outcomes: in revised TKR with high-flexion design, the loosened femoral components migrated into a position of increased flexion from a mean of 4° immediately postoperatively to a mean of 7° at the final review, whereas no migration into flexion was observed in the control TKR group [25].

Two more RSA studies compared different TKR designs at 2- [26] and 5-years [27] follow-up. The former did not find differences in MTPM between cemented (0.88 mm) and cementless (0.89 mm) TKR designs. For both groups, the MTPM was higher in the posterior condyles. Peculiarly, the only one case of revision was predicted by an MTPM up to 4.1 mm at 12 months. The authors further stated that such loosening could be caused by trabecular microfractures occurring some millimeters away from bone–implant interface, in presence of bone softened due to stress-shielding [27]. The latter study did not find differences between four TKR designs (high/conventional flexion with fixed/mobile bearing). The MTPM was always about 1 mm. The only case of loosening presented with early migration over 2 mm within the first 3 months and reached up to 12 mm at one year.

Table 1. Summary of literature related to migration of femoral component and clinical outcomes in total knee replacement

Authors	Year	Type of study	Aim	Instruments	Study subjects	Outcome	Results	Conclusions
Howard et al. [1]	2014	Observational study	To assess the morphology of the fixation interfaces in femoral component	Radiograph	Nineteen fresh-frozen knees with TKR postmortem: 16 cemented 2 cementless 1 partially cementless	Femoral component fixation (contact fraction)	Total contact friction:10.3% cemented, 10.65% cemented press-fit, 6.5% press-fit	Minimal fixation seems necessary for long-term success of TKA femoral components
Ruiter et al. [4]	2017	Finite element study	To compare PEEK and CoCr implants for mechanical performance and fixation	Finite element simulations of level gait	CoCr PEEK Intact knee (controls)	Stresses for (1) the femoral component (2) the cement mantle	Peak compressive stresses: CoCr 75 Mpa; PEEK 34 MPa Bone strain energy density distribution higher in CoCr	Stress for the cement mantle: similar for PEEK and CoCr femoral component reduced stress shielding in PEEK
Parchi et al. [7]	2014	Review	To analyze changes in periprosthetic bone	PubMed	Total knee replacement, total hip replacement	Periprosthetic bone mineral density	Constant decrease of periprosthetic bone mineral density in first 3-6 months	Femoral bone loss after TKA seems to be related to the stress shielding
Fraser et al. [9]	2015	Review	To evaluate wear and osteolysis	Not specified	Total knee replacement	Wear Rates and Osteolysis Clinical Evaluation for Osteolysis Treatment Options	Rate of particulate debris dependent on component's design, positioning, and material properties Patients with osteolysis can be completely asymptomatic	Wear rates can be reduced by achieving proper alignment and component positioning with an index procedure and by using modern highly cross-linked polyethylene inserts
Pijls BG et al. [10]	2018	Systematic review and meta-analysis	To evaluate the early and long-term migration of tibial components of all known RSA studies	Medical librarian PubMed, Embase Web-of-Science Cochrane Library	2470 patients with TKR	MTPM	6 months - 1 year = 0.04 mm MPTM 1 year - 2 years = 0.04 mm MPTM1 year: Cemented 0.44 mm / Cementless 1.09 mm	First evaluation of the safety (i.e., implant-bone fixation) of the implant at 6 months
Henricson et al. [11]	2019	Randomized controlled trial	To study the migration of the femoral component and clinical outcomes up to 10-year follow-up	Radiostereophotogrammetric analysis	41 patients:19 Cem, 22 cem.less 23 women, 18 men Age: under 60years	MTPM	Cemented 0.85 mm (median) Cementless 1.44 mm (median) No differences in migration or clinical results at 10 years	Annual migration of 0.1 mm seems compatible with excellent long-term performance

Authors	Year	Type of study	Aim	Instruments	Study subjects	Outcome	Results	Conclusions
Gao et al. [14]	2009	Prospective randomized controlled study	To compare the magnitude and pattern of migration of cemented versus uncemented fixation of the femoral component by using radiostereometry	Radiostereophotogrammetric analysis	41 patients (22 cemented, 19 uncemented) younger than 60 years	MPTM	6 week: Cem 0.41 (0.20–0.71), Cem.less 0.36 (0.31–0.46) 3 month: Cem 0.45 (0.24–0.87), Cem.less 0.53 (0.36–0.67) 12 month: Cem 0.62 (0.39–0.96), Cem.less 0.63 (0.39–1.11) 24 month: Cem 0.72 (0.38–1.62), Cem.less 0.87 (0.47–1.10)	Uncemented and non-HA-coated femoral component may behave equally as well as a cemented one in the long term.
Seehaus et al. [15]	2009	Experimental study	To evaluate the experimental accuracy and precision of the MBRSA method for four different, but typical prosthesis geometries that are commonly implanted	Radiostereophotogrammetric analysis	1 femur, 1 tibia, and 2 hip (argo-TEP and Antea)	Translation and rotation	MBRSA in-plane: better than -0.034 to 0.107 mm translation, and -0.038 to 0.162 deg out-of-plane: better than −0.217 to 0.069 mm translation, and −1.316 to 0.071 deg	MBRSA method can be used with many common implant geometries, and the method could lead to a wider application of the RSA for investing clinical implant fixation that has been possible to date.
Järvenpää et al. [19]	2014	Prospective study	To assess long-term periprosthetic BMD changes after TKR in obese and nonobese patients	DEXA	69 TKR in 61 patients	Bone mineral density	Average bone loss at 7 years: 17.6% in anterior, 30.7% in central, 17.6% in posterior, 22.2% in total metaphyseal ROIs, 10.3% in diaphyseal ROI	Bone loss is likely caused by the stress shielding and immobilization in the first postoperative phase

Authors	Year	Type of study	Aim	Instruments	Study subjects	Outcome	Results	Conclusions
Berahmani et al. [20]	2017	Experimental and pre-clinical analysis	To evaluate the primary stability of the Attune cementless femoral components, and compared it against a conventional implant under simplified gait and deep knee bend loads	DIC	6 pairs of femur	BMD Micromotion	Attune: 126 mg/cm2 BMDLCS: 136 mg/cm2 BMDGaitAttune 32 µmLCS 71 µmDKBAttune: 55 µmLCS: 83 µm	Micromotions of Attune were significantly lower than LCS under both loading conditions BMD was only a significant factor affecting the micromotions under simplified gait loading
Schroder et al. [21]	2001	Prospective study	To report long-term results with TKR in an unselected series of patients with osteoarthrosis and rheumatoid arthritis	Radiograph Questionnaire	114 patients (cementless)	Alignment Clinical score Survival rate	Alignment 10-year follow-up: 18 Varus (<2°), 37 Neutral (<2°) Excellent knee score: Preop (0%), 3 years (70%), 7 years (65%), 10 years (76%) Survival rate: 97.1 %	Cementless insertion of a nonmodular, porous-coated TKA resulted in a long-term durable bone-prosthesis interface.
Park et al. [23]	2011	Prospective randomized study	To evaluate the clinical and radiological results of the NexGen TKR cemented or cementless implanted bilaterally in the same patient	Radiograph Questionnaire	50 patients (100 knees); 39 women and 11 men, mean age of 58.4 years (51–67)	Radiological results Knee score Function score Walking distance ROM	KSSc: 96.2 Cem, 97.7 Cem.less KSSf: 85.8 Cem, 88.1 Cem.less Unlimited walking distance: 82% Cem, 82% Cem.less ROM supine: 124° Cem, 128° Cem.less Radiolucent line < 1 mm: 4% Cemented, 6% Cementless	No advantage of cementless over cemented components in total knee replacement
Wang et al. [24]	2020	Systematic review and meta-analysis	To evaluate the optimal fixation mode in TKR for young patients.	PubMed Embase Medline Web of Science full Cochrane Library	510 Knees:255 Cemented255 Cementless	Functional outcomes KSS ROM Radiolucent linesAseptic loosening Total complications Reoperation rate	Radiolucent line < 1mm: 18.4% Cem, 9.8% Cem.less KSSf: Higher in Cem.less KSSc: Higher in Cem.less KSSpain: Higher in Cem.less ROM recovery: Higher in Cem.less	Cementless TKR was substantially superior to cemented TKR in young patients

Authors	Year	Type of study	Aim	Instruments	Study subjects	Outcome	Results	Conclusions
Han et al.[25]	2007	Retrospective study	To determine whether the increased loading in the knee during deep flexion substantially increases wear of the insert or loosening of components.	Radiograph Questionnaire	72 knees of 47 patients (44 women, 3 men)	Radiolucent Clinical and functional score Survival rate	HSS pain: Preop 5.5, Postop 28.5 HSS function: Preop 14.6, Postop 20.1 Survival rate: Revised 21% (15), Well-fixed 79% (57)	The loosened femoral components were found to migrate into a more flexed position, but no migration was detected in the well-fixed group.
Nilsson et al. [26]	1995	Prospective randomized study	To evaluate the relative micromotion of cemented and cementless femoral components using RSA	RSA Questionnaire	33 knees (29 primary osteoarthritis , 4 secondary osteoarthritis)	MPTM Clinical outcomes	MPTM: 0,89 ± 0,08 mm Cementless; 0,88 ± 0,16 mm Cemented HSS: 89 Cementless; 90 Cemented	No differences in fixation of the femoral component cemented and cementless 2 years
Nieuwenhuijse et al. [27]	2013	RSA study	To compare the migration and clinical outcomes of high flexion TKR fixed and mobile bearing with conventional	Model-based RSA Questionnaire	42 knee	MPTM Clinical outcomes	Migration: no differences between groups KSS: 34.8 ± 11.7 LPS-Flex Mobile 38.4 ± 18.9 LPS-Flex Fixed 33.7 ± 10.0 LPS Mobile 32.4 ± 12.8 LPS Fixed KSS function: 23.2 ± 17.7 LPS-Flex Mobile35.8 ± 24.7 LPS-Flex Fixed27.5 ± 25.5 LPS Mobile33.8 ± 20.7 LPS Fixed	Migration of the LPS high flexion TKR was comparable with those of the LPS conventional TKR and independent of the bearing type used
Ruiter et al. [32]	2017	Finite Element study	To investigate the mechanical response of a PEEK TKR device during a deep squat	A finite element model of a TKR subjected to a deep squat loading condition	CoCr PEEK Intact knee (controls)	Stress in femoral component Stress in cement mantle Stress shielding	Femoral component: 60MPa (145°) CoCr, 30MPa (145°) PEEK Cement mantle: 12MPa (120°) CoCr, 24MPa (145°) PEEK Stress shielding: similar in PEEK implant and the intact bone remodeling stimulus	PEEK femoral implant is strong enough to endure high demand loading and has potential for periprosthetic bone stock retention

Authors	Year	Type of study	Aim	Instruments	Study subjects	Outcome	Results	Conclusions
Rankin et al. [33]	2016	Preliminary Laboratory Study	To investigate whether PEEK TKR femoral component induces a more physiologically normal bone strain distribution than a CoCr component	Digital Image Correlation (DIC) technique	CoCr PEEK Intact knee (controls)	Strain distribution in intact femur, CoCr and PEEK	Strain shielding in CoCr implant was lower than the intact case($p = 0.014$) Strain in PEEK implant deviated less from the intact case with no difference ($p = 0.231$)	PEEK femoral component could transfer more physiologically normal bone strains with a reduced stress shielding effect
Du et al. [34]	2018	Randomized controlled trial	To gather preliminary evidence on the performance and safety of a cemented PEEK-based TKR	Radiographic examination (4, 12, and 24 weeks postoperatively)	15 Adult goats: 10 experimental 5 control	Prosthesis condition Loosening Radiolucent line	Decreased BMD at 12 weeks (6%) compared to the controls Radiographic examination: no evidence of implant fracture, insert protruding, prosthesis loosening, or sinking during the 24 weeks (except 1 case of prosthesis dislocation)	PEEK device in a goat model was feasible and safe
Xiang et al. [36]	2013	Systematic review	To gather and analyze information regarding the clinical outcomes and reach a definitive conclusion about the use of ceramic femoral components	MEDLINE EMBASE Cochrane ClinicalTrials.gov databases	1245 Patients and 1438 Knees	Clinical outcomes	Clinical outcomes of Ceramic TKR improved: Range of motion Range of flexion HSS scores KSS scores	Ceramic TKA implants show similar postoperative clinical results and survival rate compared to metal ones

Authors	Year	Type of study	Aim	Instruments	Study subjects	Outcome	Results	Conclusions
Cristofolini et al. [38]	2009	Experimental study	To test in vitro whether ceramic TKR femoral components are more prone to mechanical loosening than metal ones	Knee simulator (6 degrees of freedom)	2 Cemented prosthesis (1 ceramic vs 1 metal)	Inducible migration Permanent migration	Inducible micromotions: Metal 0.010–0.200 mm (range), Ceramic 0.023–0.162 mm (range) Permanent micromotion: Metal −0.021 to −0.438 mm (range), Ceramic −0.279 to +0.201 (range)	No difference was observed for the inducible micromotion, permanent micromotion or amount of damage between both prosthesis

Alternative solutions to standard CoCr implants

The vast majority of TKR implants found in the present review were made of CoCr alloy. As evidenced from the literature search, nonsignificant migration differences were found between different TKR designs. Therefore, implant loosening might be influenced by further factors, e.g., the material properties of the component. The two main alternatives found in the literature regarded the use of nonmetal materials, i.e., the polyethylene and the ceramic. The former was found either in terms of all-polyethylene or polyetheretherketone (PEEK). Polyethylene is less stiff than CoCr alloys and is therefore claimed to reduce the stress shielding at bone–implant interface [28]. All polyethylene material was only used in tibial components in TKR, and the MPTM has been evaluated with respect to the metal-backed ones. The most recent studies [28–31] underlined a comparable amount of migration and risk of loosening between the two different materials. Furthermore, Norgren at al. [28] found a greater internal–external rotation in metal-backed tibial components and ascribed it to a greater stiffness of the latter.

Only few pre-clinical studies reported the use PEEK material in TKR context. Such material has already been used in different surgical scenarios, such as spinal and cranio-maxillofacial surgery, and it has shown a good level of rigidity, durability, and biocompatibility [4]. A finite element study analyzing the prosthetic implant loads during a gait cycle predicted that the performance of the PEEK femoral component would not be inferior to the CoCr femoral implant [4]. They also suggested that PEEK implant could cause a lower periprosthetic stress shielding compared to a standard implant [4].

The same type of analysis was performed during a high demanding activity (deep squat). PEEK implant showed higher compressive and lower tensile cement stress, thus demonstrating no increased risk of failure compared to the CoCr implant [32]. Furthermore, in the same study, the PEEK component showed bone strains more similar to the intact bone than the CoCr component [32].

Rankin et al.[33] used a digital image correlation (DIC) technique to evaluate bone strain distribution of the PEEK femoral component. Such prosthesis produced a bone surface strain field closer to that of the intact bone case. This further demonstrates that the reduced stiffness of PEEK implants compared with CoCr has the potential to reduce stress shielding and the risk of aseptic loosening, hence potentially improving long-term bone preservation [33].

This type of prosthesis has been tested on animal in vivo models, as well: Du et al. [34] demonstrated that cemented PEEK knee replacement devices in a goat model are feasible and safe, as on the basis of radiographic images, there was no evidence of implant fracture, insert protruding, prosthesis loosening, or sinking during the 24 weeks, except for one case of prosthesis dislocation, that did not affect its activity as soft tissue could maintain the stability of the joint. Moreover, the goats returned to perform activities like squatting, standing up, jumping, and running.

Although PEEK material for TKR demonstrated promising results in pre-clinical investigations, no studies have been carried out in vivo on human patients. Therefore, its dependability in a clinical context is yet to be confirmed. However, if roughly equating the two polyethylene materials (all polyethylene and PEEK), similar migration results could be argued in vivo for a femoral PEEK component.

Ceramic components are claimed for the higher biocompatibility, durability, and resistance to scratching with respect to CoCr alloy [35]. Indeed, ceramic prosthetic implant was used in the TKR procedure with excellent long-term joint function and survival [36]. A prospective study published in 2013 investigated the short-term outcomes of the ceramic femoral component TKR and found comparable results to the metal femoral TKR [37]. Furthermore, an in-vitro study published in 2008 by Cristofolini et al. [38] investigated migration of CoCr and ceramic femoral component under cycle loadings and concluded that no sign of loosening nor significant differences were present between the implants. Therefore, this study underlined that ceramic femoral component is not mechanically inferior to a standard CoCr. Nevertheless, no recent studies (less than 10 years) investigating migration on ceramic components were retrieved in the present review.

Conclusions

Only a limited number of studies evaluated micromotion of the TKR femoral component. There is no total agreement regarding the migration causes; at the same time, there are contrasting opinions about patients' clinical outcomes after surgery. At the present time, the RSA technique is the most commonly used, as well as the most accurate tool to evaluate migration. Indeed, it is recognized by the scientific literature as an instrument to predict the stability and the lifetime of the prosthetic implant, both for femoral and tibial components.

Furthermore, the study raised up possible alternative solutions, such as polyethylene and ceramics. Though the latter showed good long-term results, no recent studies were retrieved (less than 10 years). This aspect could be symptomatic of an obsolescence of such alternative. PEEK material seems a suitable solution because of reduced material stiffness, which may lead to a limited stress shielding [32]. However, further studies on patients are needed to evaluate the benefits and long-term survival of such alternative in a real clinical scenario.

Given the successful use of RSA for the assessment of migration and material deformation in presence of alternative materials in other body districts, such application could be extended to a TKR context as well.

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AIM II: ***"What factors influence BMD changes after joint replacement?"***

Variations in bone mineral density after joint replacement: A systematic review examining different anatomical regions, fixation techniques, and implant design

Abstract: This study aims to evaluate postoperative periprosthetic bone mineral density (BMD) at various time points following joint replacement with different implant designs and fixation techniques.

Database search was conducted on MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, Web of Science, and CINAHL for studies analyzing bone remodeling after joint replacement between March 2002 and January 2024. Inclusion criteria: English-language articles; total joint replacement; at least two BMD evaluations; observational studies, cross-sectional, prospective, retrospective, randomized controlled trials, and clinical trials. Exclusion criteria: no BMD measurement within one-month after surgery; BMD data only expressed as percentage changes or graphs without numerical values; no Gruen zone evaluation for hip replacement; no periprosthetic bone evaluation for knee replacement; pharmacological treatment or comorbidities affecting BMD; revision joint replacements; irrelevant articles; no full text or no original data.

Sixty-eight articles matched the selection criteria. Fifty-five focused on the hip joint, 12 on the knee, and 1 on the shoulder. After total hip arthroplasty, the greatest bone resorption occurred in the proximal femur, peaking at 6 months. Implants and tapered stems showed more bone resorption than cementless implants and anatomical stems. BMD around the acetabular component decreased in the first 6 months, increasing in regions subjected to higher load. In total knee arthroplasty, bone loss occurred in the anterior distal femur and medial tibial plateau, with cemented and posterior-stabilized implants showing more bone loss than cementless and cruciate-retaining design.

The periprosthetic BMD decrease progressively after joint replacement. The fixation technique and implant design influence the extent and pattern of this decline. These factors must be considered during the surgical planning, as they can have long-term implications for bone health and implant longevity. Further research is needed to optimize implant design and surgical techniques to mitigate BMD loss and improve patient outcomes.

Keywords: Bone mineral density; total hip replacement; total knee replacement; regions of interest; fixation technique; implant design;

Introduction

Periprosthetic bone remodeling represents a topic of great interest in the orthopedic community due to its implications on implant survival. Indeed, a decrease in bone mineral density (BMD) around the implant is linked to a higher risk of complications like fractures and loosening [84]. Although designs and materials have evolved, loosening is still one of the leading causes for implant failure [44, 89]. This process seems to be induced by stress shielding, or the variation of BMD in the periprosthetic bone in response to the different load forces distribution caused by the implant rigidity [70, 95].

The current gold standard to analyze BMD changes around an orthopedic implant is the dual x-rays absorptiometry (DXA), which is able to provide accurate and reproducible measurements with minimal radiation exposure [8, 19, 45]. Many of the studies published on this topic regards total hip arthroplasty, considered the large volume of implants per year in the world [102]. To allow a fair comparison between the results obtained by various authors, Gruen et al. introduced a standardized subdivision of the regions of interests (ROI) around the femoral stem [35]. Using this method, various studies have shown that multiple variables like body mass index (BMI), sex, comorbidities, pharmacological treatments, implant design and fixation technique can affect periprosthetic bone health, functional recovery, adverse events, and revision rate [5, 57, 69, 71, 87, 98], but the information obtained from that amount of data is very heterogeneous.

On the contrary, studies analyzing BMD changes after total knee arthroplasty (TKA) are rather limited and there is no standardized subdivision of periprosthetic ROIs among the various authors allowing a systematic analysis. Furthermore, studies that have focused on BMD changes after other joint replacements are isolated and performed on small samples.

It is evident how the literature on this topic is fragmented, and a comprehensive review which summarizes and clarifies the behavior of periprosthetic BMD following joint replacement would be needed. Hence, the aim of this systematic review was to provide an overview on the changes of periprosthetic BMD after joint replacement considering different implant designs and fixation technique.

Methods

The systematic review method was conducted in accordance with the Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [72, 79]. Before starting the search process, the systematic review's protocol was registered in the International Prospective Register of Systematic Reviews (CRD42023401291).

Eligibility Criteria

The following PICOS (Patients, Interventions, Comparators, Outcomes and Study design) question was developed using the following search terms: (P) People aged 18 or more; (I) Total joint prosthesis surgery; (C) early prosthesis surgery; (O) Bone mineral density; (S) Observational studies, cross-sectional, prospective, retrospective, randomized controlled trial, and clinical trials. Studies available in full text, published in English, with original primary data, and published after the 2002 were included. There was no limitation for gender or type of prostheses.

The inclusion criteria were the following: (i) articles written in English; (ii) patients who underwent total joint replacement; (iii) at least two BMD evaluation per patient; (iv) observational studies, cross-sectional, prospective, retrospective, randomized controlled trial, and clinical trials. The exclusion criteria were the following: (i) no BMD measurement within one month after surgery (ii) BMD expressed as only percentual changes or graphs, without numerical values (iii) no Gruen zone (ROI) evaluation for hip replacement (iv) no periprosthetic bone evaluation for knee replacement (v) pharmacological treatment (such as steroids, bisphosphonates, estrogens etc…) or comorbidities that could affect the BMD (vi) revision joint replacements; (vii) articles not relevant for the research area; (viii) no full text available or no original data.

Search Strategy and Data Sources

The literature search was performed by searching the following databases: MEDLINE (PubMed), Scopus, Cochrane Central Register of Controlled Trials, Web Of Science, and CINAHL. The databases were consulted on January 16th, 2024. Search strategy was created following the search string, with terms and Boolean logical operator, used on the PubMed. The keywords used for the screening were related to bone mineral density and joint arthroplasty. The strings were adapted to meet the specific search requirements of each database. The complete strings for each database are available on supplementary material (Annex A - Tab. S1). Moreover, a grey literature search of other papers was conducted using hand searches of key conference proceedings, journals, professional organizations' websites and guideline clearing houses. Finally, was used the snowball technique, to examine references cited in the primary papers to identify potential papers that fit the eligibility criteria and could be included in this review. Among the complete list of items found for each database, duplicate articles were excluded using EndNote (EndNote X9.3.3) and then manually.

Based on the PICOS criteria, the titles and abstracts were screened by eight authors (D.A., R.Z., M.S.M., G.B., D.V., E.P., A.I.M., and L.B), and studies that did not meet the purpose of the present review were excluded. Then, full texts of all remaining papers were reviewed to identify which could be included in this article. Moreover, each author individually screened all studies. Title, abstract and full texts were checked twice to minimize the risk of missing relevant articles. Any doubt or disagreements regarding inclusion or exclusion were discussed by all authors together. Five authors (Blinded for submission) extracted data from included studies following a formatted table to standardize data collection rules. The data collected includes first's author's name, journal name (quartile and year of publication), level of evidence, study design, aim, population, joint, materials and methods assessment time (follow up), type of prosthesis, type of implant (cemented or cementless), and outcomes. The study's authors were contacted to have additional information where necessary.

The variable analyzed in the present review was BMD. The weighted average of BMD values (g/cm2) postoperatively (baseline) and at subsequent follow-ups was calculated. Because variability was present in the baseline BMD values of the included studies, the variation between baseline BMD and subsequent follow-ups was calculated as percentage. The data analysis was performed using Microsoft® Excel (version 2402).

Study Selection

A total of 9,158 records were identified through database screening (PUBMED: 2,047; WEB OF SCIENCE: 1,917; COCHRANE LIBRARY: 442; SCOPUS: 3,877; CINAHL: 875), of which 3,473 were removed as duplicates by EndNote. Then, after screening titles and abstracts, 5,064 more were excluded (774 more duplicates and 53 study protocol). Finally, after full text screening according to the exclusion criteria, 68 out of 621 articles were included in the systematic review (Fig. 1). Descriptive statistics were used to summarize and present the results.

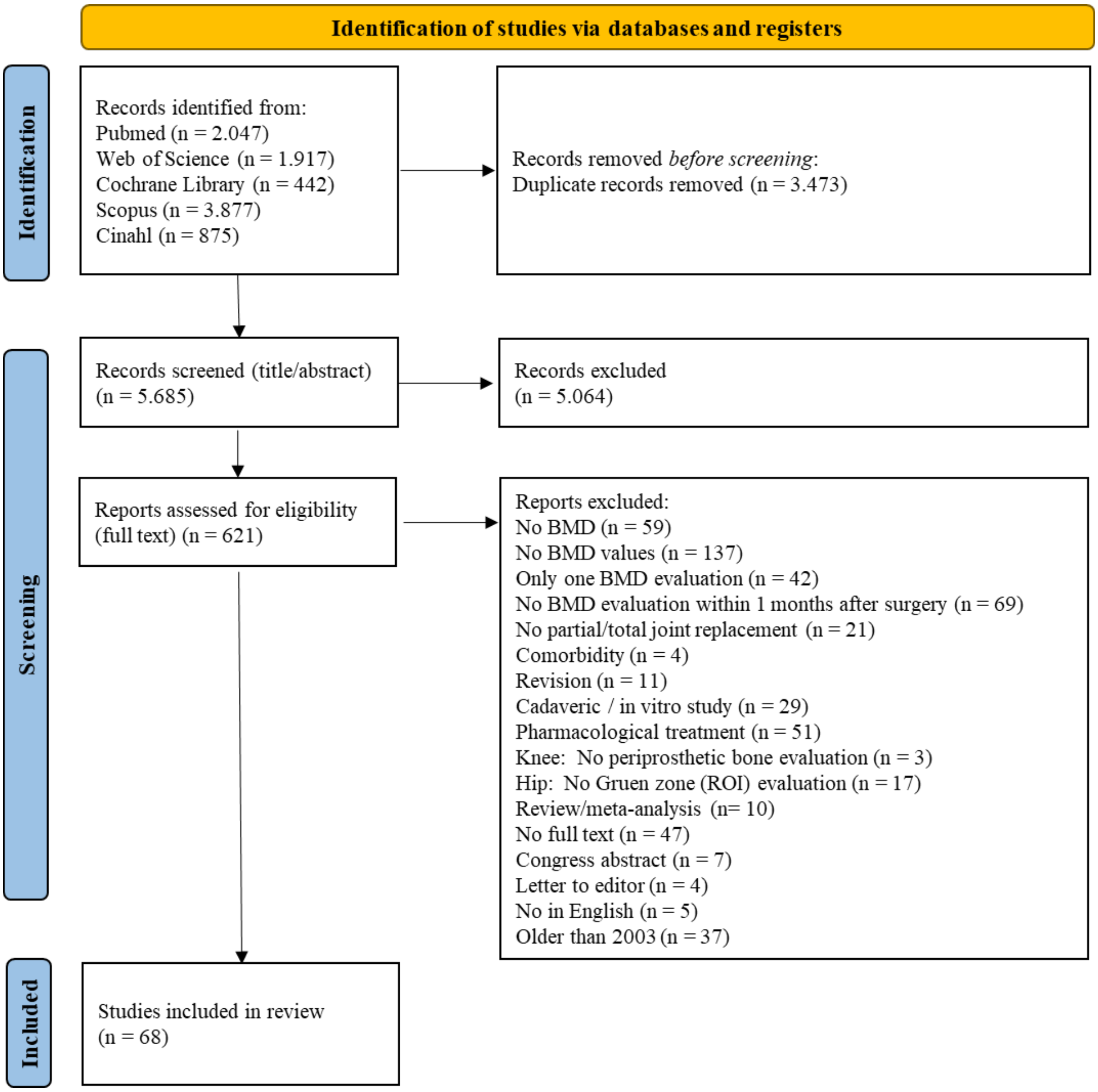

Figure 1. PRISMA flow diagram.

Quality Assessment and Risk of Bias

A Risk of bias critical appraisal of each article included in the review was conducted independently and blinded by three authors (EP, MSM, LB), using the "Revised Cochrane risk-of-bias tool for randomized trials" (ROB2) for randomized controlled trial [93], and the Joanna Briggs Institute (JBI) Critical Appraisal tools was used according to the specific study design [73]. Any disagreement or conflict between the quality scores separately assigned by the three blind reviewers was discussed and resolved by majority vote. The ROB2 is organized into five bias domains, focusing on various aspects of trial design, conduct, and reporting.

The Joanna Briggs Institute Critical Appraisal (JBI) Critical Appraisal tools contain from eight to eleven questions whose answers could be "yes," "no," "unclear," and "not applicated." The number of questions depends on the type of study design.

Results

Study characteristics

All data necessary for the analysis have been extracted and are presented in Table 1. A great heterogeneity among the studies emerged as the methods of BMD analysis were not standardized among the various authors and among the various joints. It was therefore decided to divide the included articles according to the evaluated joint, the regions of interest (ROI) adopted, the fixation technique and the implant design, analyzing the percentage change in BMD compared to baseline. The main findings of the subgroups in which a systematic analysis was not possible were presented separately.

Table 1. Data extraction

First Author	Journal name, Quartile, Year	Study Design	Aim	Population	Joint	Materials and Methods	Assessment time	Prosthesis	Cemented / Cementless	Outcomes
Ahrens, P. [20]	Hip International, Q2 (2004)	Prospective study	To correlate the gross radiographic changes with the DXA	n° = 19 -Mean age = 54 years -Age range = 43-62 years Male = 8 Females = 11	Hip	DXA	T0 = Post surg T1 = 32m T2 = 89m	Anatomic Medullary Locking (AML) uncemented femoral component (DePuy, International, Leeds, UK)	Cementless	Gruen Zone ROI 7 Femur
Aldinger, P. R. [2]	Calcified Tissue International, Q1 (2003)	Prospective longitudinal study Cross-sectional study	To evaluate the pattern of periprosthetic bone remodeling around stable uncemented tapered hip stems	n° = 35 Male = 17 -Mean age = 54.6 ± 9.1 years Female = 18 -Mean age = 55.2 ± 9.9 years	Hip	DXA	T0 = Post surg T1 = 3m T2 = 6m T3 = 12m T4 = 36m T5 = 60m T6 = 84m	Press-fit titanium Spotorno stem, Sulzer Orthopedic	Cementless	Gruen Zone ROI 7 Femur
Alm, J. [22]	Acta Orthopaedica, Q1 (2009)	Prospective study	To investigate the association between early changes in periprosthetic BMD and patient-related factors	n° = 39 Female = 39 -Mean age = 63 years -Age range = 41-79 years	Hip	DXA	T0 = Post surg (7d) T1 = 3m T2 = 6m T3 = 12m T4 = 24m	Anatomic Benoist Girard II, ABG II, Stryker	Cemented	Gruen Zone ROI 7 Femur
Andersen, M.[23]	Journal of Clinic Densitometry: Assessment & Management of Musculoskeletal Health, Q1 (2018)	Prospective study	To investigate the adaptive bone remodeling of the distal femur after TKA using the uncemented Nexgen CR flex femoral component	n° = 65 -Mean age = 61.0 years Male = 30 Female = 35	Knee	DXA	T0 = Post surg T1 = 3m T2 = 6m T3 = 12m T4 = 24m	Uncemented Titanium Zimmer Nexgen CR-Flex Femoral Component (Zimmer Inc, Warsaw, IN)	Cementless	ROI 3 Femur
Bieger, R et al.[24]	Hip International, Q2 (2011)	Prospective study	To evaluate differences in periprosthetic BMD in 25 patients undergoing cementless and in 18 patients undergoing cemented unilateral THA using the Optan stem	n° = 43 Cementless = 25 - Mean age = 61 years - Age range = 42-67 years Cemented = 18 - Mean age = 74 years - Age range = 63-94 years	Hip	DXA	T0 = 14ds T1 = 3m T2 = 12m	Uncemented titanium base alloy with porous coated proximal third + Cemented stem made of CoNCrMo alloy wOptan stem (Zimmer Germany GmbH, Freiburg, Germany)	Cemented and Cementless	Gruen Zone ROI 7 Femur

Boller, S et al.[25]	Archieves of Orthopaedic and Trauma Surgery (2018)	Prospective study	To examine potential differences between patients under and over 60 years who underwent a total short hip stem arthroplasty in a 24-month follow-up in a clinical setting	n° = 67 <60 years = 39 -Mean age = 50.9 years -SD = 6.4 >60 years = 28 -Mean age = 66.3 years -SD = 5.5	Hip	DXA	T0 = Post surg T1 = 6m T2 = 12m T3 = 24m	Metha® (BBraun, Aesculap, Tuttlingen, Germany) short hip stem prosthesis	Cementless	Gruen Zone ROI 7 Femur
Brinkmann, V et al.[26]	Journal of Orthopaedics and Traumatology, Q2 (2015)	Prospective randomized study	To investigate osseointegration and bone remodeling after implantation of the MethaTM or NanosTM prostheses, to analyze whether proximal load transfers could be achieved and whether there are differences between the two implants	n° = 50 -Mean age = 58.7 years -Age range = 43-70 years MethaTM = 24 - Male = 12 - Female = 12 - Mean age = 58.7 years NanosTM = 26 -Male = 16 -Female = 10 - Mean age = 59.7 years	Hip	DXA	T0 = Post surg T1 = 3m T2 = 12m	MethaTM (Aesculap AG, Tuttlingen, Germany) + NanosTM (Smith & Nephew GmbH, Marl, Germany)	Cementless	Gruen Zone ROI 7 Femur
Brinkmann, V et al.[27]	Acta Orthopaedica, Q1 (2017)	Prospective randomized study	To analyze bone remodeling around the Nanos® (Smith & Nephew) and Metha® (Aesculap AG) implants as a function of varus/valgus stem positioning	n° = 75 -Mean age = 58.7 years -Age range = 43-70 years Metha™ = 24 Nanos™ = 51	Hip	DXA	T0 = Post surg (5d) T1 = 3m T2 = 12m	MethaTM (Aesculap AG, Tuttlingen, Germany) + NanosTM (Smith & Nephew GmbH, Marl, Germany)	Cementless	Gruen Zone ROI 7 Femur
Buckland, A et al.[28]	The Journal of Arthroplasty (2010)	Prospective case series	To assess with DXA the changes in periprosthetic BMD around a triple-taper stem, with particular attention to the changes in proximal femoral BMD to identify the relationship between age, sex, preoperative BMD, mobility, and surgical approach to postoperative changes in calcar BMD	n° = 103 -Mean age = 71.6 years -Age range = 61-88 years Male = 47 Female = 56	Hip	DXA	T0 = Post surg T1 = 3m T2 = 9m T3 = 18m T4 = 24m	Highly polished, triple-taper, cemented C-stem (DePuy, Warsaw, Ind)	Cemented	Gruen Zone ROI 7 Femur
Burchard, R et al.[29]	Archieves of Orthopaedic and Trauma Surgery, Q1 (2007)	Prospective study	To collect prospective medium term (5 years) volumetric CT density data after cemented femoral stem implantation	n° = 7 -Mean age = 63.9 years	Hip	Volumetric CT density	T0 = Post surgery T1 = 24 m T2 = 60 m	Marburg system; Sulzer Orthopedics	Cemented	Gruen Zone ROI 7 Femur

Christiansen, J et al.[30]	The Journal of Bone and Joint Surgery (2020)	Pilot study	To evaluate the 2-year performance of the Primoris in terms of implant migration and BMD around the implant	n° = 50 -Mean age = 52 years -Age range = 25-65 years Male = 45 Female = 5	Hip	DXA	T0 = Post surg (1d) T1 = 24 m	Primoris femoral neck-preserving hip implant (Biomet)	Cementless	Gruen Zone ROI 4 Femur
Damborg, F et al.[31]	Acta Orthopaedica, Q1 (2008)	Prospective study	To quantify the changes in BMD for 5 years after insertion of the cemented Exeter stem in women	n° = 18 Female = 18 -Age range: 55-79 years	Hip	DXA	T0 = Post surg T1 = 18m T2 = 60m	Exeter stem	Cemented	Gruen Zone ROI 7 Femur
Dan, D et al.[32]	Rheumatology International, Q2 (2006)	Prospective study	To evaluate periprosthetic bone loss and to compare it with the bone loss in other areas of the body	n° = 50 Male = 40 Female = 10 Cemented = 23 Uncemented = 27	Hip	DXA	T0 = Post surg T1 = 12m	-	Cemented and Cementless	Gruen Zone ROI 7 Femur
Decking, R et al.[33]	BMC Musculoskeletal Disorders, Q1 (2008)	Prospective study	To investigate the changes of BMD in the proximal femur and the clinical outcome after implantation of a short femoral-neck prosthesis	n° = 20 -Mean age = 47 years -SD = 11.6 Male = 12 Female = 8	Hip	DXA	T0 = Post surg (10d) T1 = 3m T2 = 12m	ESKA Cut 2000 femoral	Cementless	Gruen Zone ROI 7 Femur
Digas, G et al.[34]	Acta Orthopaedica, Q1 (2006)	Prospective study	To compare the changes of BMD using DXA analysis in three types of fixation up to 2 years post-operatively	n° = 90 -Mean age = 70 years Palacos = 24 -Mean age = 73 years Cemex-F = 30 -Mean age = 71 years Uncemented = 34 -Mean age = 65 years	Hip	DXA	T0 = Post surg T1 = 12m T2 = 24m	All-polyethylene cups (Smith & Nephew, Memphis, TN)	Cemented and Cementless	ROI 5 Cup of Hip
Digas, G et al.[35]	International Orthopeadics (2009)	Prospective study	To evaluate the longitudinal changes of BMD during the follow-up period and to what extent gender, age at operation, weight, side operated, stem size, postoperative BMD and stem subsidence as measured with radiostereometric analysis (RSA) influenced the observed bone remodelling	n° = 88 -Mean age = 60 years Age range 37-78 years Male = 30 Female = 58	Hip	DXA	T0 = Post surg T1 = 12m T2 = 24m T3 = 60m	Spectron Primary, Smith and Nephew, Memphis TN, USA	Cemented	Gruen Zone ROI 7 Femur

Ebert, J et al.[36]	Orthopaedic Surgery, Q2 (2022)	Prospective clinical study	To evaluate the clinical outcome and periprosthetic bone change up until 2 years in a prospective series of patients undergoing primary THA for osteoarthritis with the Absolut cemented stem, together with an investigation of stem migration in a subset of the cohort	n° = 47 -Mean age = 74.2 years -Age range = 36-89 years	Hip	DXA	T0 = Post surg T1 = 12m T2 = 24m	Absolut femoral stem (Global Orthopaedic Technology Pty Ltd., Sydney, Australia)	Cemented	Gruen Zone ROI 7 Femur
Freitag, T et al.[37]	Arch Orthop Trauma Surg, Q1 (2016)	Prospective randomized study	To evaluate implant-specific BMD changes during 1-year follow-up after THA following short and straight stem implantation	n° = 138 Fitmore = 57 -Mean age = 58.8 years -SD = 10.2 years Male = 36 Female =21 CLS = 81 -Mean age 59.1 years -SD= 9.3 Male = 52 Female = 31	Hip	DXA	T0 = Post surg (7d) T1 = 3m T2 = 12m	Trochanter-sparing short stem (Fitmore; Zimmer, Winterthur, Switzerland) + Cementless straight stem (CLS; Zimmer, Winterthur, Switzerland)	Cementless	Gruen Zone ROI 7 Femur
Galli, M et al.[38]	Skelatal Radiology, Q2 (2008)	Prospective cohort study	To evaluate BMD changes around the proximal femur after implantation of two different anatomical stems	n° = 36 Bihapro = 23 -Mean age = 60.9 years Citation = 13 -Mean age 59.7 years	Hip	DXA	T0 = Post surg (7d) T1 = 12m	Bihapro + Citation stem implant (Howmedica, Rutherford, NJ, USA)		Gruen Zone ROI 7 Femur
Gauthier, L et al.[39]	Hip International, Q2 (2013)	Prospective randomized study	To quantify BMD on the acetabular side with a large-head MoM bearing and compare it with that of a standard MoP bearing in primary THR	n° = 50 MoM = 25 -Mean age = 60.2 years -SD = 7.2 Male = 14 Female = 11 MoP = 25 -Mean age = 63.0 years -SD = 5.5 Male = 9 Female = 16	Hip	DXA	T0 = Post surg (14d) T1 = 12m T2 = 24m	CONSERVE A-Class Total Hip System with Big Femoral Head (BFH) technology (Wright Medical Technology, Memphis, Tennessee) + Acetabular system with a highly cross-linked polyethylene liner (Wrigh Medical Technology)		ROI 4 Peri-acetabular area

Gazdzik, T et al.[40]	Journal of Clinical Densitometry, Q1 (2008)	Prospective cohort study	To analysis BMD changes at the knee joint arthroplasty site in the course of the first year after surgery	n° = 106 -Mean age = 69.8 years -SD = 9.4	Knee	DXA	T0 = Post surg (2w) T1 = 1m T2 = 3m T3 = 6m T4 = 12m	AGC II Biomet Merck prothesis + PFC Sigma Johnson & Johnson + Scorpio type Stryker prothesis		ROI 4 Tibia + Femur
Gerhardt, D et al.[41]	Hip International, Q2 (2019)	Randomised controlled trial	To compare periacetabular BMD changes between 2 types of MoM hip arthroplasties	n° = 71 RHA = 38 -Mean age = 54.4 years -SD = 9.5 THA = 33 -Mean age 56.5 years -SD = 7.3	Hip	DXA	T0 = Post surg (2w) T1 = 3m T2 = 6m T3 = 12m T4 = 24m T5 = 36m T6 = 60m			ROI 5 Cup of Hip
Grochola, L et al.[42]	Arch Orthop Trauma Surg, Q2 (2008)	Prospective study	To investigate the effect of the stem design on periprosthetic bone remodelling after insertion of an anatomic stem with proximal fixation and the direct comparison to a straight stem prosthesis	n° = 66 - Mean age = 49.1 years - Age range = 25-69 years Female = 37 Male = 29 Hip = 68	Hip	DXA	T0 = Post surg (7d) T1= 12m T2= 24m	CTX-S implants + PPF prostheses	Cementless	Gruen Zone ROI 7 Femur
Hayaishi et al.[43]	The Journal of Arthroplasty, Q1 (2007)	Prospective cohort study	To examine whether the Freeman cementless THA, with femoral neck preservation and a large metal head, can prevent stress shielding in a manner similar to resurfacing THA	n° = 26 Group A = 10 Female = 10 -Mean age = 53.0 years -SD = 8.0 Group B = 16 Female = 16 -Mean age = 61.0 years -SD = 11.0	Hip	DXA	T0 = Post surg (3w) T1 = 6m T2 = 12m	BHR system (MMT, Birmingham, UK) + BHR Socket and Freeman stem (Finsbury, Surrey, UK)	Cementless	Gruen Zone ROI 7 Femur
Herrera et al.[44]	Journal of Biomechanics, Q1 (2007)	Prospective cohort study Control group	- To analyse the long-term changes of BMD in the femur after the implantation of ABG-I - To make two 3D FE models from the scanned geometry corresponding to the healthy femur - To check if the results of the FE simulation make it possible to explain the biomechanical changes	n° = 61 -Mean age = 59.0 years	HIp	DXA	T0 = Post surg T1 = 6m T2 = 12m T3 = 36m T4 = 60m T5 = 72m T6 = 120m	ABG-I stem (Stryker)	Cementless	Gruen Zone ROI 7 Femur

Herrera et al.[45]	Journal of Arthroplasty, Q1 (2014)	Prospective cohort study Control group	To identify the relationship between changes in bone mass and mechanical stimulus variation, in two cemented stems models, in a mid-term follow-up period (five years)	n° = 64 -Mean age = 78.3 years ABG-II = 32 -Mean age = 76.3 years -Male = 5 -Female = 27 VerSys = 32 -Mean age = 72.9 years -Male = 5 -Female = 27	Hip	DXA	T0 = Post surg (15d) T1 = 3m T2 = 12m T3 = 24m T4 = 36m T5 = 48m T6 = 60m	ABG-II (Stryker) + VerSys (Zimmer)	Cemented	Gruen Zone ROI 7 Femur
Huang et al.[46]	Journal of Arthroplasty, Q1 (2013)	Prospective cohort study	To investigate the changes in BMD of acetabulum and proximal femur after total hip resurfacing arthroplasty	n° = 48 Hip = 51 Group A = 25 -Mean age = 46.5 years Male = 11 Female = 14 Hip = 26 Group B = 23 -Mean age = 49.0 years Male = 15 Female = 8 Hip = 25	Hip	DXA	T0 = Post surg (2w) T1 = 6m T2 = 12m T3 = 24m T4 = 36m	Wright Medical Technologies, Arlington, TN + Depuy ASR XL Head system		Gruen Zone ROI 7 Femur
Jahnke, A et al.[47]	International orthopaedics, Q1 (2014)		To examine the concept of proximal load initiation of a total short-stemmed hip arthroplasty on the basis of bone variations	n° = 40 -Mean age = 55.4 years Male = 20 Female = 20	Hip	DXA	T0 = Post surg (1w) T1 = 6m T2 = 12m	Metha® short-stem prosthesis	Cementless	Gruen Zone ROI 7 Femur
Kim, Y et al.[48]	The Bone & Joint Journal (2007)	Randomized study	To compare the BMD around cementless acetabular and femoral components which were identical in geometry and had the same alumina modular femoral head, but differed in regard to the material of the acetabular liners	n° = 50 -Mean age = 51.0 years -Age range = 35-66 years Male = 38 Female = 12	Hip	DXA	T0: Post surg (1w) T1: 12m T2: 24m T3: 36m T4: 48m T5: 60m	Femoral component (IPS, DePuy, Leeds, United Kingdom)	Cementless	Gruen Zone ROI 7 Femur ROI 3 Acetabulum

Kim, Y et al.[49]	The journal of arthroplasty (2011)	Randomized study	To compare BMD Changes Around Short, Metaphyseal-Fitting, and Conventional Cementless Anatomical Femoral Components	G proxima n° = 50 -Mean age = 54.3 years Male = 22 Female = 28 G Pofile n° = 50 Mean age = 51.8 years Male = 24 Female= 26	Hip	DXA	T0: Post surg (1w) T1: 3y	DePuy	Cementless	Gruen Zone ROI 2 Femur
Kim, Y et al.[50]	Clinical Orthopaedics and Related Research, Q1 (2014)		To evaluat long-term clinical results using validated scoring instruments; osseointegration and bone remodeling; complications; and rates of revision and osteolysis in patients younger than 65 years who underwent THA with a short, metaphyseal-fitting anatomic cementless stem	n° = 500 -Mean age = 52.7 years Male = 314 Female = 186	Hip	DXA	T0: Post surg (1w) T1: 15.8y	Short, metaphyseal-fitting anatomic cementless stem	Cementless	Gruen Zone ROI 7 Femur ROI 3 Acetabulum
Koppens, D et al.[51]	The Journal of Arthroplasty (2020)	RCT	To examine the influence of systemic and periprosthetic BMD on migration of the tibial component of cemented medial UKA with 2 years follow-up	n° = 65	Knee	DXA	T0: Post surg (1w) T1: 4M T2: 12M T3: 24M	Mobile-bearing (MB) UKA (Oxford Partial Knee; Zimmer Biomet, Bridgend, UK) + Fixed-bearing (FB) UKA (Sigma High Performance Partial Knee System; DePuy International Ltd, Leeds, UK)		ROI 4 Tibia
Leichtle, U et al.[52]	The Bone & Joint Journal (2006)		To investigate the clinical results related to the bony integration of a femoral component in the medium term, as well as the peri-prosthetic bone remodelling processes, over approximately a five-year period after surgery	n° = 43 -Mean age = 54 years Male = 24 Female = 19	Hip	DXA	T0: Post surg (8d) T1: 3M T2: 6M T3: 3.6y T4: 4.6y	Evolution K (Fehling Medical AGI, Karlstein, Germany) + Harris-Galante acetabular component.	Cementless	Gruen zone ROI 7 Femur
Lerch, M et al.[53]	Journal of orthopaedic research, Q1 (2012)	Prospective investigation	To answer the following research questions: (i) what is the effect of THA with the Metha® short stem on femoral bone remodeling?; (ii) can numerical computations be confirmed by DXA measurement of bone remodeling?; and (iii) what are the differences and can we explain them?	n° = 25 -Mean age = 58.9 years Male = 16 Female = 9	HIp	DXA	T0: Post surg (1w) T1: 6M T2: 1y T3: 2y	Bicontact® total hip arthroplasty system (AESCULAP AG, Tuttlingen, Germany) + Plasmacup SC press-fit acetabular component or the SC-Screwcup (both BBraun, Aesculap, Tuttlingen, Germany)	Cementless	Gruen Zone ROI 7 Femur

Liu, Y et al.[54]	Orthopaedic Surgery, Q2 (2022)	Retrospective study	To compare the periprosthetic BMD changes around Tri-Lock "Bone Preserving Stem" with the other two common and longer stems (Corail and Summit) after THA	n° = 138 Tri-Lock stem = 49 Corail stem = 44 Summit stem = 45	Hip	DXA	T0 = Post surg (1w) T1 = 5y	Tri-Lock BPS stem (Depuy, Eagan, MN, USA) + Corail stem (DePuy Synthes, Raynham, MA, USA) + Summit stem (Depuy Orthopedics, Inc., Warsaw, In, USA)	Cementless	Gruen Zone ROI 7 Femur
López-Subías, J et al.[55]	Journal of Clinical Densitometry, Q2 (2019)	Prospective study	To establish the pattern of bone remodelling caused by a cementless, and anatomic implant	n° = 37 -Mean age = 57.3 years -Age range: 36-75 years Male = 31 Female = 6	Hip	DXA	T0 = Post surg T1 = 3m T2 = 6m T3 = 1y	ANATO® stem (Stryker®, USA)	Cementless	Gruen Zone ROI 7 Femur
MacDonald, S et al.[56]	Clinical Orthopaedics and Related Research, Q1 (2010)	Randomized controlled trial	To examine differences in clinical scores, incidence of thigh pain, and development of stress shielding	n° = 388 SynergyTM = 198 -Mean age = 61 years ProdigyTM = 190 -Mean age = 60 years	Hip	DXA	T0 = Post surg (2w) T1 = 6m T2 = 1y T3 = 2y	Tapered, titanium, proximally porous-coated (titanium bead) stem (SynergyTM; Smith and Nephew Inc, Memphis, TN) + Cylindrical, cobalt-chrome, fully porous-coated (cobaltchrome-molybdenum alloy bead) stem (ProdigyTM; DePuy Inc, Warsaw, IN)	Cementless	Gruen Zone ROI 7 Femur
Merle, C et al.[57]	Sage journals (2012)	Comparative longitudinal study	To determine the extent and the pattern of femoral periprosthetic bone remodelling following uncementened THA around straight, double-tapered, grit-blasted titanium stems comparing a muscle sparing anterolateral surgical approach to a muscle detaching transgluteal surgical approach	Group A (anterolateral) = 16 -Mean Age = 63 years Male = 6 Female = 10 Group B (transgluteal) = 26 -Mean age = 58 years Male = 14 Female = 12	Hip	DXA	T0 = Post surg T1 = 3m T2 = 6m T3 = 1m	CLS stem (Zimmer, Warsaw, USA)	Cementless	Gruen zone ROI 7 Femur

Meyer, J et al.[58]	Journal of Clinical Densitometry: assessment & management of muscoloskeletal health (2018)	Prospective randomized DXA-analysis	To evaluate the implant-specific femoral BMD changes 5 yr after THA, comparing a cementless bone preserving stem (Fitmore, Zimmer Biomet, Warsaw, IN) and a cementless straight stem (CLS Spotorno, Zimmer Biomet, Warsaw, IN), using DXA	Fitmore short stem = 57 -Mean age = 56.8 years Male = 36 Female = 21 CLS straight stem = 83 -Mean age = 59.1 years Male = 52 Female =31	Hip	DXA	T0 = Post surg (7d) T1 = 12m T2 = 60m	Fitmore, Zimmer Biomet, Warsaw, IN + CLS Spotorno, Zimmer Biomet, Warsaw, IN	Cementless	Gruen zone ROI 7 Femur
Meyer, J et al.[59]	Orthopaedics & Traumatology: surgery & research, Q1 (2020)	Prospective randomized study without control group	To evaluate if there is an influence of gender on implant-specific stress shielding after implantation of a curved bone preserving hip stem (Fitmore, Zimmer Biomet, Warsaw, IN, USA) 5 years postoperatively	n° = 57 Male = 37 - Mean age = 59.3 ± 8 years Female = 20 - Mean age = 55.4 ± 11.2 years	Hip	DXA	T0 = Post surg (7d) T1 = 12m T2 = 60m	Fitmore, Zimmer Biomet, Warsaw, IN + CLS Spotorno, Zimmer Biomet, Warsaw, IN	Cementless	Gruen Zone ROI 7 Femur
Minoda, Y et al.[60]	Knee Surgery, Sports Traumatology, Arthroscopy, Q1 (2022)	Prospective comparative stud	To determine whether the advantage of mobile-bearing TKA over conventional fixed-bearing TKA changes even at a mean of 11 years postoperatively	Mobile-bearing prosthesis = 28 Fixed-bearing prosthesis = 28	Knee	DXA	T0 = Post surg (2w) T1 = 3m T2 = 6m T3 = 12m T4 = 18m T5 = 24m T6 = 5y then annually thereafter	Fixed-bearing posterior stabilized (PS) prosthesis (NexGen LPS-Flex; Zimmer Biomet, Warsaw, IN, USA) + Mobile-bearing PS prosthesis (P.F.C. Sigma RP; DePuy Synthes, Raynham, MA, USA)	Cemented	ROI 3 Femur
Minoda, Y et al.[61]	The Knee, Q2 (2022)	Prospective cohort study	To compare the peg position and BMD around the peg in a cementless porous tantalum tibial component after TKA using the same study population of our previous report	n° = 27 -Mean age = 74 ± 7 years Male = 6 Female = 21	Knee	DXA	T0 = Post surg (2w) T1 = 1y T2 = 2y	Porous tantalum tibial component (Trabecular metal monoblock tibial component; Zimmer) + Fixed bearing posterior stabilized prosthesis (NexGen LPS-Flex; Zimmer)	Cementless	ROI 3 Tibia
Minoda, Y et al.[62]	The journal of arthroplasty (2013)	Matched cohort study	To compare the BMD in the proximal part of the tibia between TKA using a porous tantalum tibial component than that using a conventional cemented cobalt-chromium tibial component for 5 years	Trabecular metal group = 21 -Mean age = 72.6 ± 6.7 years Male = 4 Female = 18 Cemented group = 21 -Mean age = 71.1 ± 6.3 years Male = 5 Female = 17	Knee	DXA	T0 = Post surg (2w) T1 = 3y T2 = 4y T3 = 5y	Porous tantalum tibial component and cemented cobalt-chromium femoral component (NexGen LPS-Flex; Zimmer) + Cemented cobalt-chromium-alloy tibial component (P.F.C. Sigma RP; DePuy, Warsaw, IN)	Cemented	ROI 3 Tibia

Minoda, Y et al.[63]	The journal of arthroplasty (2020)	Clinical Trial	To update a matched cohort study at a minimum of 6 years' follow-up period	Trabecular metal group = 20 -Mean age = 72.4 ± 6.5 years Male= 2 Female = 18 Cemented group = 18 -Mean age = 70.7 ± 6.7 years Male = 5 Female = 13	Knee	DXA	T0 = Post surg (2w) T1 = 1y T2 = 5y T3 = 11y	Porous tantalum tibial component and a cemented cobaltchromium femoral component (NexGen LPS-Flex; Zimmer) + Cemented cobalt-chromiumalloy tibial component (P.F.C. Sigma RP; DePuy, Warsaw, IN),	Cemented	ROI 3 Tibia
Morita, D et al.[64]	Journal of Orthopaedic Science, Q2 (2016)	Prospective study	To prospectively quantify longitudinal changes in BMD for more than 3 years after the insertion of a cemented Exeter universal stem and determine the extent to which gender, age at surgery, weight, height, body mass index (BMI), surgical side, stem subsidence, and Japanese Orthopedic Association (JOA) score affected these changes	n° = 150 Hip = 165 Male= 20 Female = 130	Hip	DXA	T0 = Post surg (2w) T1 = 3y	Stryker Orthopaedics, Mahwah, New Jersey, USA	Cemented	Gruen Zone ROI 7 Femur
Motomura, G et al.[65]	Scientific reports, Q1 (2022)	Multicenter randomized controlled study	To compare stems with a porous tantalum surface versus a titanium fiber mesh surface stem in terms of periprosthetic bone remodeling	n° 118 Male= 11 Female= 107 Trabecular metal = 59 -Mean age= 62.1 ± 8.5 years Male= 4 Female = 55 VerSys = 59 -Mean age = 60.9 ± 8.0 years Male= 7 Female = 52	Hip	DXA	T0 = Post surg (1w) T1 = 6m T2 = 12m T3 = 24m	Trabecular Metal Primary Hip Prosthesis; Zimmer-Biomet, Warsaw, IN + VerSys HA-TCP Fiber Metal Taper Stem; Zimmer-Biomet	Cementless	Gruen Zone ROI 7 Femur
Nysted, M et al.[66]	Acta Orthopaedica, Q1 (2011)	Prospective comparative study	To compare the medium-term changes in BMD in the proximal femur after insertion of an uncemented, customized femoral stem and an uncemented, standard anatomical femoral stem	n° = 87 Male= 31 Female = 56 ABG-I femoral stem = 41 Unique femoral stem = 46	Hip	DXA	T0 = Post surg T1 = 3m T2 = 6m T3 = 12m T4 = 24m T5 = 36m T6 = 60m	SCP, Trondheim, Norway + Stryker-Howmedica, Allendale, NJ	Cementless	Gruen Zone ROI 7 Femur
Nyström, A et al.[67]	Acta Orthopaedica, Q1 (2022)	Prospective cohort study	To examine the long-term changes in periprosthetic BMD and stability of the CFP stem	n° = 21 -Mean age = 64 years -Age range = 55-73 years Male= 11 Female = 10	Hip	DXA	T0 = Post surg (2d) T1 = 1y T2 = 2y T3 = 8y	Uncemented CFP stem + Uncemented trabeculae-oriented pattern (TOP) cup (Waldemar Link GmbH & vCo. KG, Hamburg, Germany)	Cementless	Gruen Zone ROI 7 Femur

Panisello, J et al.[68]	International Orthopaedics (2009)	Prospective cohort study	To quantify the effect that a thinner, shorter and polished diaphyseal part of the stem had on promoting better metaphyseal load transfer by analysing the BMD changes in the proximal femur	ABG-I group = 56 -Mean age = 60.1 years -Age range = 39–85 years Male = 27 Female = 29 ABG-II group = 54 -Mean age = 59,2 years -Age range = 38–83 years Male = 26 Female = 28	Hip	DXA	ABG-I stem T0 = Post surg T1 = 6m T2 = 1y T3 = 10y ABG-II stem T0 = Post surg (15d) T1 = 6m T2 = 1y T3= 5y	ABG-I stem + ABG-II stem	Cementless	Gruen Zone ROI 7 Femur
Panisello, J et al.[69]	The Journal of Arthroplasty (2009)	Prospective and controlled study	-To determine the pattern of remodeling produced by this stem -To quantify the changes of BMD in the 7 zones of Gruen throughout the follow-up -To prove or reject the presence of positive long term remodeling -To quantify the effect of aging on periprosthetic BMD	n° = 61	Hip	DXA	T0 = Post surg T1 = 6m T2 = 1y T3 = 10y	ABG-I stem (Stryker, Howmedica)	Cementless	Gruen Zone ROI 7 Femur
Pitto, R et al.[70]	International Orthopedics (2008)	Prospective study	To assess femoral bone adaptive remodelling around an uncemented femoral component with a taper design and hydroxyapatite (HA) coating	n° = 29 - Mean age = 58 years -Age range = 30–80 years Male = 16 Female = 13 Hip = 32	Hip	qCT	T0 = Post surg T1 = 1y T2 = 2y	THA with a taper-design femoral component coated with HA (Summit; DePuy International, Leeds, UK) + Press-fit titanium cup (Duraloc; DePuy) with alumina-alumina pairing (Biolox, CeramTec, Plochingen, Germany)	Cementless	2mm slice ROI 5 Femur
Pitto, R et al.[71]	International Orthopedics (2010)	Prospective study one-cohort	To assess femoral bone adaptive remodelling around an uncemented femoral component with a taper design and hydroxyapatite (HA) coating five years after the index operation	n° = 29 -Mean age = 58 years Male = 16 Female = 13 Hip = 31 hips	Hip	qCT	T0 = Post surg T1 = 1y T2 = 2y T3 = 5y	THA with a taper-design femoral component coated with HA (Summit; DePuy International, Leeds, UK) + Press-fit titanium cup (Duraloc; DePuy) with ceramic−ceramic pairing (Biolox Delta, CeramTec, Plochingen, Germany)	Cementless	2mm slice ROI 5 Femur
Rathsach Andersen, M et al.[72]	Acta Orthopedica, Q1 (2019)	Randomized controlled trial	To quantify bone remodeling of the proximal tibia after implantation of the Trabecular Metal Technology (TMT) Zimmer Nexgen	n° = 70 Age < 70	Knee	DXA	T0 = Post surg (1w) T1 = 3m T2 = 6m T3 = 12m T4 = 24m	Zimmer Nexgen Flex	Cementless	ROI 3 Tibia

Saari, T et al.[73]	Journal of Orthopedic research (2007)	Randomized trial	To compare BMD changes in Resection vs retention of PCL in TKA	PCL retained and flat insert -Mean age = 69 years -Age range = 51–77 years Male = 1 Female = 12 PCL retained and concave insert -Mean age = 66 years Age range = 59–79 years Male = 3 Female = 8 PCL resected and concave insert -Mean age = 69 years Age range = 50–82 years Male = 4 Female = 11 PCL resected and posterior stabilized insert -Mean age = 78 years -Age range = 55–81 years Male = 3 Female = 4	Knee	DXA	T0 = Post surg (7d) T1 = 1y T2 = 2y T3 =5y	AMK TKR (DePuy; Johnson & Johnson, Leeds, UK)	Cemented	ROI 3 Tibia
Soininvaara, T et al.[74]	Clinical Physiology and functional imaging, Q2 (2008)	Comparative study	To investigate early regional periprosthetic BMD changes in comparison with metabolic activity detected by single photon emission computed tomog-raphy (SPECT)	n° = 16 -Mean age = 66 years Male = 5 Female = 11	Knee	DXA	T0 = Post surg T1 = 6m T2 = 1y T3 = 2y	Duracon modular (Howmedica Inc. Rutherford, NJ⁄International Division of Pfizer) + Nexgen (Zimmer, Warsaw, IN, USA) + AMK (DePuy, Division of Boehringer Mannheim Corporation⁄De Puy, Warsaw, IN, USA).	Cemented	ROI 3 Tibia ROI 3 Femur
Soininvaara, T et al.[75]	The knee, Q1 (2013)	Prospective case control study	To determine whether UKA preserves periprosthetic BMD, particularly in the femoral regions	n° = 21 -Mean age = 65.2 years Male = 8 Female = 13	Knee	DXA	T0 = Post surg (7d) T1 = 3m T2 = 6m T3 = 1y T4 =2y T5 =4y T6 =7y	Duracon unicondylar (Howmedica International Inc., Division of Pfizer Hospital Product Group, Shannon Industrial Estate, Ireland) + Miller-Galante (Zimmer, Warsaw, IN, USA)		ROI 3 Tibia ROI 5 Femur ROI 1 Patella

Steens, W et al.[76]	BMC Musculoskeletal Disorders, Q1 (2015)	Prospective study one-cohort	To prospectively investigate the in vivo changes of BMD as a parameter of bone remodeling around a short, femoral neck prosthesis over the first 5 years following implantation	n° = 20 Male = 12 Female = 8	Hip	DXA	T0 = Post surg (10d) T1 = 3m T2 = 12m T3 = 60m	"Stemless" ESKA CUT 2000 femoral neck prosthesis (ESKA Orthodynamics, Luebeck, Germany)	Cementless	Gruen Zones ROI 7 Femur
Stilling, M et al.[77]	Orthopaedic Surgery, Q4 (2012)	Randomized controlled trial	To present preliminary clinical and radiological results at 6 months follow-up after Copeland and Global Cap RHHI	n° = 21 -Mean age = 64 years -Age range = 39–82 years Male = 11 Female = 10 Copeland group = 10 -Mean age = 66 years -Age range = 40–82 years Male = 6 Female = 3 Global C.A.P. group = 11 -Mean age = 61 years -Age range = 53–83 years Male = 4 Female = 6	Shoulder	DXA	T0 = Post surg T1 = 6m	Copeland (Biomet Inc.) + Global C.A.P. (DePuy Int)	Cementless	ROI 1 Humerus
Synder, M et al.[78]	Orthopedics, Q1 (2015)	Prospective study	To evaluate early bone remodeling around the Metha stem during 12 months of follow-up	n° = 36 -Mean age = 50.4 years Male = 18 Female = 18	Hip	DXA	T0 = Post surg (10d) T1 = 3m T2 = 6m T3 = 12m	Metha stem		Gruen Zone ROI 7 Femur
Tapaninen, T et al.[79]	Scandinavian Journal of Surgery, Q2 (2012)	Clinical trial	To study the BMD changes 3 and 12 months after RHA	n° = 26 -Mean age = 55.2 years Male = 22 Female = 4	Hip	DXA	T0 = Post surg T1 = 3m T2 = 1y	Birmingham hip resurfacing system (Smith & Nephew UK, London, WC2N 6LA, UK.) + Conserve (plus) (Wright Medical Technology, Inc. Arlington, TN 38002, USA) + Cormet (Stryker, Kalamazoo, MI 49002, USA) + Biomet Recap (Biomet, Inc. Warsaw, Indiana, 46581-0587, USA)		Gruen Zone ROI 4 Femural neck
ten Broeke, R et al.[80]	Hip international, Q1 (2012)	Randomized clinical trial	To compare bone remodelling around two uncemented stems	Symax stem = 25 Omnifit-HA = 24	Hip	DXA	T0 = Post surg (1w) T1 = 6w T2 = 3m T3 = 6m T4 = 1y T5 = 2y	SymaxTM (n=25) + Omnifit® (n=24) stems	Cementless	Gruen Zone ROI 7 Femur

Venesmaa, P et al.[81]	Acta ortopedica scandinava (2003)	Prospective study	To eter-mined the periprosthetic BMD change in femoral bone after cemented THA over a 5-year period	n° = 17 -Mean age = 68 years Male = 7 Female = 10	Hip	DXA	T0 = Post surg (2w) T1 = 3m T2 = 6m T3 = 1y T4 = 2y T5 = 3y T6 = 5y	Cobalt-chrome Lubinus SPII stems with a collar (Waldemar Link MBH&CD, Germany)	Cemented	Gruen Zone ROI 7 Femur
Vidovic, D et al.[82]	Injury, Q1 (2013)	Randomized clinical trial	To evaluate the magnitude of BMD as well as the clinical results after cemented and cementless haemiarthroplasty (HA) for femoral neck fracture	n° = 60 Cemented group A = 30 -Mean age = 82.90 ± 4.63 years Uncemented group B = 30 -Mean age = 82.04 ± 4.32 years	Hip	DXA	T0 = Post surg (1m) T1 = 3m T2 = 6m T3 = 1y	Cemented + Cementless haemiarthroplasty (HA)	Cemented and Cementless	Gruen Zone ROI 7 Femur
Winther, N et al.[83]	International orthopaedics, Q1 (2015)	Randomized controlled trial	To evaluate the adaptive bone remodeling of the proximal tibia after uncemented TKA using a tibial tray with Regenerex coating compared to a well-proven standard porous coated (PPS) tibial tray	n° = 61 Regenerex = 31 -Mean age = 63 years Male = 16 Female = 15 Porous plasma = 30 -Mean age = 62 years Male = 11 Female = 19	Knee	DXA	T0 = Post surg (1w) T1 = 3m T2 = 6m T3 = 12m T4 = 24m	Vanguard PPS (Biomet, Warsaw, Indiana, USA) + Vanguard Regenerex Primary Tibial Tray (Biomet, Warsaw, Indiana, USA)	Cementless	ROI 3 Tibia
Zerahn, B et al.[84]	Hip International, Q1 (2011)	Prospective randomized study	To assess whether different bearing materials have an impact on femoral bone remodeling within the first four years after a hybrid THA	n ° 398 Group A: Zirconia ceramic head, polyethylene cup = 97 Group B: Cobalt-Chrome-Molybdenum head and cup = 88 Group C: Zirconia ceramic head, polyethylene moulded on the Titanium shell of the Asian cup = 122 Group D: Alumina head and cup = 91	Hip	DXA	T0 = Post surg (1w) T1 = 4y	Universal RingLoc Ti6Al4V-alloy (Biomet, Warsaw, Indiana, USA)	Cemented	Gruen Zones ROI 7 Femur

NB. DXA: Dual-Energy X-ray Absorptiometry; ROI: region of interest; BMD: bone mineral density; BMI: body mass index; TKA: total knee arthroplasty; THA: total hip arthroplasty; RHA: resurfacing hip arthroplasty; UKA: Unicompartmental knee arthroplasty; PS: Posterior stabilized; MB: Mobile-bearing; FB: Fixed-bearing; PCL: Posterior cruciate ligament; TOP: trabeculae-oriented pattern; AMK: Anatomic Modular Knee; AML: Anatomic Medullary Locking; BFH: Big Femoral Head; TMT: Trabecular Metal Technology; HA: hydroxyapatite; PPS: standard porous coated; Surg.: surgery; m: month; w: week; d: day;

Among the articles included, 55 articles analyzed the hip joint, of which 45 used the standard 7 Gruen zones to determine the ROIs around the femoral component, while 5, 4, 2 ROIs were evaluated by three, two, and one studies respectively.

The acetabulum was investigated in 7 studies, the majority (4) considered 3 ROIs, 2 papers inspected 5 ROI and 4 ROI were studied in one publication. Three articles analyzed both the acetabulum and the femur with 4 and 7 ROI respectively.

Since there is no standardized description of periprosthetic ROIs in total knee arthroplasty, the 12 articles[4, 32, 49, 65–68, 84, 88, 90, 91, 105] that investigated this joint measured BMD in different regions. The tibia was evaluated in 8 studies, the femur in 4 studies and 2 articles investigated both districts. Unicompartmental knee arthroplasty (UKA) was the topic of interest of 2 included articles, one of which assessed the tibial, femoral, and patellar periprosthetic bone, while the other only the tibia.

Furthermore, concerning the fixation technique used for the implant, 16 studies evaluated cemented hips, 42 cementless hip implants, 4 both cemented and cementless. Cemented knee implants were evaluated in 8 studies and 6 papers assessed cementless knee prosthesis. Two analyzed both cementless and cemented knee prostheses.

Only 1 article measured BMD variation after total shoulder replacement was found.

Risk of bias in studies

A total of 68 articles were reviewed, and out of these, 16 were evaluated using ROB2. Eleven of the 16 articles had a moderate risk of bias, and five of the 16 had a high risk. The JBI evaluated the other articles. The JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies was used to evaluate a total of 32 articles; the JBI Critical Appraisal Checklist for Cohort Studies was used to evaluate 17 articles; the JBI Critical Appraisal Checklist for Case Series was used to evaluate one article; and the JBI Critical Appraisal Checklist for Quasi-Experimental Studies was used to evaluate two articles. In supplementary material (Annex A - Tab. S2-5), the methodological quality's results are documented.

Total Hip Arthroplasty

A comparison of the weighted mean BMD among the articles over the time was performed. Concerning the femoral component, only studies with hip replacement that used the standard Gruen Zone (7 ROI) method for the femoral periprosthetic BMD evaluation and that reported the results in g/cm2 were taken into consideration. Consequently, a total of 3,473 hips were included in this analysis. The evaluations performed within the first month of surgery were considered as baseline. All the absolute values of BMD and percentage differences between the baseline and follow-up are reported in Supplementary material (Annex A - Tab. S7-8).

To conduct our analysis, only follow-up periods with over 800 patients, which corresponded to 3, 6, 12, 24, and 60 months, were considered (Tab. 2). The overall baseline BMD in THA was 1.49 g/cm2 considering all 7 Gruen zones, and 1.04 g/cm2 in the acetabular ROIs (Annex A - Tab. S9). The negative peak of BMD decrease has been observed at 6-month follow up (-7.6% from baseline), then BMD increased at 60 months (0.4%).

Table 2. Bone mineral density after THA

ROI	Post surg	3m		6m		12m		24m		60m	
	Mean (g/cm^2)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)
1	0.90	0.83	-7.8%	0.72	-19.3%	0.78	-12.7%	0.83	-7.7%	0.81	-9.7%
2	1.55	1.48	-4.5%	1.42	-8.2%	1.51	-2.7%	1.55	0.0%	1.52	-1.5%
3	1.74	1.83	5.1%	1.67	-4.4%	1.82	4.6%	1.79	2.7%	1.85	6.2%
4	1.75	1.87	7.1%	1.71	-2.1%	1.84	5.2%	1.84	5.4%	1.84	5.3%
5	1.79	1.84	3.2%	1.72	-3.5%	1.85	3.4%	1.83	2.7%	1.87	4.7%
6	1.51	1.48	-2.3%	1.41	-7.2%	1.48	-2.1%	1.51	-0.5%	1.51	-0.4%
7	1.21	1.06	-12.2%	1.00	-17.8%	1.05	-13.3%	1.05	-13.1%	1.09	-10.2%
Mean	1.49	1.48	-0.5%	1.38	-7.6%	1.48	-1.1%	1.49	-0.4%	1.50	0.4%
Hip (n°)	3473	898		1383		2255		1277		836	

Considering the variation of each Gruen zone, ROI 1 (equivalent to the greater trochanter) and 7 (equivalent to the calcar region) registered the greatest BMD decrease at every follow up measurement, with a nadir at 6 months and at 60 months. Conversely, ROIs 3, 4, 5 and 6 showed a different trend, with a decrease of BMD at 6 months, whereas, at 60 months, they registered an increase from baseline (Fig. 2).

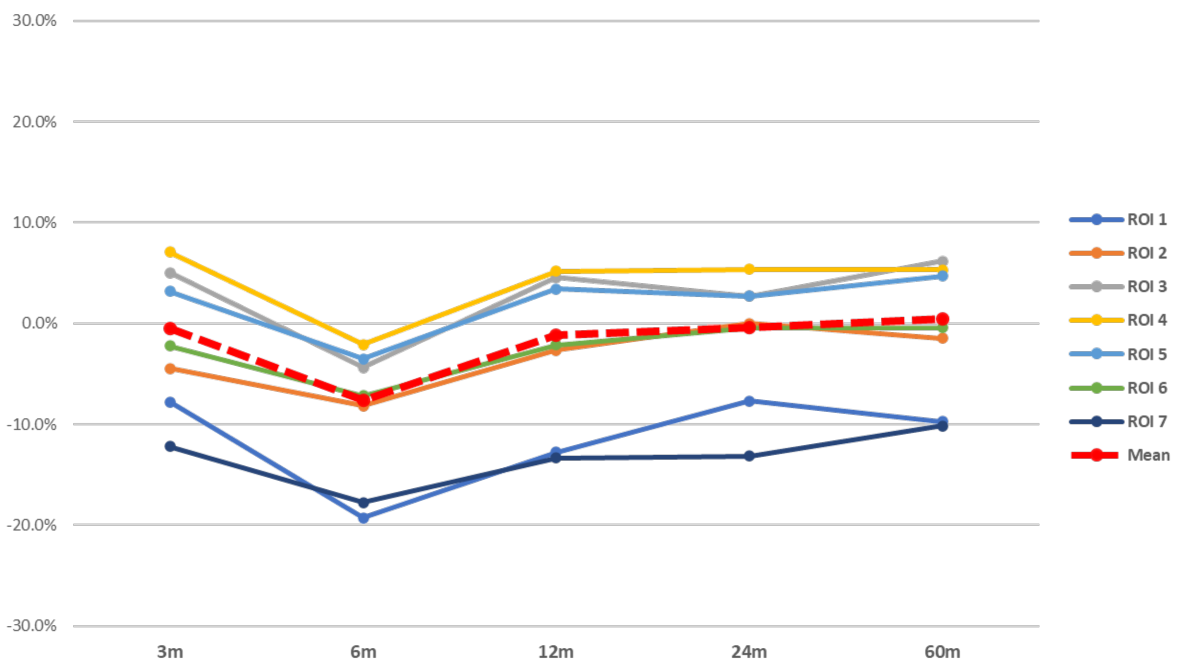

Figure 2. Overall BMD variation (%) after THA

Fixation technique in THA

A total of 813 cemented hips and 2,660 cementless femoral implants were included in this analysis (Tab. 3). The comparison of the weighted means showed a greater average BMD decrease in cemented compared to cementless implants at 60 months follow-up. Furthermore, cemented implants showed a considerable BMD decrease compared to cementless stems at 3 and 6-months follow-up. However, an increased bone resorption was observed at the level of the proximal femur in both designs, with a more pronounced decrease in cementless stems (Fig. 3).

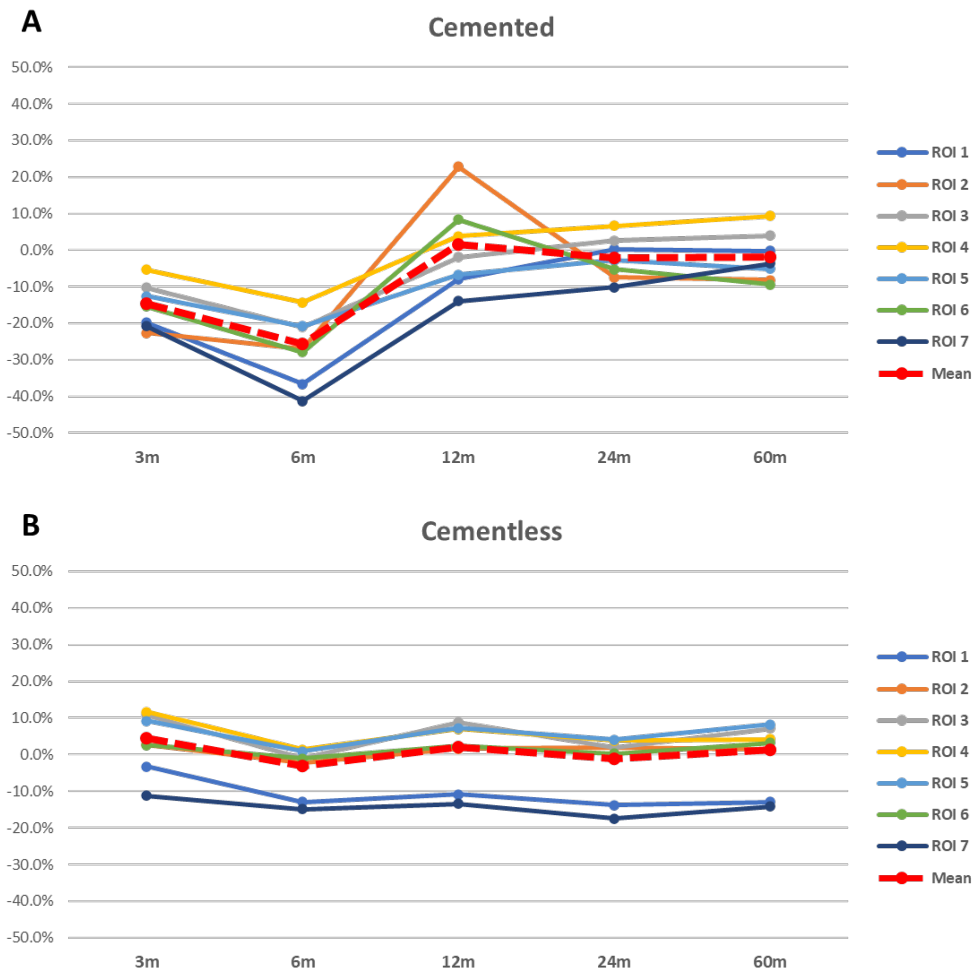

Figure 3. Femoral Bone Mineral Density comparison between Cemented and Cementless stems in THA across ROIs between the baseline and Follow-up times

Note: A, Cemented stems BMD; B, Cementless stems BMD

Table 3. Comparison of BMD variation (%) between Cemented and Cementless Hip replacement between the baseline and follow-up times

	Cemented					Cementless				
ROI	3m	6m	12m	24m	60m	3m	6m	12m	24m	60m
1	-19.8%	-36.6%	-7.9%	0.2%	-0.3%	-3.3%	-12.9%	-10.8%	-13.7%	-12.9%
2	-22.7%	-27.0%	22.9%	-7.4%	-8.1%	2.8%	-2.2%	1.6%	2.0%	1.3%
3	-10.3%	-21.0%	-2.0%	2.5%	3.9%	10.8%	-1.0%	8.8%	2.0%	7.1%
4	-5.4%	-14.3%	3.8%	6.6%	9.3%	11.6%	1.4%	7.0%	3.8%	4.2%
5	-12.6%	-20.8%	-6.7%	-2.8%	-5.2%	9.1%	0.8%	7.3%	4.1%	8.3%
6	-15.4%	-28.0%	8.4%	-5.3%	-9.4%	2.6%	-1.0%	2.3%	0.3%	3.2%
7	-20.8%	-41.2%	-13.9%	-10.1%	-3.6%	-11.2%	-14.9%	-13.4%	-17.5%	-14.1%
Mean	-14.7%	-25.6%	1.6%	-2.1%	-1.8%	4.5%	-3.1%	2.0%	-1.2%	1.2%
Hip (n°)	241	86	326	358	187	657	1297	1929	919	649

Implant design in THA

Concerning the THA stem design, a total of 1,187 tapered and 1,646 anatomic stems were analyzed (Tab. 4). Tapered stems showed a greater average BMD decrease at each follow-up compared to anatomic stems. The greatest bone resorption was recorded at 6 months of follow-up at the level of the proximal femur in both designs, however tapered stems showed a greater decrease in BMD than anatomical ones. At 60 months follow-up the anatomical stems recorded a considerable loss of BMD at the level of the proximal femur (ROI 1 and 7), whereas tapered stems showed a more uniform distribution of bone loss around the stem (Fig. 4).

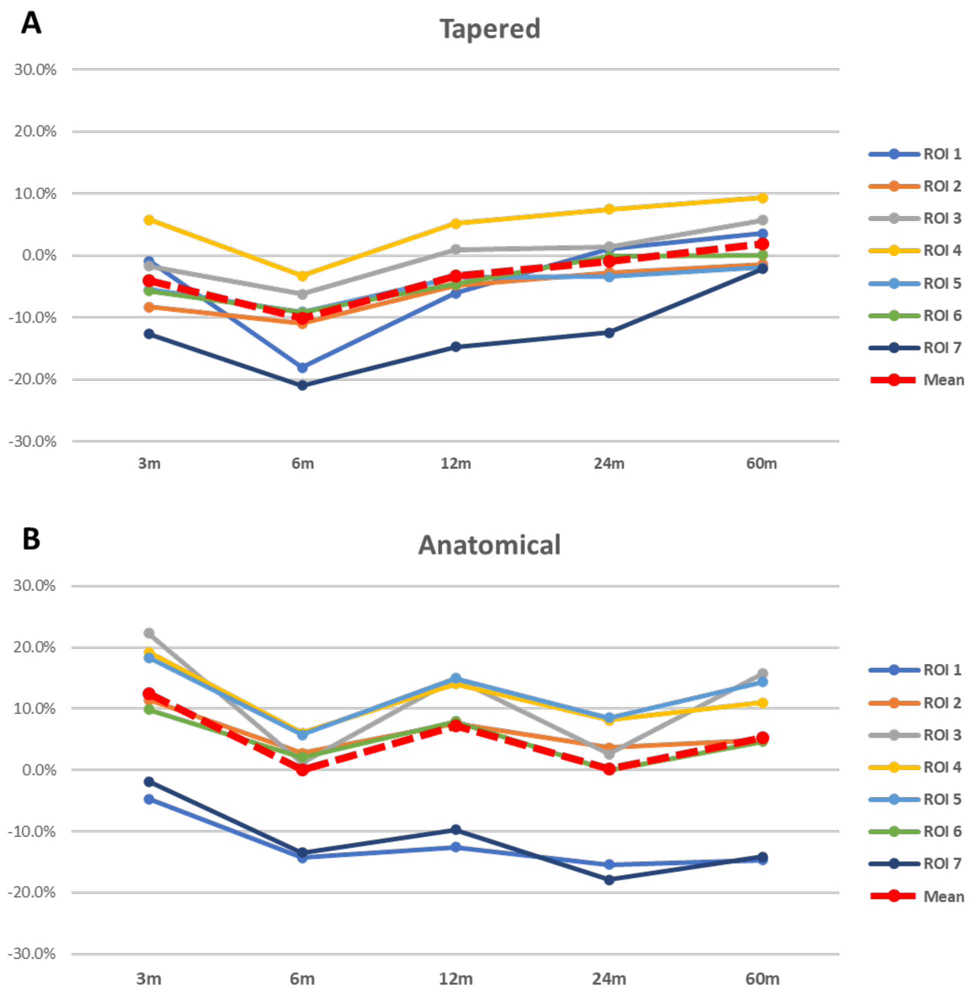

Figure 4. Femoral BMD Comparison between Stem Designs THA across ROIs between the baseline and Follow-up times

Note: A, Tapered stems; B, Anatomical stems

Table 4. Comparison of BMD between Tapered and Anatomic designs in Hip

	Tapered					Anatomic				
ROI	3m	6m	12m	24m	60m	3m	6m	12m	24m	60m
1	-0.9%	-18.1%	-6.1%	1.1%	3.6%	-4.7%	-14.3%	-12.5%	-15.4%	-14.7%
2	-8.3%	-11.0%	-4.8%	-2.8%	-1.4%	11.5%	2.8%	7.5%	3.7%	4.9%
3	-1.7%	-6.2%	1.0%	1.4%	5.7%	22.3%	1.2%	14.9%	2.6%	15.7%
4	5.7%	-3.2%	5.2%	7.5%	9.3%	19.2%	6.0%	14.1%	8.1%	11.0%
5	-5.5%	-9.1%	-3.5%	-3.4%	-1.9%	18.3%	5.8%	14.9%	8.5%	14.4%
6	-5.7%	-9.2%	-4.6%	-0.1%	0.1%	9.9%	2.1%	8.0%	0.0%	4.6%
7	-12.7%	-21.0%	-14.7%	-12.5%	-2.1%	-1.8%	-13.5%	-9.7%	-17.9%	-14.1%
Mean	-4.0%	-10.1%	-3.2%	-1.0%	1.9%	12.5%	0.0%	7.3%	0.2%	5.2%
Hip (n°)	326	515	763	708	311	434	602	1053	456	315

Acetabular component

A total of 7 studies including 609 cups measured periprosthetic acetabular bone density. A standardized description of the ROIs around the acetabular cup was described by DeLee and Charnley, who identified 3 regions: lateral, central and medial[23]. Nevertheless, 4 studies among them used these ROIs[28, 41, 47, 48], while Digas et al.[25] and Gerhardt et al.[33] analyzed 5 ROIs, and Gauthier et al. 4 ROIs[31].

The authors who utilized DeLee and Charnley's zones observed the following pattern: BMD in ROI 1 (lateral) increased from baseline to 6, 12, 24, and 60 months. A similar behavior was evident in ROI 2 (central) with a smaller increase. Whereas BMD in ROI 3 (medial) showed an initial decline at 6 months and a subsequent increase at 12 months follow-up. However, BMD decreased in later follow-up periods (24-60 months).

Data obtained from articles that used three ROI to assess the acetabular BMD were reported in Table S9 (Annex A – Tab. S9). Articles using more then three ROI were escluded from the analysis to reduce the heterogenity of the data.

Total Knee Arthroplasty

Studies analyzing the variation of BMD in knee replacements showed a high variability in the method of measurement. A systematic analysis of the data was only possible for studies concerning the BMD variation around the tibial component, where 2 ROIs, medial and lateral, were identified. Only data presented as g/cm2 were analyzed, with a minimum sample of 50 knees. Finally, a total of 476 tibiae were included in this analysis, with an overall periprosthetic BMD (medial and lateral) of 0.95 g/cm2. On average, a steady decrease in BMD was observed around the tibial component at each follow-up measurement (Tab. 5). However, the medial compartment showed a greater decrease than the lateral, which started to decrease after 12 months (Fig. 5).

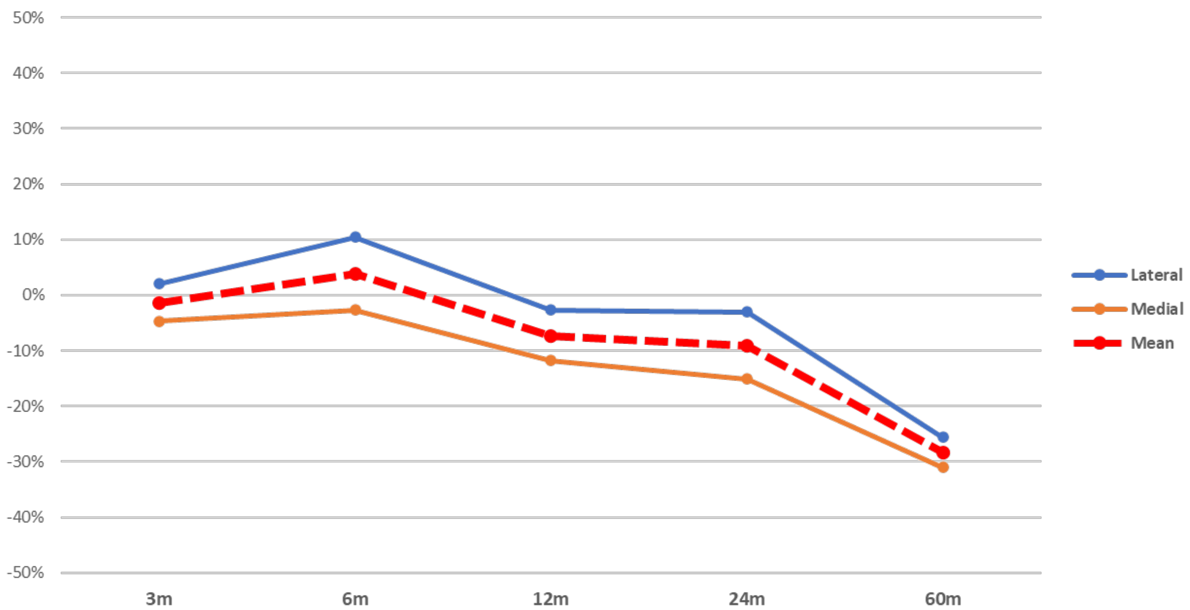

Figure 5. Overall BMD variation (%) after TKA

Table 5. Bone mineral density around tibial component after TKA

ROI	Post surg	3m		6m		12m		24m		60m	
	Mean (g/cm^2)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)	Mean (g/cm^2)	Difference (%)
Medial	0.95	0.91	-4.7%	0.93	-2.7%	0.84	-11.8%	0.81	-15.1%	0.66	-31.0%
Lateral	0.94	0.96	2.0%	1.04	10.4%	0.91	-2.7%	0.91	-3.0%	0.70	-25.6%
Mean	0.95	0.93	-1.4%	0.98	3.8%	0.88	-7.3%	0.86	-9.1%	0.68	-28.4%
Diff M-L (%)	1.6%	-5.1%		-10.5%		-7.9%		-11.1%		-5.8%	
Knee (n°)	476	307		217		396		290		88	

NB. Diff: difference; M: Medial; L: Lateral

Fixation technique in TKA

A total of 207 cemented and 269 cementless implants were examined, with 3, 12 and 24 months follow-up (Tab. 6). Due to the small sample size, 6 months follow up was excluded from this analysis. Cemented implants showed a greater decrease in mean BMD at tibial level in each follow-up than cementless implants. Furthermore, the greatest decrease in BMD was reported in the lateral compartment in cemented implants and in the medial compartment in cementless implants (Fig. 6).

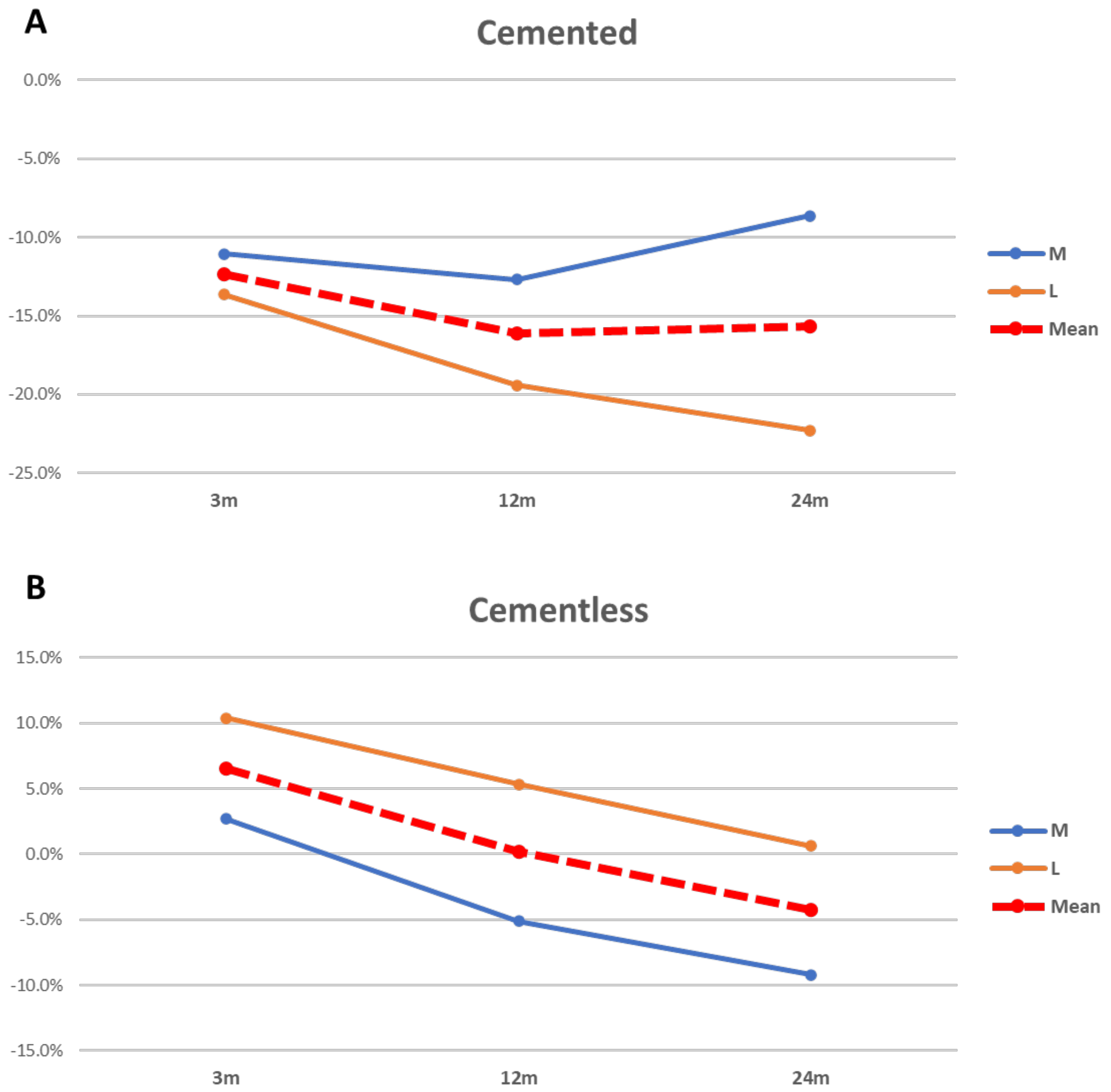

Figure 6. BMD Comparison between Cemented and Cementless TKR across ROIs between the baseline and Follow-up times

Note: A, Cemented knee prosthesis; B, Cementless knee prosthesis

Table 6. BMD of tibial component after cemented vs cementless TKA

	Cemented			Cementless		
ROI	3m	12m	24m	3m	12m	24m
M	-11.0%	-12.7%	-8.6%	2.7%	-5.1%	-9.2%
L	-13.6%	-19.4%	-22.3%	10.4%	5.3%	0.6%
Mean	-12.4%	-16.1%	-15.6%	6.6%	0.1%	-4.3%
Knee (n°)	106	168	62	201	228	228

Implant design in TKA

Data about BMD changes in posterior stabilized (PS) and cruciate retaining (CR) were analyzed and compared. At baseline (post-surgery), periprosthetic BMD was measured in 114 PS and 240 CR implants, then at 12, 24 and 60 months follow up (Tab. 7). PS implants showed a greater decrease in BMD than CR implants, with greater bone resorption in the medial compartment. On the other hand, CR implants showed a similar trend of BMD decrease between the two compartments (Fig. 7).

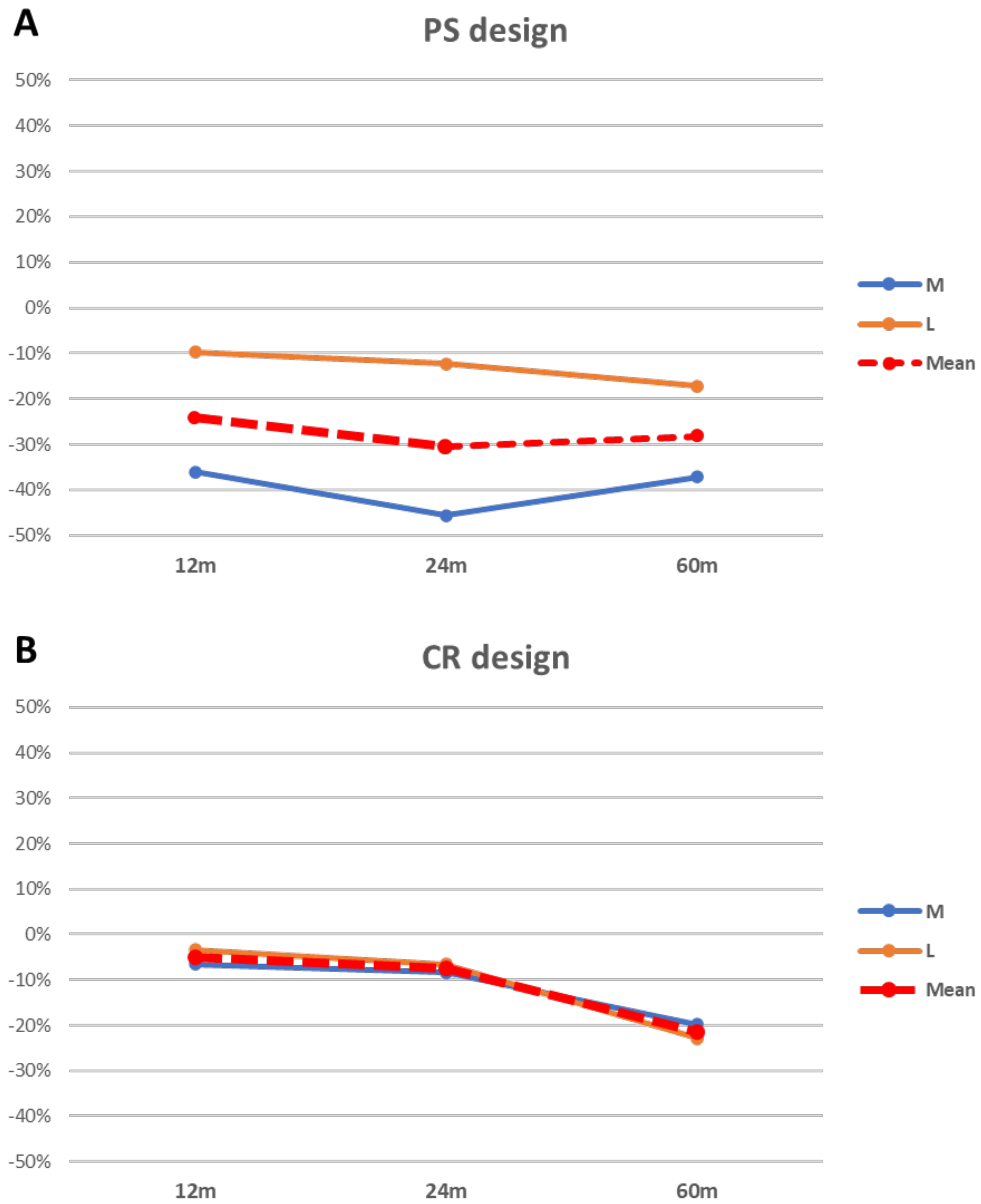

Figure 7. BMD Comparison between Knee prosthesis design across ROIs between the baseline and Follow-up times

Note: A, Posterior stabilized design; B, Cruciate retaining design

Table 7. BMD of different knee prosthesis designs

	PS			CR		
ROI	12m	24m	60m	12m	24m	60m
M	-36%	-10%	8%	-7%	-8%	-20%
L	-10%	-3%	-5%	-3%	-7%	-23%
Mean	-24%	-6%	2%	-5%	-7%	-21%
Knee (n°)	34	34	49	240	240	39

NB. PS: posterior stabilized; CR: cruciate retaining; ROI: region of interest

Femoral component in TKA

Due to the absence of a standardized method for analyzing the variation of BMD in the femoral component, it was not feasible to conduct a comparative assessment of the results across different studies. However, the analysis of femoral BMD changes after TKA indicated greater overall bone resorption in the anterior femur, a region often susceptible to periprosthetic fractures, while one study comparing different type of inserts, showed more pronounced bone resorption at the level of posterior femoral condyles when using mobile bearing insert [65].

Total Shoulder Arthroplasty

Only one study analyzed periprosthetic bone in 22 shoulder arthroplasties[94]. The BMD was assessed at the humeral level, parallel to a line passing through the apex of the resurfacing implant. The BMD decreased of 22.4% from the baseline to 3 month-follow up and of 1.4% to 6 month-follow up (Annex A - Tab. S10).

Discussion

The main finding of this systematic review was that, after joint replacement, BMD changes depending on the anatomical region, fixation technique, and implant design. In THA, a significant overall bone resorption was reported at the level of the proximal femur. The use of cemented stems generally induced more bone loss than cementless stems, with a rapid decrease in the first post-operative months, to then stabilize at mid-term follow-up. Anatomical stems better preserved BMD but with a higher risk of fractures and a more pronounced bone loss in the proximal femur compared with cemented stems.

In TKA, the medial tibial compartment and the anterior region of the distal femur reported the greater BMD loss, while considering the fixation technique, cementless implants showed a lower bone loss compared to cemented implants. Additionally, posterior-stabilized design produced a more pronounced bone resorption compared to cruciate-retaining design.

Total Hip Arthroplasty

The variation in BMD after THA was well documented and the use of Gruen zones allowed a direct comparison between different studies.

Regardless of the type of stem or fixation technique used, a negative peak of average BMD was reported 6 months after surgery, due to the adaptive response of bone to surgical stress[2, 9]. Analyzing Gruen's zones separately, it emerged how different patterns of load transfer produced a great bone resorption in the proximal femoral metaphysis (ROI 1 and 7), a region subjected to a high strain energy density, while the Gruen zones 3, 4 and 5, showed a decrease of BMD at 6 months and an increase at 60 months compared to the baseline[38].

As demonstrated by Xu et al. in a finite element analysis, the bone mass of the proximal femur presents a triangular high-modulus distribution, which bore the main stress of the proximal femur. Our findings indicate that implanting a prosthesis with greater stiffness than bone shields the latter from absorbing loads, leading to stress shielding and a gradual depletion of the bone mineral matrix. [108]. Furthermore, as discussed below, this phenomenon is also influenced by the fixation technique and implant design used.

Fixation technique in THA

The use of cemented implants induced more bone resorption than cementless implants, with a marked difference at 6 months follow-up. This phenomenon could be attributable to the thermic stress to the endosteal bone induced by cement polymerization. However, the interface area of a cemented stem has been described as approximately 65 times greater than an uncemented calcar bearing stems[103, 104]. The uniform distribution of forces assured by the cement mantle could explain the preservation of BMD at the proximal femur in the medium term compared to cementless stems. A recent metanalysis comparing cemented and cementless THA did not demonstrate overall superiority of either method of fixation as measured by a difference in survival. However, it was found that cementless stems showed a higher survival rate in studies after 1995, while cemented stems showed a higher survival rate when considering studies not restricted to patients aged 55 or less[75]. This suggests that cemented stems should be preferred in elderly patients with poor bone quality that does not allow for proper osseointegration or that exposes them to the risk of intraoperative fractures, while modern uncemented stems should be implanted in younger patients in order to preserve the bone stock for the subsequent implant revision.

Implant design in THA

Regarding the stem design, anatomical stems showed an overall better preservation of BMD than tapered stems, with a more pronounced BMD loss at the proximal femur at medium-term follow-up. This could be due to the stronger fixation on metaphyseal region of the anatomical stems compared to the wider and more distal distribution of the forces with tapered stems. Moreover, while the use of anatomical stems has increased in recent years driven by the advent of minimally invasive surgery and supported by the evidence of the preservation of bone stock and reduction of stress shielding [16, 52], an increased risk of periprosthetic fractures has also been reported [7, 27]. Hence, based on our results, anatomical stems should be preferred in young subjects with good bone quality. However, considered the described complications, careful consideration must be given to the quality of the recipient bone and to the implant sizing to prevent inadequate primary stability in osteoporotic patients or when implanting undersized stems, and post-operative pain or intra-operative fractures using oversized stems.

Acetabular component

Only a few studies analyzed BMD changes around the acetabular component. Such phenomenon is influenced by several factors like the type of implant and the specific regions of interest examined. It appears that initial declines in BMD are not uncommon but may stabilize or even reverse in certain regions over time, according with Wolff's law [106] and particularly with specific implant types (more pronounced BMD losses in with threaded cups). Further research is likely needed to better understand the underlying mechanisms and clinical implications of these observed patterns.

Total Knee Arthroplasty

Data on BMD changes after TKA were more heterogeneous and a direct comparison between the various studies was only partially possible. Most of articles were focused on the tibia which, due to its geometry, is subject to higher peak forces and thus a higher rate of loosening than the femoral component, particularly in case of malalignment [42, 86]. In the studies analyzed, the medial tibial compartment showed a higher decrease in BMD compared to lateral compartment in each follow up. From a kinematic point of view, the medial tibiofemoral compartment is exposed to higher contact force in the native knee[50, 51]. As described by Winther et al.[105], this leads to a greater BMD decrease in the medial tibia after TKA. A gap in the literature emerges from these findings that would be interesting to investigate. Can tibial component alignment influence BMD variation at the implant/bone interface? This would provide interesting insights into the safety of current kinematic/personalized alignments.

Fixation technique in TKA

Analyzing fixation technique, cementless tibial components better preserved the BMD with respect to cemented implants, where the cementation technique, cement viscosity and other factors could influence the postoperative bone remodeling [85]. Furthermore, it was found that cemented implants showed a greater loss of BMD on the lateral compartment, whereas cementless tibial components showed a progressive BMD decrease in both medial and lateral compartment (Fig. 6). However, the data available was not sufficient to generalize this behavior, and further investigation is needed in future studies to explore this aspect thoroughly. Given the more extensive experience with cemented implants compared to cementless ones, cemented implants maintain their status as the gold standard in knee prosthetics.

Implant design in TKA

Comparing the trend of the PS and CR designs, the former showed a greater decrease in BMD than CR implants, with greater bone resorption in the medial compartment. Kinematic studies showed that PS implants generate a more pronounced medial pivot in loaded knee flexion than CR implants, where the translation has been shown similar between the two compartments[11]. This could cause a different distribution of forces to the periprosthetic bone [107].

However, conventional symmetrical CR implants are more challenging to balance due to the variable tension of the posterior cruciate ligament, which can lead to instability through what is known as paradoxical anterior translation of the femur. In contrast, PS implants offer greater intrinsic stability, and their balancing is more reproducible. Furthermore, implants with a CR femoral component and ultra-congruent or medially stabilized insert have been increasingly used in recent years, as they offer intrinsic stability comparable to PS implants. This could ensure greater preservation of periprosthetic BMD and will be investigated in future research by this study group.

Femoral component in TKA

Analysis of femoral BMD changes after TKA showed increased bone resorption in the anterior portion of the femur, an area frequently subject to periprosthetic fractures[59, 99]. Moreover, it seems that mobile bearing TKA may better preserve BMD at the femoral level compared to fixed bearings. However, there is no strong evidence, and further investigation with larger sample size is needed. Furthermore, studies involving SPECT for the evaluation of bone metabolism showed a prolonged uptake at the level of the distal femur compared to the proximal tibia. This technique has been recently used to evaluate unhappy patients with pain, stiffness or swelling after TKA, showing potential for identifying typical patterns of bone tracer uptake for specific pathologies [40]. The use of SPECT in combination with DXA could be promising for investigating the influence of materials with lower stiffness on periprosthetic BMD at the femoral level.

Total Shoulder Arthroplasty

The BMD trend after total shoulder arthroplasty was similar to that observed in other joints examined. However, the literature lacks comparisons of different designs and fixation techniques. This area deserves further investigation in future studies.

Limitations

This systematic review has several limitations. BMD values at baseline were highly variable between different studies, and this may depend on the patient's related factors (age, sex, comorbidities, pharmacological treatment, rehabilitation and level of physical activity), the quality of the bone tissue and the time between surgery and the first baseline DXA. These variables were not taken into account. Thus, to compare BMD trends between different studies, the percentage variation was considered for analysis instead of the nominal values. Moreover, despite the vast amount of data obtained from the reviewed studies, some of them included follow-ups that had a small sample size. Therefore, to reduce bias, unbalanced follow ups were excluded from the analysis.

Conclusions

This systematic review showed that periprosthetic BMD tends to decrease progressively after joint replacement surgery. The extent and pattern of this decline are influenced by the fixation technique and the implant design. These factors must be considered during the surgical planning, as they can have long-term implications for bone health and implant longevity. Further research is necessary to optimize implant design and surgical techniques to mitigate BMD loss and improve patient outcomes.

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AIM III: ***"Is it feasible to analyze BMD changes after TKA in clinical setting?"***

The analysis of BMD after TKA is still a developing area of research. There are some gap of knowledge on the topic and, how emerged from the systematic review presented above, there are no standardized methods of evaluating periprosthetic ROIs that allow a fair comparison of data from different studies. It was therefore decided to investigate this topic in order to introduce periprosthetic BMD evaluation in knee replacements implanted at the Rizzoli Orthopedic Institute.

Several methodologies for BMD analysis have been described, but DEXA is still considered the gold standard for low radiation exposure, non-invasiveness, speed of execution, and easy availability in hospitals [85]. However, it presents a considerable risk of measurement error in case of patient mispositioning [86–89], the methods are not well defined, especially in the knee, and the data obtained cannot be used for 3D modelling. Other methods used to assess BMD after TKA include Quantitative Computed Tomography (qCT) and Single Positron Emission Computed Tomography (SPECT). However, these techniques are more invasive, expose the patient to a higher dose of radiation or radioactive drugs, methods are not well standardized for knee evaluation and are not often available in all hospital facilities [90,91].

Therefore, having DEXA available at our Institute, it has been decided to use it to conduct a clinical trial in which we analyzed changes in BMD after TKA.

DEXA setup for periprosthetic BMD evaluation after TKA

As this was the first time this technology was used for this purpose, a feasibility study was performed during the first part of the project to assess the repeatability and reliability of the setup. The DEXA device used in this study was the Discovery (Hologic Inc. Marlborough, Massachusetts, U.S).

Test-retest were performed repositioning a cadaver femur and tibia during DEXA scans and utilizing defined ROIs each time to verify reliability. The articular regions were packed in rice in order to mimic soft tissues as described by Clavert et al. [92] (Fig. 1).

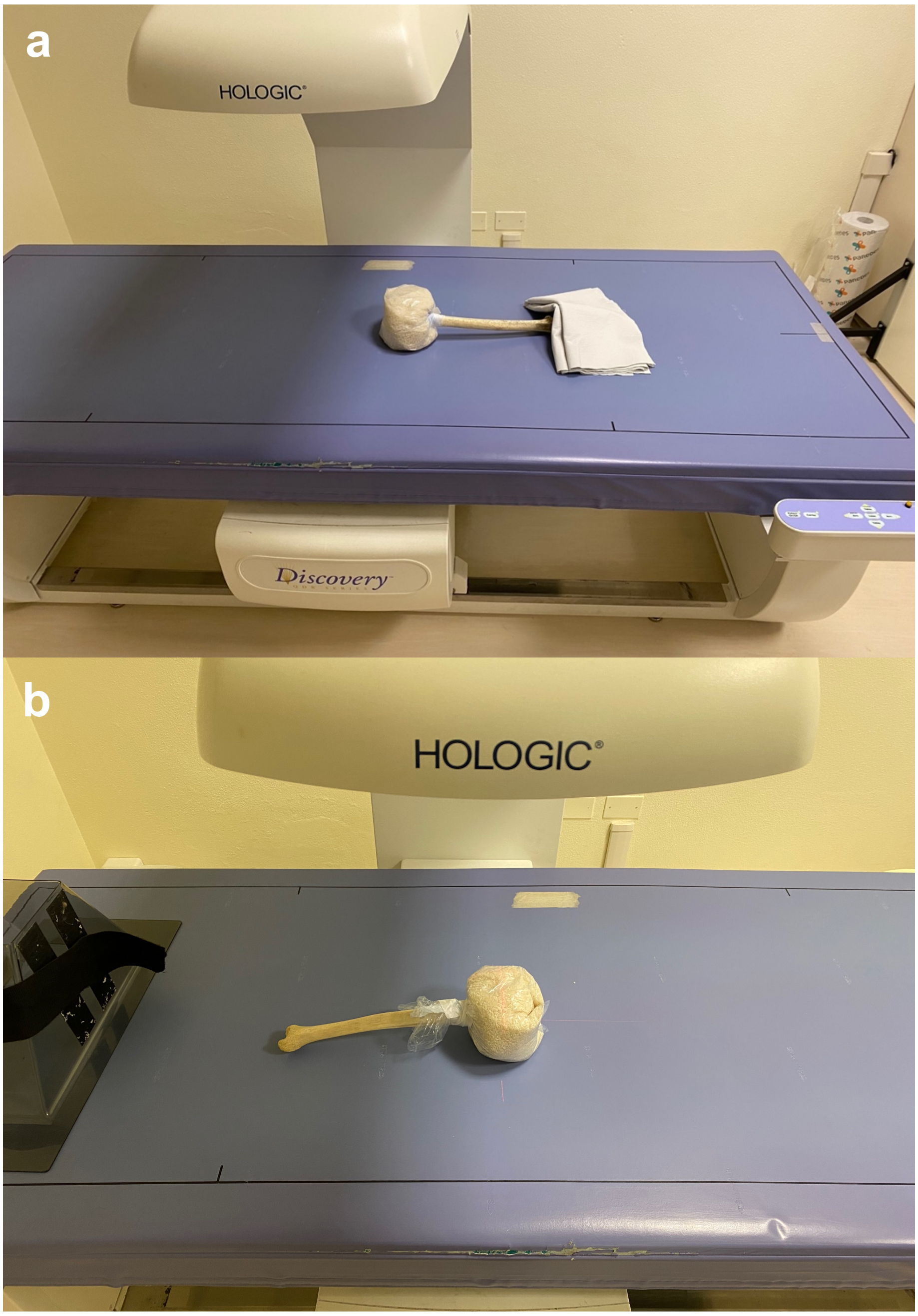


Figure 1. Positioning of the femur (a) and tibia (b) during DEXA feasibility test. The articular regions were packed in rice to mimic soft tissues

In detail, 10 scans were performed for the femur and 10 for the tibia, 5 with prosthesis and 5 without, each time repositioning the bone in the desired position.

4 ROIs were manually identified on the frontal plane for the tibial component, and 4 ROIs were manually identified on the sagittal plane for the femoral component (Fig. 2). A symmetrical division of the medial-lateral width of the tibia and anterior-posterior width of the femur was used to define the size of the ROIs. ROI 4 was positioned in the metaphyseal region to serve as a comparison with ROIs positioned at the prosthetic bone interface. The software permitted to re-use initially identified ROIs for subsequent acquisitions.

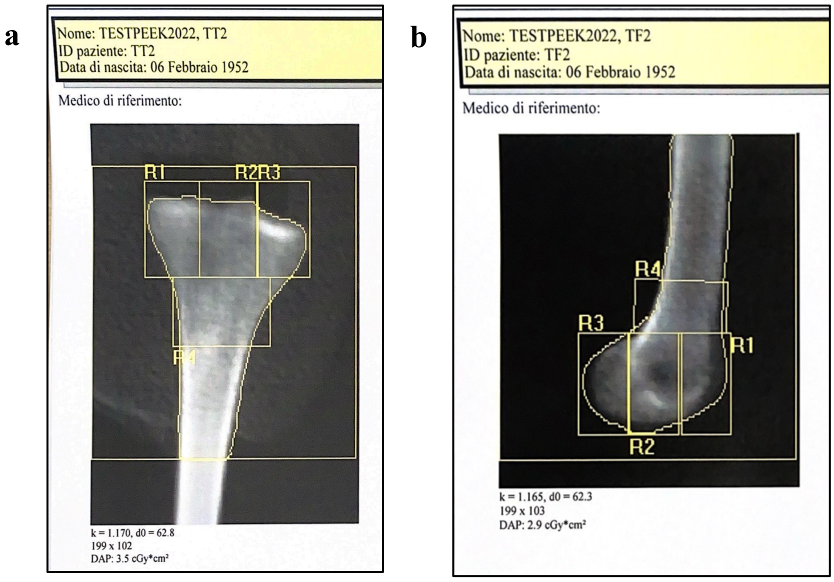


Figure 2. Tibial (a) and Femoral (b) peri-articular ROIs

Table 1 shows BMD values in grams per square centimeter, the average standard deviation, standard error of the mean and the coefficient of variation in the various acquisitions performed on the tibia and femur, with and without prosthesis. Minimal variation emerged for all regions of interest among the different measurements, with an average coefficient of variation of 3.6% indicating good repeatability within the same condition (i.e., no prosthesis or with prosthesis).

Low coefficient of variation values suggested that repeated DEXA scans yielded consistent results for the same individual under the same conditions.

Table 1. Average BMD measurement among 5 repetitions.

Average BMD measurement among 5 repetitions								
g/cm2	No prosthesis				With prosthesis			
	R1	R2	R3	R4	R1	R2	R3	R4
Tibia								
Mean	0.76	0.653	0.815	0.81	0.819	0.745	0.804	0.98
Std. Deviation	0.024	0.024	0.019	0.041	0.032	0.05	0.031	0.052
Std. Error of the mean	0.011	0.011	0.009	0.018	0.014	0.022	0.014	0.023
Coefficient of variation	3%	4%	2%	5%	4%	7%	4%	5%
Femur								
Mean	0.8	1.18	0.857	1.293	0.858	1.221	0.856	1.332
Std. Deviation	0.019	0.023	0.077	0.022	0.022	0.024	0.01	0.026
Std. Error of the mean	0.01	0.011	0.039	0.011	0.01	0.011	0.004	0.012
Coefficient of variation	2%	2%	9%	2%	3%	2%	1%	2%

Table 2 shows the intraclass correlation coefficient between the measurements with and without prosthesis. A low to moderate reliability emerged, but the interference of the prosthesis was generally low, below 0.06 g/cm^2. The mean BMD differences (g/cm^2) between the *no prosthesis* and *with prosthesis* conditions in both the tibia and femur were substantial in certain regions, indicating that the presence of the prosthesis could affect the accuracy of DEXA scan, especially in CoCr prosthesis, due to metal artifacts. However, this did not appear to be a limitation, as it was planned to perform DEXA scans starting post-operatively, with the prosthesis already implanted. In addition, to reduce metal artifacts, it was decided to use the 'metal removal' function available in the DEXA software.

Table 2. Intraclass correlation coefficient between the measurements with and without prosthesis

Test-retest Reliability (between no prosthesis and with prosthesis)					
Measure	ICC (3.1)	Lower 95% CI	Upper 95% CI	Mean Diff (g/cm2)	% Diff
Tibia					
R1	0	-0.811	0.811	-0.059	-8%
R2	0.368	-0.632	0.908	-0.091	-14%
R3	0.48	-0.543	0.929	0.011	1%
R4	0.525	-0.499	0.937	-0.170	-21%
Femur					
R1	0.594	-0.42	0.948	-0.058	-7%
R2	0.182	-0.738	0.866	-0.042	-4%
R3	0	-0.811	0.811	0.001	0%
R4	0.00	-0.811	0.811	-0.039	-3%

In order to minimize measurement errors due to differences in limb rotation between scans, a dedicated foam positioner, as described by Stilling et al. [89], was realized, allowing reproducible leg positioning of approximately 25° of knee flexion and neutral rotation (Fig. 3).

Figure 3. Foam leg positioner to reduce measurement errors during DEXA scans

Clinical study

The local Ethics Committee approved an interventional, controlled, single-center study conducted on 2 parallel cohorts with the primary objective of comparing BMD changes by DXA in periprosthetic femoral and tibial bone between two groups of patients undergoing cemented TKA (DXA-TKA: approved by EC AVEC with clearance no. 0000873 of 19/01/2023).

The secondary objective was to correlate BMD values with clinical and functional scores, such as Knee Society Clinical Score (KSSc) and Functional Score (KSSf), Western Ontario and Mc Master University (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Short Form Health Survey (SF-36).

The Inclusion Criteria were:

1. Patients aged ≥ 45 years

2. Patients who are candidates for primary cemented total knee replacement based on physical examination and history, including a diagnosis of severe knee pain and disability due to at least one of the following causes:

a. Primary or secondary osteoarthritis

b. Collagen disorders and/or avascular necrosis of the femoral condyle

c. Moderate deformity in valgus, varus or flexion (HKA between ± 10°, contracture in flexion <10°)

3. Consenting patients and able to complete planned study procedures and follow-up assessments

4. Patients informed about the nature of the study who have signed the 'informed consent' approved by the ethics committee.

The Exclusion criteria were:

1. Patients aged < 45 years;

2. Patients who have already undergone hip or ankle arthroplasty, previous osteotomy, severe axial deformities or suffer from rheumatoid arthritis, diabetes or neuromuscular diseases. This will ensure homogeneity of the investigated cohort;

3. Pregnant women.

Primary outcome

Evaluation of BMD by DEXA immediately post-operatively (baseline) and at 6, 12, 24 months post-operatively.

Secondary outcomes

Administration of following questionnaires for the calculation of clinical and functional scores during follow-up visits:

- ***Knee Society Clinical Score (KSSc) and Functional Score (KSSf);*** introduced into clinical practice in the late 1980s by the American Knee Society for the evaluation of osteoarthritis and modified into its current structure by Dr. John Insall in 1993 [93]. It is divided into two sections designed to describe the clinical status of the knee and the patient's perceived level of subjective function. The first section - the Clinical Knee Score - assesses the patient's reported pain, presence of flexion contractures, extension deficit, and range of motion. Alignment in varus-valgus under load, antero-posterior stability (Lachman's test measured in mm) and medio-lateral stability (varus-valgus stress test measured in degrees) are evaluated. The second section - Functional Knee Score - assesses the patient's knee function, quantifying the ability to walk, climb stairs and use aids such as a cane, crutches or a walker.

Scores range from 0 to 100 for both the clinical and functional Knee Score with values divided into four groups (80-100 excellent, 70-79 good, 60-69 sufficient, <60 poor);

- ***Western Ontario and Mc Master University (WOMAC)***; developed in 1982, it is used to measure the condition of patients with hip and knee osteoarthritis [94]. The test evaluates key aspects of the condition such as pain, joint stiffness, and function of the joints in question (hip and knee). The test is submitted to the patient, who fills it out independently. The score is the result of the summation of 3 groups of questions with 5 possible answers (between 0 and 4) to choose from for the self-assessment of:

- pain: five questions (score from 0 to 20);
- joint stiffness: two questions (score from 0 to 8);
- functional limitations: 17 questions (score from 0 to 68);

The score obtained varies from 0 to 96 according to the symptomatology described. Higher scores indicate worse pain, stiffness, and functional limitations. Statistical analysis of the WOMAC values before and after the treatments considered allows the effectiveness of the treatments to be assessed;

- Knee Injury and Osteoarthritis Outcome Score (KOOS); it is a self-administered questionnaire of 42 items and 5 sub-scales investigating different aspects

- Symptoms (7 items, 2 inherent to stiffness);
- Pain (9 items);
- Functions and activities of daily living (17 items);
- Sports and recreational activities (5 items);
- Quality of life in relation to the knee (4 items);

The scores of each subscale are transformed, following a dedicated formula, into a percentage score ranging from 0 (severely disabled condition) to 100 (excellent condition). An aggregate score is not recommended as it is considered desirable to analyze and interpret the five dimensions separately;

- ***Short Form Health Survey (SF-36)***; is a generic test consisting of 36 questions that can be subdivided into 8 scales and investigates the subject's perceived level of physical and mental health [95]. It consists of:

- SF-6D (health status from 1, full health, to 10, death);
- PF (physical functioning);
- PSC (physical component score)

It provides a score from 0 to 100 for each of the 8 sub-categories, which is directly proportional to the perceived level of quality of life. In addition, this test also allows the level of pain felt by the patient to be investigated.

Preliminary results

To date, 12 patients implanted with Posterior Stabilized Mobile bearing CoCr TKA have been enrolled in DXA-TKA study. 6 of them reached 6 months follow up, while only 1 patient reached 12 months follow up. Demographic data and clinical scores of patients with 6M follow up are reported in Table 3.

Table 3. Demographic data and clinical scores

Patient	1	2	3	4	5	6
Sex	M	M	F	F	M	M
Age	75	64	81	82	78	68
BMI	33	24	28	36	31	29
Side	R	R	R	R	L	L
Prosthetic Design	PS	PS	PS	PS	PS	PS
cKSS pre-op	43	48	56	49	52	66
fKSS pre-op	50	60	45	45	70	70
WOMAC pre-op	61	51	54	80	59	61
KOOS pre-op	41	45	41	35	44	50
SF-36 pre-op	Physical functioning: 25 % Role limitations due to physical health: 0 % Role limitations due to emotional problems: 0 % Energy/fatigue: 55 % Emotional well-being: 68 % Social functioning: 50 % Pain: 55 % General health: 55 % Health change: 50 %	Physical functioning: 35 % Role limitations due to physical health: 0 % Role limitations due to emotional problems: 100 % Energy/fatigue: 60 % Emotional well-being: 68 % Social functioning: 75 % Pain: 32.5 % General health: 55 % Health change: 50 %	Physical functioning: 30 % Role limitations due to physical health: 0 % Role limitations due to emotional problems: 66.7 % Energy/fatigue: 50 % Emotional well-being: 60 % Social functioning: 25 % Pain: 32.5 % General health: 40 % Health change: 25 %	Physical functioning: 45 % Role limitations due to physical health: 0 % Role limitations due to emotional problems: 0 % Energy/fatigue: 45 % Emotional well-being: 64 % Social functioning: 50 % Pain: 45 % General health: 40 % Health change: 25 %	Physical functioning: 45 % Role limitations due to physical health: 100 % Role limitations due to emotional problems: 0 % Energy/fatigue: 50 % Emotional well-being: 56 % Social functioning: 62.5 % Pain: 45 % General health: 50 % Health change: 50 %	Physical functioning: 45 % Role limitations due to physical health: 25 % Role limitations due to emotional problems: 0 % Energy/fatigue: 50 % Emotional well-being: 60 % Social functioning: 50 % Pain: 45 % General health: 55 % Health change: 50 %
cKSS 6M FU	85	77	71	37	54	50
fKSS 6M FU	100	90	40	65	70	90
WOMAC 6M FU	6	9	9	10	6	40
KOOS 6M FU	89	85	45	31	69	59
SF-36 6M FU	Physical functioning: 95 % Role limitations due to physical health: 100 % Role limitations due to emotional problems: 100 % Energy/fatigue: 80 % Emotional well-being: 80 % Social functioning: 75 % Pain: 77.5 % General health: 70 % Health change: 75 %	Physical functioning: 85 % Role limitations due to physical health: 50 % Role limitations due to emotional problems: 66.7 % Energy/fatigue: 50 % Emotional well-being: 60 % Social functioning: 62.5 % Pain: 77.5 % General health: 50 % Health change: 75 %	Physical functioning: 40 % Role limitations due to physical health: 0 % Role limitations due to emotional problems: 0 % Energy/fatigue: 45 % Emotional well-being: 36 % Social functioning: 25 % Pain: 22.5 % General health: 30 % Health change: 50 %	Physical functioning: 10 % Role limitations due to physical health: 0 % Role limitations due to emotional problems: 0 % Energy/fatigue: 45 % Emotional well-being: 36 % Social functioning: 25 % Pain: 22.5 % General health: 20 % Health change: 0 %	Physical functioning: 75 % Role limitations due to physical health: 75 % Role limitations due to emotional problems: 100 % Energy/fatigue: 55 % Emotional well-being: 64 % Social functioning: 50 % Pain: 55 % General health: 50 % Health change: 75 %	Physical functioning: 80 % Role limitations due to physical health: 50 % Role limitations due to emotional problems: 33.3 % Energy/fatigue: 55 % Emotional well-being: 64 % Social functioning: 50 % Pain: 55 % General health: 50 % Health change: 75 %

The operated limb was placed on the foam positioner and two DEXA scans were acquired in anterior-posterior (AP) and lateral (LL) view, after appropriate calibration (Fig. 4).

a b

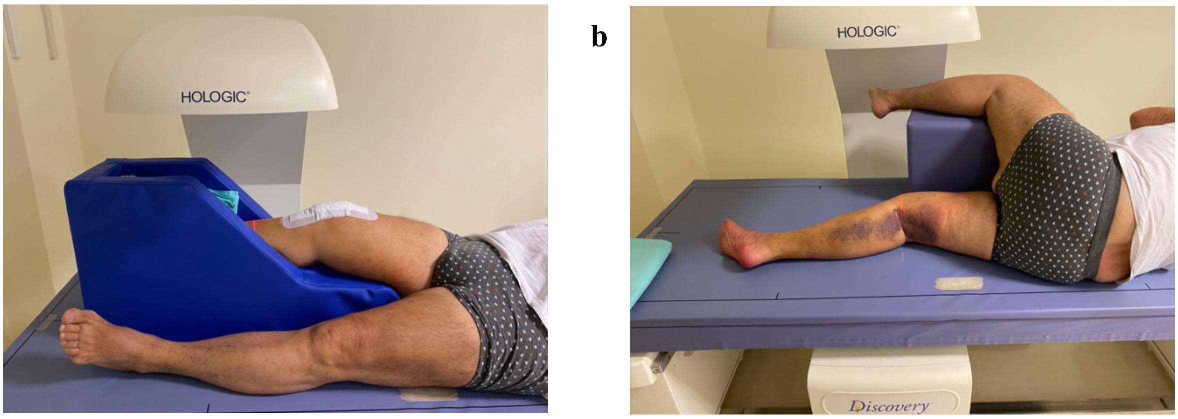
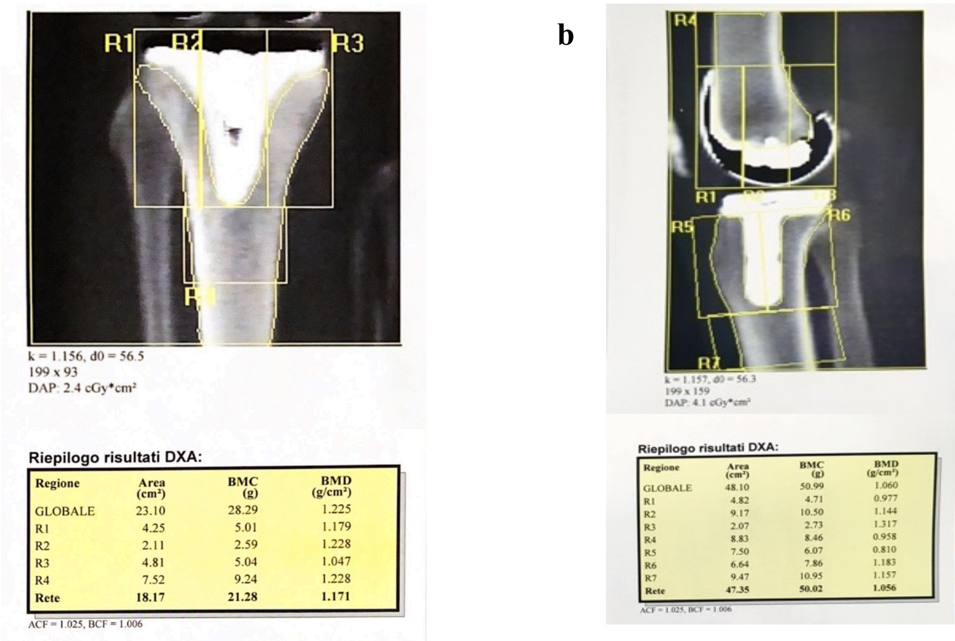


Figure 4. Limb positioning during DEXA scan in anterior-posterior (a) and lateral position (b).

On the AP view, 3 ROIs were identified at the tibial bone-implant interface plus one ROI below them, in the metaphyseal region.

On the LL view, 3 ROIs were identified at the femoral bone-implant interface and 2 ROIs at the tibial bone-implant interface, plus 1 ROI in the femoral and 1 ROI in the tibial metaphyseal region (Fig. 5).

a b



Riepilogo risultati DXA:

Regione	Area (cm²)	BMC (g)	BMD (g/cm²)
GLOBALE	23.10	28.29	1.225
R1	4.25	5.01	1.179
R2	2.11	2.59	1.228
R3	4.81	5.04	1.047
R4	7.52	9.24	1.228
Rete	**18.17**	**21.28**	**1.171**

ACF = 1.025, BCF = 1.006

Riepilogo risultati DXA:

Regione	Area (cm²)	BMC (g)	BMD (g/cm²)
GLOBALE	48.10	50.99	1.060
R1	4.82	4.71	0.977
R2	9.17	10.50	1.144
R3	2.07	2.73	1.317
R4	8.83	8.46	0.958
R5	7.50	6.07	0.810
R6	6.64	7.86	1.183
R7	9.47	10.95	1.157
Rete	**47.35**	**50.02**	**1.056**

ACF = 1.025, BCF = 1.006

Figure 5. Data processing of AP (a) and LL (b) DEXA scans

The preliminary results of the first 6 patients showed that BMD decreased in almost all ROIs between baseline and 6M follow up. In particular, the average decrease in tibial BMD was 4%, while that in femoral BMD was 5%. Around the tibial component, BMD reported a significant decrease of 20% ($p = 0.02$) on the anterior region in LL view (ROI 5) and of 8% in ROI 2, around the keel. On the femoral side, BMD decreased of 16% in ROI 3 (posterior femoral condyles), according to Minoda et al., which found similar results in a study comparing fixed versus mobile bearing TKA [60]. Data are reported in Table 4 and Figure 6.

Table 4. Average BMD changes between baseline and 6M follow-up after TKA.

	ROI TIBIA							TOTALE TIBIA	ROI FEMORE				TOTALE FEMORE
	ROI 1	ROI 2	ROI 3	ROI 4	ROI 5	ROI 6	ROI 7		ROI 1	ROI 2	ROI 3	ROI 4	
MEDIA	1,451	1,513	1,188	1,126	0,908	1,296	1,083	1,254	0,943	1,090	0,949	1,167	1,062
SD	0,469	0,326	0,209	0,221	0,190	0,230	0,186	0,286	0,209	0,166	0,280	0,140	0,162
t-test pre-post	0,519	0,097	0,936	0,462	0,020	0,061	0,706	0,255	0,425	0,341	0,075	0,817	0,154
diff: pre-post	0,082	0,121	0,007	-0,084	0,181	-0,073	-0,026	0,046	0,048	0,027	0,154	-0,006	0,051

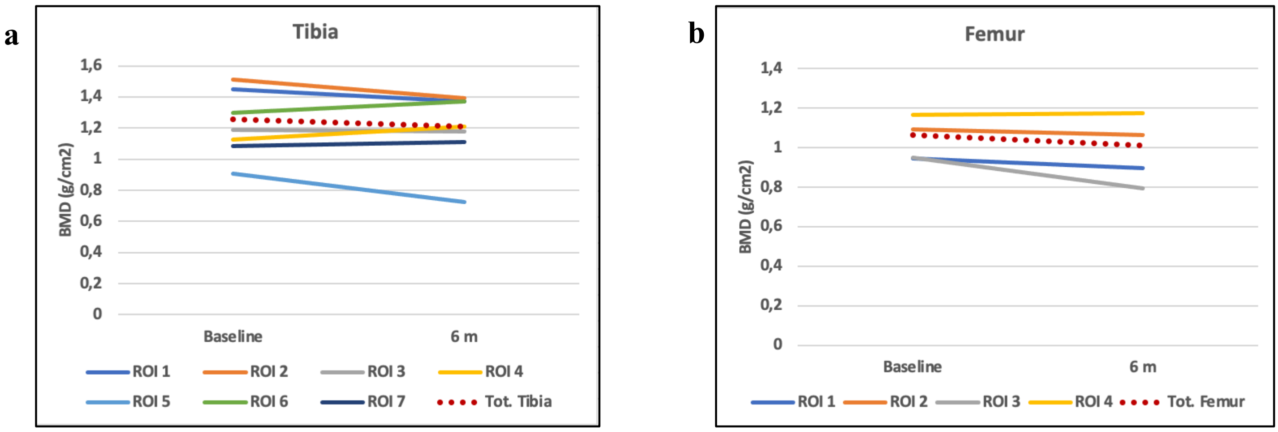


Figure 6. Overall BMD variation after TKA around tibial (a) and femoral (b) component

Considering the patient who reached 12M follow up, an average decrease in tibial BMD of 32% from baseline emerged, with the most pronounced decrease at ROI 1 (-49%). In contrast, the mean femoral BMD increased by 5% at 12 months follow-up compared to baseline, decreasing by 8% at ROI 1 (anterior femur). Data are reported in Figure 7.

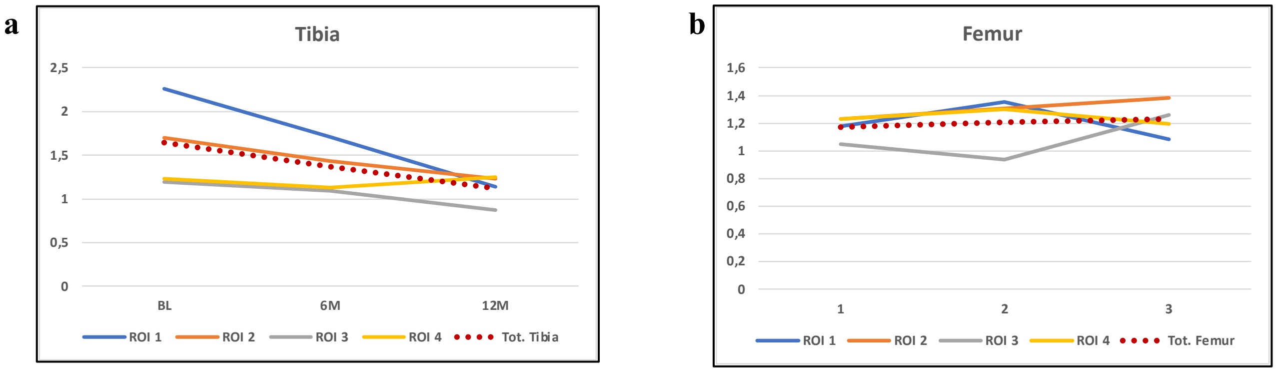


Figure 7. BMD variation in a patient reached 12M Follow up

It was decided not to perform correlations with clinical outcomes in this thesis due to the small sample size with low statistical power.

AIM IV: ***"Does heat generation influence the perception of the knee after TKA?"***

The influence of the implant material thermal properties on the patient's subjective perception is a topic of recent interest. Knee replacement patients often report discomfort after physical activity or when exposed to extreme environmental temperatures. This phenomenon could be due to the different thermal conductivity of metal compared to that of bone.

Some recent papers have shown a correlation between clinical parameters, patient reported outcomes and temperature variation after TKA [96,97].

A clinical trial on patients undergoing knee prosthesis has therefore been initiated to assess by infrared thermography the joint temperature before and after surgery, also considering the impact of exercise and the correlation with clinical outcomes. In the future, these data will be compared with those measured in prostheses made of alternative materials.

Demographic data

37 patients undergoing primary TKA were consecutively enrolled during pre-operative outpatient visit. The first evaluations were performed during that visit, together with the administration of questionnaires for clinical scores (Womac, EQ-5D, EQ-VAS, Tegner, KOOS, VAS, Oxford). Subsequent evaluations were performed at 6 months post-surgery.

Patients with rheumatoid arthritis, skin disorders (psoriasis) or unable to sign and understand the informed consent were excluded from the study.

Infrared Thermography Procedure, Exercise, and Analysis

The infrared imaging evaluation was performed in a dedicated outpatient clinic shielded from direct sunlight and with the temperature controlled at 23.0 ◦C [98,99] and a mean humidity of 45 ± 3%. Image acquisition was performed between 14:00 and 17:00 to minimize the circadian temperature variations. According to Marins et al. [100], the thermalization period was 10 min.

To speed up thermalization, patients were asked to remove trousers, shoes, and socks, remain seated and undressed on the lower limbs with light clothing (such as a t-shirt) on the top, and not touch their knees. The patient only rested the buttocks region on the medical bed, while the remaining parts of the lower limbs had no contact with other objects or body parts; only feet without socks touched a paper towel, thus separating them from direct contact with the floor. Thermograms were acquired using a FLIR T1020 thermographic camera (FLIR® Systems, Stockholm, Sweden) with a resolution of 1024 × 768 pixels and a thermal sensitivity of 0.02 ◦C. The camera was positioned at a distance of 1 m, perpendicular to the knee and adjusted to the patellar height [101]. After the patient was acclimatized, he was positioned on a designated floor map, and image acquisition (T0) of an anterior view was performed using the autofocus mode (Fig. 1).

Figure 1. Setup of thermographic camera acquisition

Then, one 2 kg anklet was positioned on the ankle of the symptomatic lower limb of the patient. At this point, with the patient seated, a knee flexion–extension exercise was performed for 2 min at the rate of one extension every 2 s (1 s flexion phase and 1 s extension phase). A metronome was used to standardize pacing (Fig. 2).

Figure 2. Knee flexion–extension exercise with 2 kg anklet

Immediately after performing this exercise, the anklet was removed, and the patient was positioned again on the floor map and a second anterior view image was acquired (T1). Afterwards, the patient waited in the room for 5 min in a sitting position without touching or moving the lower limbs. At the end of this resting period, the patient was positioned on the floor map and a third anterior view image was acquired (T2) (Fig. 3 and 4). Finally, maintaining the same position of the knee, an anatomical marker (circular adhesive of 2 cm in diameter) was placed at the center of the patella to obtain a further image in the anterior view in order to facilitate the precise subsequent location of the patella in the analysis of the previous infrared images.

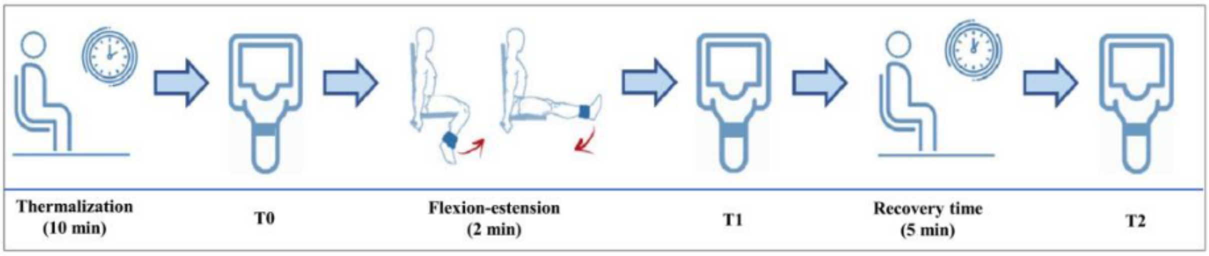


Figure 3. Timeline of the study.

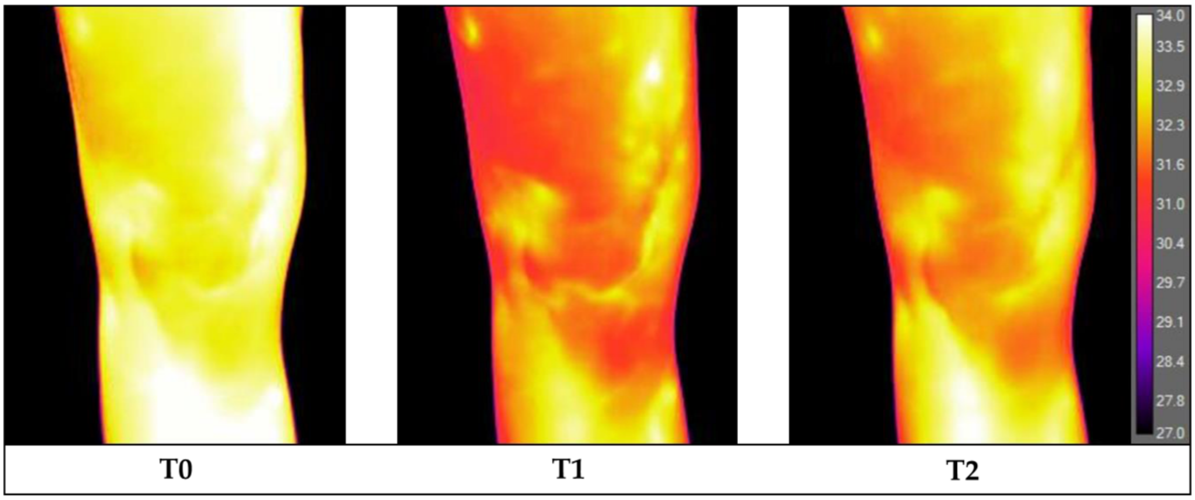


Figure 4. Thermographic basal image (T0), at the end of the 2-min flexion–extension exercise (T1) and after the 5-min rest period (T2)

During the image analysis process, the three anterior images acquired at T0, T1, and T2 were aligned side by side with the image with the patellar marker on the computer screen, and a template indicating the region of interests (ROIs) was centered over the patella of each unmarked image, using the marked image as a guide [102,103]. The ROIs were defined as follows: the patellar area was a square of 6 cm in width centered on the patella, the suprapatellar area was the area 3 cm over the patella; and the medial and lateral areas were the regions 3 cm under the patella and on its medial and lateral sides, respectively (Fig.11). The mean temperatures were extracted using ResearchIR software (FLIR® Systems, Stockholm, Sweden) to determine the overall knee area and the 4 ROIs: patella, medial, lateral, and suprapatellar (Fig. 5).

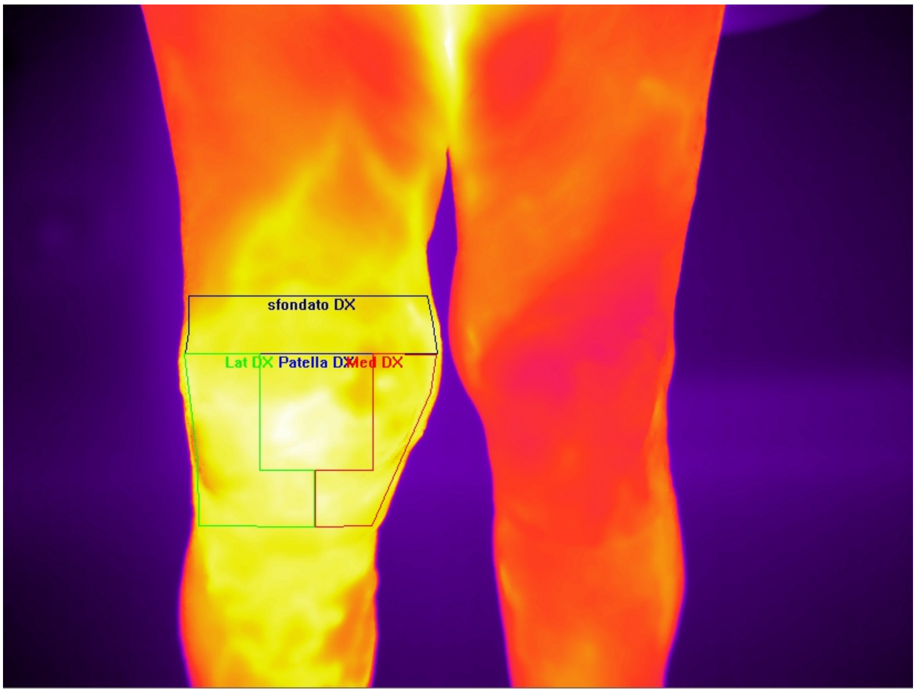


Figure 5. Knee ROIs for temperature evaluation.

Preliminary results

Demographic data of the first 10 patients with 6M follow up are reported in Table 1.

Table 1. Demographic data

Sex, M/W	3/7
Age, Years (Range)	71,2 (52-82)
BMI Kg/m^2	31,3
Side	8 Right, 2 Left
Kellgren-Lawrence grade	6 Grade IV, 4 Grade III

From the analysis two interesting finding emerged. Firstly, temperature after TKA was higher than pre-op during each of three scans (Fig. 6). Secondly, higher temperature after TKA correlated with poor clinical outcomes (Womac) (Fig. 7).

Analysis of the final data will make it possible to evaluate this correlation with greater statistical power and to compare the thermal behavior of CoCr prostheses with those of alternative materials.

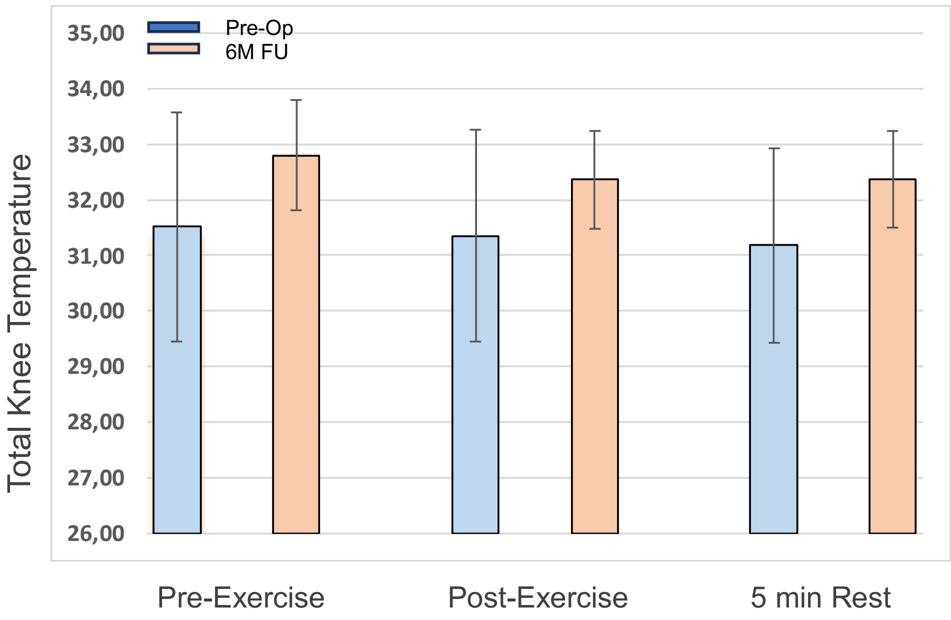


Figure 6. Average temperature before and after TKA

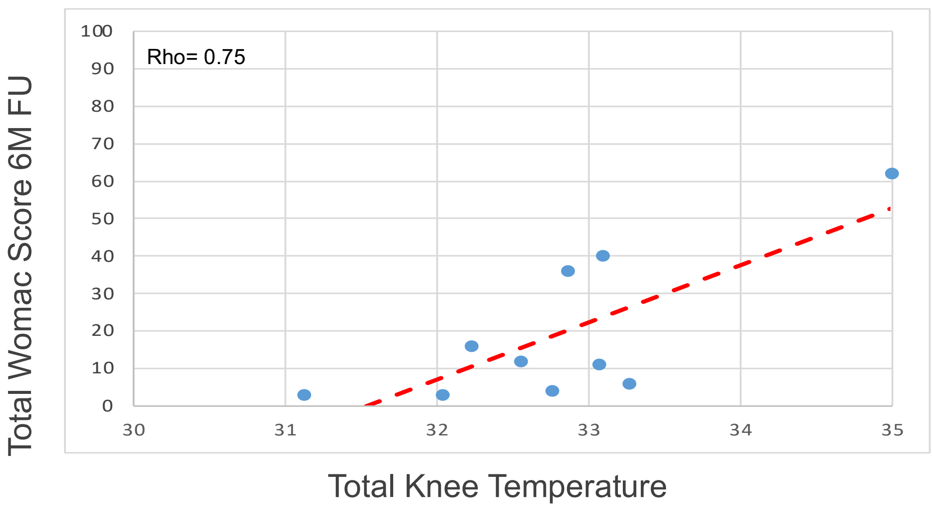


Figure 7. Correlation between Womac Score at 6M FU and Total Knee Temperature

CONCLUSIONS AND FUTURE DIRECTIONS

The present PhD thesis investigated the impact of joint prostheses on periprosthetic bone remodeling and joint temperature trends, focusing on Total Knee Arthroplasty (TKA).

Through the research presented it was shown how it is possible to predict the loosening of an implant by monitoring the migration in relation to the periprosthetic bone, even before clinical symptoms appear. An annual migration cut-off correlating with good long-term survival and good clinical and functional outcomes has been identified.

It was also shown how periprosthetic BMD tends to decrease progressively after joint replacement surgery, and that the extent and pattern of this decline are influenced by the anatomical region, the fixation technique and the implant design.

A method of DEXA analysis of BMD after knee joint replacement was implemented for the first time at the Rizzoli Orthopaedic Institute, presenting preliminary data from the first enrolled patients. It emerged that BMD decreases significantly in the first months after surgery, in line with evidence from the literature. This study is still ongoing and the final data will be published after the completion of the follow-up, comparing them with those of prostheses made of alternative and more biocompatible materials, such as PEEK.

The topic of joint temperature variation after TKA was also addressed, showing that there is an increase compared to preoperative both at rest, during and after controlled exercise. A correlation was also found between high temperatures and low clinical scores.

The findings of this thesis provide critical insights into the impact of current knee prosthetic materials on bone remodeling and temperature variation, paving the way for future innovations in more biocompatible and durable materials. Ultimately, these advancements will aim to improve patient outcomes and extend the functional lifespan of orthopedic implants, ensuring better long-term results for a growing and increasingly diverse patient population.

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