Realigning the Future

Joint Preservation in Knee Osteoarthritis

Eva A. Bax

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Promotoren:
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Whenever possible, the native joint should be preserved

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Chapter 1

General Introduction and Thesis Outline

General introduction and thesis outline

The Global Burden and Epidemiology of Knee Osteoarthritis

Osteoarthritis (OA) is a leading cause of chronic pain and long-term disability among adults worldwide[1–3]. As of 2020, approximately 595 million people were affected by OA, accounting for 7.6% of the global population and reflecting a 132% increase in total cases since 1990[4]. Among the various subtypes, knee osteoarthritis (KOA) is the most prevalent form[4]. The development of KOA is associated with several well-established risk factors, including increasing age[4–7], obesity[4,6,7], and female sex[4,6,7]. Additional contributors include previous knee trauma or surgery[6–8], occupations involving frequent heavy lifting, kneeling, or squatting[6,7,9], physically demanding work[7,10], and elite-level participation in high-impact sports[7,11,12].

In addition to these individual-level risk factors, substantial geographic variation in KOA prevalence has been observed. The highest prevalence rates were observed in high-income regions such as North America and Asia Pacific, while the lowest rates were reported in Southeast Asia and Eastern Sub-Saharan Africa[4]. These regional disparities may be partially attributed to variations in lifestyle factors, life expectancy, obesity prevalence, availability of public health resources, and biomechanical practices such as habitual squatting or frequent knee flexion[6,9,13–15].

Beyond population-level prevalence, increasing attention has been directed toward classifying KOA based on phenotypes to better understand disease mechanisms and guide personalized treatment[16–18]. Commonly described KOA phenotypes include metabolic, inflammatory, chronic pain, bone-and-cartilage metabolism, minimal joint disease, and malaligned biomechanical phenotypes[16,17]. The latter is primarily driven by lower limb malalignment such as varus (bow-legged) or valgus (knock-knee) deformities[16,17], and is considered to be responsible for the disease in 12%-22% of individuals with KOA[17]. For every 1° increase in varus alignment, the load transmitted through the medial compartment during walking increases by approximately 5%[19]. Reflecting these biomechanical effects, lower limb malalignment has been associated with a 1.5- to nearly 3-fold increased risk of developing KOA[20,21], and with an almost 4-fold higher risk of incident cartilage damage[22]. In addition, varus alignment increases the load on the medial knee compartment and is therefore strongly associated with an increased risk of medial compartment degeneration and a lower risk of lateral compartment involvement[20,23]. In contrast, valgus alignment overloads the lateral compartment, which is liked to greater lateral cartilage degeneration and reduced medial degeneration[20,23].

Looking ahead, the global burden of KOA is projected to increase substantially in the coming decades, not only among older adults but also among younger individuals (Figure 1)[24]. By 2050, the number of KOA cases is projected to rise substantially compared to 2020[4], largely due to population aging and increasing obesity rates[4]. However, even after adjusting for age and obesity, KOA prevalence in postindustrial populations (1976–2015) remains more than twice as high as in early industrial populations (1905–1940) in Western countries[25]. Furthermore, the increasing prevalence of joint injuries continues to play a substantial role in KOA development[26,27]. As KOA becomes more widespread globally, the resulting healthcare costs, productivity losses, and reduced quality of life present a pressing and multifaceted public health challenge for individuals, healthcare systems, and societies as a whole[7,28,29].

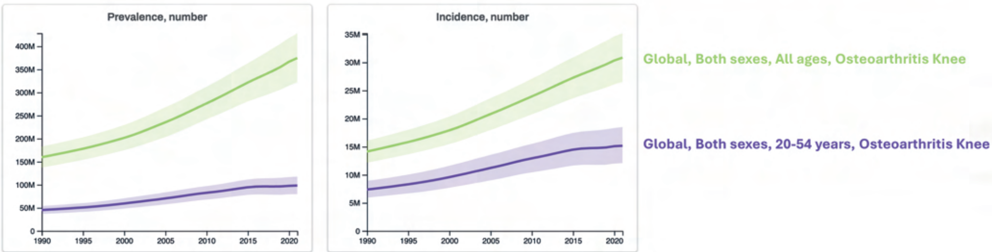

Figure 1 - The global prevalence and incidence in numbers of patients presenting knee osteoarthritis, divided in all patients (green line) and aged between 50-54 years (purple line).[24]

Radiological Assessment of Knee Osteoarthritis

Radiographic assessment is a widely used method for diagnosing and monitoring the severity of KOA[30,31]. A widely applied tool is the Kellgren and Lawrence (K&L) grading system, which assesses disease severity based on the presence of osteophytes, joint space width (JSW) narrowing, subchondral sclerosis, and joint deformity[32,33]. The system categorizes KOA into five grades (0–4), where grade 0 indicates no radiographic features of OA, and grades 1 to 4 represent doubtful, mild, moderate, and severe disease[34], respectively (Figure 2). Although the K&L system provides a global structural assessment, its categorical nature limits sensitivity to subtle changes, particularly in JSW[31,35]. JSW serves as a surrogate measure for the structural integrity of both articular cartilage and the meniscus[31,36–38]. Among the various JSW metrics, the minimum joint space width (mJSW)—defined as the narrowest distance between the femoral and tibial margins within a defined region of interest—is most frequently used in clinical and pharmacological studies[39]. Its quantitative nature makes it a valuable outcome measure for assessing disease progression and evaluating the efficacy of disease-modifying interventions in KOA.

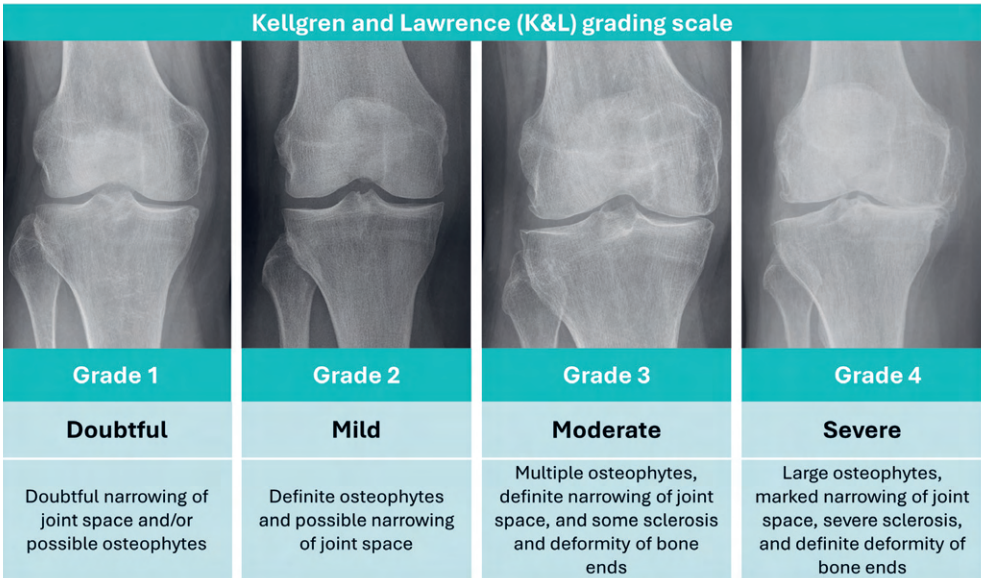

Figure 2 – Kellgren and Lawrence classification knee osteoarthritis.

Discordance Between Symptoms and Radiographic Findings in Knee Osteoarthritis

Typical clinical symptoms of KOA include gradual-onset knee pain that worsens with activity, stiffness, swelling, pain after prolonged sitting or rest, and progressive worsening of pain over time[40]. Clinicians commonly diagnose KOA based on clinical criteria, such as those established by the American College of Rheumatology[41] (ACR) and the guidelines from the European League Against Rheumatism (EULAR)[42], which emphasize patient-reported symptoms alongside findings from physical examination[43]. In contrast, radiographic definitions of KOA—such as the K&L grading system—focus primarily on structural joint changes, including osteophyte formation, subchondral sclerosis, and joint space narrowing[32].

However, evidence indicates that clinical symptoms do not consistently correspond with radiographic findings. Several studies have demonstrated that knee pain is an unreliable predictor of radiographic KOA[43–46]. Hannan *et al.*[45] reported that nearly 50% of individuals with moderate-to-severe radiographic KOA experience knee pain, while only 15% of individuals reporting knee pain show radiographic evidence of KOA. Conversely, other research has found significant associations between clinical symptoms—such as pain, stiffness, and functional limitations—and radiographic severity, particularly in more advanced KOA stages[43,47]. In these cases, higher grades of radiographic structural damage were associated to increased odds of knee pain and disability[43,47]. Collectively, this mixed evidence highlights the complex relationship between structural joint changes and symptomatic aspects of KOA.

Radiographic Assessment of Lower Limb Alignment

Visual assessment of lower limb alignment is insufficient to provide clinically relevant information[48]. Therefore, it is typically complemented by whole leg radiographs (WLRs), which allow for assessment of the mechanical hip–knee–ankle angle (mHKAA). To obtain reliable and reproducible mHKAA measurements, consistency and accuracy in radiographic technique are essential, necessitating the use of a standardized WLR-protocol[49,50].

Lower limb alignment is determined by three components: femoral alignment, tibial alignment, and intra-articular alignment within the knee joint. Accordingly, the mHKAA is the sum of three key angles: the mechanical lateral distal femoral angle (mLDFA), the mechanical medial proximal tibial angle (mMPTA), and the joint line convergence angle (JLCA) (Figure 3)[51]. The mLDFA reflects the angle between the femoral mechanical axis and distal femoral joint line, the mMPTA measures the tibial plateau's orientation relative to the mechanical axis, and the JLCA represents the angle between the tibial and femoral joint lines[51,52]. Normal values are 85°–90° for both mLDFA and mMPTA, and 0°–2° for JLCA. A varus deformity is characterized by an mLDFA > 90°, mMPTA < 85°, and/or JLCA > 2°, whereas a valgus deformity presents with an mLDFA < 85°, mMPTA > 90°, and/or JLCA < 0°[51,52]. Thus, a varus or valgus mHKAA reflects a composite deviation across all three angular components.

Growth and Load-Dependent Changes in Lower Limb Alignment

Lower limb alignment undergoes dynamic development throughout the first and second decades of life, with substantial changes in alignment observed over this period[53]. At birth, the lower limbs typically exhibit a varus alignment, which gradually transitions toward a valgus alignment, peaking between the ages of 3 and 5. By the age of 7, lower limb alignment generally stabilizes to a physiological reference value like those observed in adults, with notable ethnic and gender differences[53,54]. This developmental pattern is also reflected in bony alignment, including the mMPTA and mLDFA[54].

The ethnic and gender differences become more pronounced in adulthood[55,56]. Men generally demonstrate a more varus mechanical hip-knee-ankle angle (mHKAA) than women, although both sexes tend to fall slightly below the neutral mHKAA of 180°, indicating a mild varus tendency[55,57–59]. Specifically, men tend to have more varus in the tibia (mMPTA), while women show more valgus in the femur (mLDFA)[55–57]. Ethnic variations are also well-documented; for instance, Caucasians generally present with less varus and reduced femoral valgus compared to Asians, who often exhibit a more pronounced varus alignment[56].

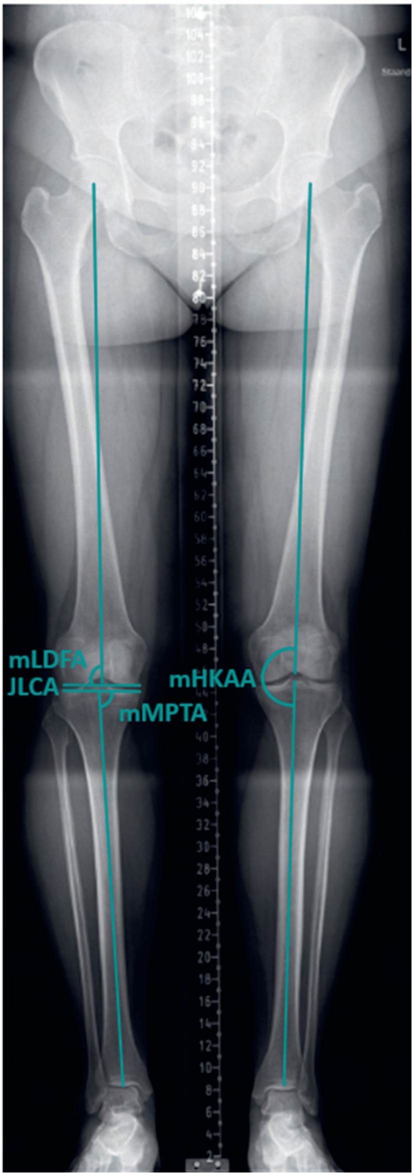

Figure 3 – The Mechanical Hip–Knee–Ankle Angle (mHKAA), Mechanical Medial Proximal Tibial Angle (mMPTA), Mechanical Lateral Distal Femoral Angle (mLDFA), and Joint Line Convergence Angle (JLCA) measured on a whole-leg radiograph.

Among individuals without KOA, the prevalence of varus malalignment ranges from approximately 13% to 25%[55–58]. Valgus malalignment is less common, with reported rates varying between 2% and 11%[55–58]. Consequently, most individuals without KOA exhibit a neutral lower limb alignment, typically falling within the range of 3° varus to 3° valgus[55–58]. The variations in prevalence likely reflect differences in study populations, including factors such as age, ethnicity, and the imaging modalities or alignment measurement techniques used. In contrast, among individuals with symptomatic KOA, the prevalence of malalignment is more than three times higher compared with the general population. Varus malalignment is particularly common, reported in approximately 64% to 75% of patients, whereas valgus malalignment occurs in 7% to 28% of cases[60–62].

In contrast to the neutral lower limb alignment typically observed in adults, athletes—especially those engaged in high-impact sports such as soccer—frequently develop varus alignment during growth. Multiple studies have reported a significantly higher degree of varus deformity in athletic populations relative to non-athletes[63–67], most prominently characterized by a decreased mMPTA[68]. In the literature, the Hueter–Volkmann law is frequently cited as an underlying explanation for this phenomenon. This law states that increased compressive forces perpendicular to the growth plate axis inhibit longitudinal growth, while reduced loading accelerates it[69–74]. In athletic populations, repetitive loading and elevated knee adduction moments increase medial compression at the proximal tibial physis[75,76], leading to asymmetric growth and progressive varus alignment[69–74]. However, while this mechanism is widely referenced as an explanation for coronal plane growth modulation, empirical evidence supporting a direct causal relationship remains limited and is primarily based on observational or biomechanical modeling studies[77–86].

The Evolving Role of Joint-Preserving Strategies in Knee Osteoarthritis

Knee arthroplasty remains a widely accepted treatment for patients with end-stage symptomatic KOA who experience insufficient symptom relief with conservative treatments[87]. Globally, the number of primary knee arthroplasties is increasing, accompanied by a notable rise in revision procedures[88–90]. Revision arthroplasties are associated with significantly higher surgical costs and lower patient satisfaction compared to primary procedures[87,91]. Younger patients are particularly at increased risk for revision surgery, partly due to their higher functional demands and longer life expectancy[91,92] (Figure 4). As highlighted earlier, both the incidence and prevalence of KOA are increasing, with a particularly concerning trend observed among relatively younger individuals, aged between 20 and 54 years, who are not yet suitable candidates for joint replacement (Figure 1)[87,91,93]. In this population, joint-preserving strategies are essential to delay the need for arthroplasty and to maintain joint function[94,95]. A realignment osteotomy is a joint-preserving surgical intervention particularly indicated for young, active patients with symptomatic unicompartmental KOA in combination with a lower limb malalignment[96]. This procedure redistributes mechanical loading from the affected to the unaffected compartment, thereby reducing pain, slowing down disease progression, and improving functional outcomes[97]. During an osteotomy, the bone is surgically cut and realigned—typically using an open- or closed-wedge technique (Figure 5) in either the distal femur or the proximal tibia—to correct the mechanical axis. In addition to these clinical benefits, partial and even full regeneration of the articular cartilage in the previously overloaded compartment has also been observed[98,99].

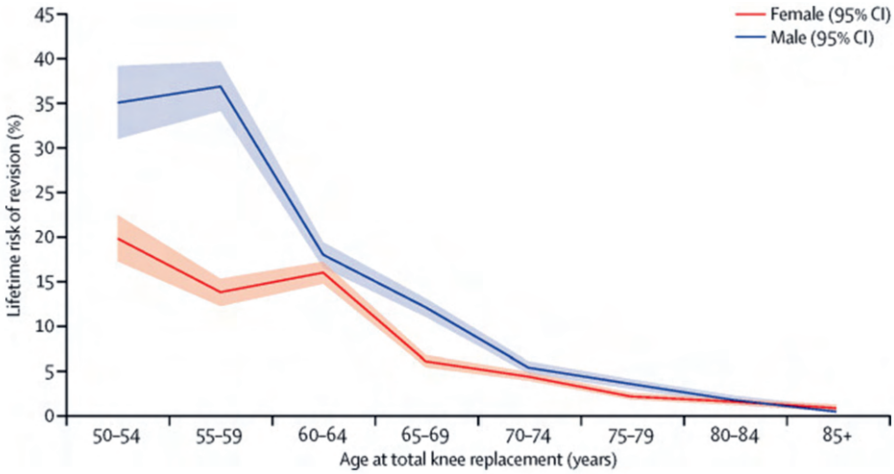

Figure 4 - Lifetime risk of revision following total knee replacement.[91]

Historical Evolution of Osteotomy

The concept of deformity correction dates to Hippocrates (460–370 BC), who utilized the Hippocratic Scamnum—a traction device for bone realignment. In the sixteenth century, the precursor to osteotomy was osteoclasia, a procedure in which a deformed bone was intentionally fractured and then stabilized in a corrected position to allow for proper healing. The field evolved gradually, with various osteotomy techniques being described by early pioneers. A major milestone occurred in 1880 when Macewen published the first dedicated book on osteotomy, detailing 1,800 successful cases without significant complications. By the mid-20th century, osteotomy had become more refined. In 1948, Brittain introduced distal femoral osteotomy for treating valgus alignment in children unresponsive to conservative therapy and adults with lateral compartment KOA. Around the same time, Wardle reported his series of high tibial osteotomies (HTOs), initiated in 1941, as a treatment of medial compartment KOA. His technique involved performing the osteotomy just below the tibial tubercle, at the junction of the upper and middle thirds of the tibia[100,101].

Figure 5 - Anteroposterior radiograph of a double-level osteotomy, consisting of a medial open-wedge osteotomy of the proximal tibia and a lateral closed-wedge osteotomy of the distal femur.

Indications osteotomy

The traditional ideal candidate for realignment osteotomy has traditionally been defined as a physically active individual aged 40–60 years with isolated unicompartmental KOA, a body mass index (BMI) below 30 kg/m^2, non-smoking status, varus deformity less than 15°, a bony malalignment greater than 5°, full range of motion, intact ligamentous stability, and adequate pain tolerance[102]. However, in recent years, clinical indications have begun to shift, with increasing consideration of osteotomy in broader patient populations. Recent evidence indicates that age, BMI, and smoking are no longer absolute contraindications[96]. Younger patients (under 50–55 years) generally have better outcomes, while obesity and smoking increase surgical complications but do not clearly worsen functional results[96]. Mild degeneration in the unaffected or patellofemoral compartments does not negatively impact outcomes, though advanced cartilage damage may raise failure risk[96].

Long-Term Survival

Osteotomies around the knee, including both medial open-wedge and lateral closed-wedge techniques, have demonstrated good clinical benefits and long-term survival. Patient-reported outcome measures show significant improvement following osteotomies, with sustained benefits observed even in longer-term follow-up. These improvements have been consistently documented across multiple studies involving both open- and closed-wedge approaches[103–107]. Additionally, return to sport outcomes are favorable, with over 80% of patients typically returning to physical activity following osteotomies around the knee[104,108–110]. Although there is often a shift toward lower-impact sports, a considerable proportion of patients return to their preoperative sport level[104,108,109]. Notably, return to sport rates and performance levels appear to be superior in osteotomy patients compared to those undergoing unicompartmental knee arthroplasty (UKA)[111,112]. In addition to their clinical benefits, osteotomies have demonstrated favorable long-term survival outcomes. A systematic review reported survival rates—defined as the percentage of osteotomies not converted to total knee arthroplasty (TKA)—ranging from 86–100% at 5 years, 64–97.6% at 10 years, and 44–93.2% at 15 years[97]. These findings are also supported by individual studies reporting comparable outcomes[113–117].

Impact of Osteotomies on Knee Arthroplasty Outcomes

Despite these advantages, osteotomies are performed relatively infrequently and are greatly outnumbered by knee arthroplasty procedures[118–120]. This reluctance may be attributed to concerns about postoperative pain, rehabilitation, complications, and more favorable financial model for arthroplasty[121]. Additionally, there has been ongoing debate about the impact of prior osteotomy on the outcomes of subsequent knee arthroplasty. However, several studies have shown that prior high tibial osteotomy (HTO) does not negatively impact TKA outcomes. A self-matched case-control study and a large population-based analysis found no significant differences in implant survival up to 15 years post-TKA between patients with and without previous HTO[114,122]. A recent meta-analysis further confirmed comparable short- to midterm survival and complication rates[123]. Notably, a Dutch registry study reported superior 12-year revision-free survival for TKA after HTO compared to TKA after UKA, with a significantly lower revision risk in the former group[124].

Thesis aim

The rise in the global burden of KOA—particularly among younger and physically active individuals—highlights the growing need for accurate diagnostics and effective joint-preserving treatment strategies. In this context, osteotomy has gained attention, as it has shown promising clinical outcomes and long-term joint preservation in these young patients. To support the development and refinement of such joint-preserving strategies, this thesis aims to advance four interrelated domains of KOA research:

1. Evaluating and optimizing radiographic assessment of KOA
2. Determining the impact of lower limb malalignment
3. Enhancing osteotomy care
4. Assessing the impact of previous osteotomy on TKA

Contents of this thesis

First, the thesis explores how radiographic and magnetic resonance imaging-based imaging modalities can more accurately evaluate joint structure and disease progression, while accounting for technical factors such as patient positioning. These efforts aim to establish more reliable and clinically relevant methods for monitoring KOA progression and evaluating treatment effects. Second, the thesis examines the impact of lower limb malalignment through both longitudinal and cross-sectional analyses. It investigates how sporting activities influence alignment parameters and explores the consequences of malalignment on joint health—not only in the knee, but also in the hip, providing insights into the complex interplay between physical activity, biomechanical alignment, and the long-term musculoskeletal health of the lower extremities. Third, the thesis focuses on improving osteotomy care by refining preoperative planning, enhancing the assessment of bone healing, and optimizing surgical techniques. By evaluating new planning concepts, biomaterials, and standardized outcome measures, this work aims to advance the quality of care and improve outcomes for patients undergoing realignment surgery. Finally, the thesis investigates the impact of previous osteotomy on TKA, clarifying how joint-preserving surgery influences subsequent reconstructive procedures and their outcomes. Collectively, this thesis contributes to more precise diagnostics and more effective joint-preserving strategies for individuals with KOA—particularly relevant for the growing population of younger, active patients in the midst of their professional and social lives, who strive to maintain mobility and function while delaying or avoiding joint replacement.

Part I

Imaging in Knee Osteoarthritis

02

Chapter 2

Impact of Knee Positioning on Differences Between Weight-Bearing minimal Joint Space Width and Non-Weight-Bearing MRI Cartilage Thickness: A Cross-Sectional and Longitudinal Analysis in the IMI-APPROACH

Eva A. Bax, H. Chien Nguyen, Roel J.H. Custers, Nienke van Egmond, Vahid Arbabi, Hassan Rayegan, Willem Paul Gielis, Claudia Lindner, Tim F. Cootes, Margreet Kloppenburg, Francisco J Blanco, Ida K. Haugen, Francis Berenbaum, Mylène P. Jansen, Simon C. Mastbergen, Frank W. Roemer, Felix Eckstein, Wolfgang Wirth, Moyo C. Kruyt, Harrie Weinans

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Abstract

Objective: Correlations between minimum joint space width (mJSW) and MRI-based cartilage thickness are strong in cross-sectional analyses and moderate in longitudinal analyses, possibly due to knee rotation and flexion. This study investigates the effect of knee positioning during radiographic acquisition on the difference between mJSW and MRI-based cartilage thickness.

Methods: Radiographic mJSW from the index knee was determined from baseline (265 patients) and 24-month follow-up (165 patients) on fixed-flexion radiographs from IMI-APPROACH (multicenter OA study) patients using automated software. Statistical Shape Models were used to quantify knee rotation and flexion on radiographs. Cartilage thickness was assessed by manual segmentation from MRI. Differences between mJSW (radiographs) and cartilage thickness (MRI) were assessed at baseline and follow-up. Multivariable linear regression was used to evaluate the impact of knee flexion and rotation on the difference between mJSW and cartilage thickness.

Results: In cross-sectional analysis, differences between X-ray and MRI were significantly influenced by knee rotation (β = -0.18, $P < 0.001$). Longitudinal change in differences between X-ray and MRI were associated with changes in knee flexion (β = 0.19, $P=0.002$). Increases of one standard deviation in internal rotation and extension at follow-up resulted in a 0.2 mm false surrogate measurement of cartilage changes on radiographs.

Conclusion: Quantified knee positioning significantly affects differences between mJSW measured on radiographs and MRI-based cartilage thickness. The longitudinal analyses revealed that knee flexion was related to these differences, while knee rotation was only related to cross-sectional differences. These findings highlight the importance of knee positioning during radiographic acquisition in contributing to false surrogate measurement of cartilage status and cartilage change.

1. Introduction

Radiographic evaluation is a widely used method for diagnosing and monitoring the severity and progression of knee osteoarthritis (OA)[30,31]. The minimum joint space width (mJSW) measured on a posteroanterior knee radiograph in semi-flexed joint position under loading is commonly used as a surrogate measure of cartilage and meniscus integrity and/or degeneration, with the intent to monitor progression of knee OA[31,36–38]. The JSW is integrated into widely adopted categorical grading systems that try to capture knee OA severity on radiographs, such as the Kellgren & Lawrence (KL) score[32,33,38,125]. However, the KL score is less sensitive to subtle changes in quantitative parameters, such as changes in the continuous measure of mJSW[31]. Accurate and reliable measurement of radiographic OA parameters are essential for assessing structural changes in knee OA, especially when evaluating the effectiveness of new treatments[126].

Radiographic JSW reflects not only cartilage thickness, but is also influenced by additional factors, such as the meniscus and positional differences during aquisition[127–130]. While cross-sectional studies often reveal strong correlations between JSW and cartilage thickness measurements obtained from non-weight-bearing Magnetic Resonance Imaging (MRI)[131,132], longitudinal analyses demonstrate only moderate correlations between changes in JSW and cartilage thickness[133–135]. Possible explanations for these differences include positional differences during radiographic acquisition, changes in meniscal extrusion and lower cartilage quality[136]. Variations in knee rotation and flexion are well-recognized limitations in assessing knee OA progression when using radiographs[50,129,130,137,138]. For instance, Kan *et al.*[129] reported significantly smaller medial JSW in flexion views compared to extended views, while Kinds *et al.*[130] observed that full leg extension increased JSW measurements.

Positional differences during radiographic acquisition, such as knee rotation and flexion, can be captured with statistical shape models (SSM). SSMs describe bone shapes observed in radiographs, capturing both anatomical differences (e.g., wider condyles) and positioning effects (e.g., knee rotation or flexion). The SSMs quantify subtle variations in knee positioning on radiographs. Shape variations are categorized into distinct shape modes, allowing separation between true anatomical characteristics and those due to patient positioning[139–142]. Hence, if sequential radiographs are being made in time and no large changes in bone geometry are expected, the SSM will mostly represent the positioning with respect to radiographic acquisition. The aim of this study was twofold. Firstly, to determine whether cross-sectional differences between radiographic based mJSW and MRI-based cartilage thickness can be attributed to positioning during radiographic acquisition. Secondly, to evaluate the effect of change of positioning during radiographic acquisition over time. This longitudinal analysis provides insights into the impact of positioning on the thoughtfulness of progressors and non-progressors of KOA. We hypothesized that differences in positioning of knee flexion and rotation during radiographic acquisition will bias the interpretation of measured mJSW (surrogate) when compared to MRI-based cartilage thickness.

2. Methods

2.1 Patients

The prospective Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH cohort) cohort is an observational, longitudinal cohort that enrolled patients with predominantly femorotibial OA selected from five European cohorts[143] ((CHECK (Utrecht, The Netherlands), HOSTAS (Leiden, The Netherlands), MUST (Oslo, Norway), PROCOAC (A Coruña, Spain), and DIGICOD (Paris, France)) or from their outpatient departments. Recruitment relied on machine-learning models to predict the probability of increased or sustained knee pain or structural progression during the two-year follow-up[143]. The index knee of the participants was selected based on American College of Rheumatism (ACR) criteria. If both knees met the ACR criteria, participants indicated their most affected knee to use as index knee; if participants indicated no difference, the right knee was chosen as index knee. A detailed description of the inclusion and exclusion criteria has been published previously[143]. Medical ethics committees of all participating centers approved the study, and all patients provided written informed consent. The study was registered under clinicaltrials.gov nr: NCT03883568.

2.2 Imaging protocol for knee radiography and MRI

Knee radiographs and MRI-scans of the patients were included in this study. The radiographs were obtained following the Buckland-Wright protocol, with a posteroanterior view of the knee in semi-flexed position (7° - 10°) and under weight-bearing conditions[36,143]. The MRI protocol included sagittal 3D spoiled or volume-interpolated gradient echo sequences, incorporating selective water excitation or fat suppression techniques for quantitative cartilage morphometry. These 3D MRI scans were independent of patients positioning. Furthermore, sagittal, axial, and coronal intermediate-weighted fat-suppressed sequences were acquired for the assessment of the MRI Osteoarthritis Knee Scores (MOAKS). Among the five participating centers, two centers used 1.5T scanners, while the remaining three centers deployed 3T systems.

2.3 Imaging assessment

This study included knee radiographs of the index knee at baseline and 24 months follow-up. The radiographic mJSW (mm) in the medial compartment was provided by automated software (Orthopedic Digital Image Analysis (ODIA))[144]. The KL score (range: 0-4) was determined at both time points by one experienced reader[143].

The medial femorotibial compartment cartilage thickness (mm) of the index knee was determined on MRI-scans at baseline and 24-months follow-up. Cartilage thickness was manually segmented from the MRIs by experienced readers using custom software (Chondrometrics, GmbH, Freilassing, Germany). This involved measuring the mean cartilage thickness (mm) of the medial tibia (MT) and the weight-bearing (central) part of the medial femur (cMF). The cartilage thickness for the weight-bearing medial femorotibial compartment (MFTC) was calculated (MFTC = MT + cMF)[145]. The quantitative cartilage measurements performed on MRI were used in this study as a reference (ground truth) for the surrogate cartilage thickness of mJSW measurements on radiographs, thereby including the meniscus status (based on MRI) as relevant parameter for radiographical mJSW.

Meniscal extrusion and meniscus damage were assessed using the semi-quantitative MOAKS instrument by an experienced radiologist blinded to clinical data, as meniscal extrusion and damage also influences the mJSW[146]. In both the medial and lateral compartment, medial and lateral meniscal extrusion was scored. Each score ranges between 0-3: Grade 0: <2mm; Grade 1: 2 to 2.9mm, Grade 2: 3-4.9mm; Grade 3: >5mm[146]. The presence of meniscal extrusion was defined as a displacement of more than 3 mm of the medial or lateral meniscus[147]. Meniscal damage of the medial and lateral body was classified on a scale from 0 to 8, with grades 0 and 1 indicating an intact meniscus without a tear. Grades 2 to 4 correspond to varying types of tears, while grades 6 to 8 reflect maceration, signifying loss of meniscal substance[146]. A distinction was made between an intact meniscus (grades 0 and 1) and a non-intact meniscus (all other grades).

2.4 Statistical shape modelling

We used the validated software BoneFinder® (www.bone-finder.com, The University of Manchester, UK) to automatically annotate landmarks on knee radiographs[148–150]. The landmarks included the edges of the distal femur, proximal tibia, and patella[144]. These annotated landmarks served as input for generating the SSM based on a principal component analysis (PCA) to identify the predominant factors responsible for the observed variations in bone morphology. PCA simplified the data, generating independent modes of shape that reflect the variation from the average shape[142]. Each shape mode was quantified in standard deviations. As knee flexion and rotation with respect to the radiographic source and detector is also represented in the 2D projection of the radiograph, this positioning is also revealed in the SSM. SSMs can quantify subtle variations in knee positioning that are not always visually apparent (Figure 1), by comparing each individual radiograph to the average knee positioning of the cohort. In this way, the SSM serves as a measurement method to quantify positioning variations. SSM was generated from knee radiographs of the index knee at baseline and at 24-month follow-up. Shape analyses of the IMI-APPROACH cohort revealed that the two largest principal components indicate knee rotation (shape mode 1) and knee flexion (shape mode 2), both expressed in standard deviations (SD).

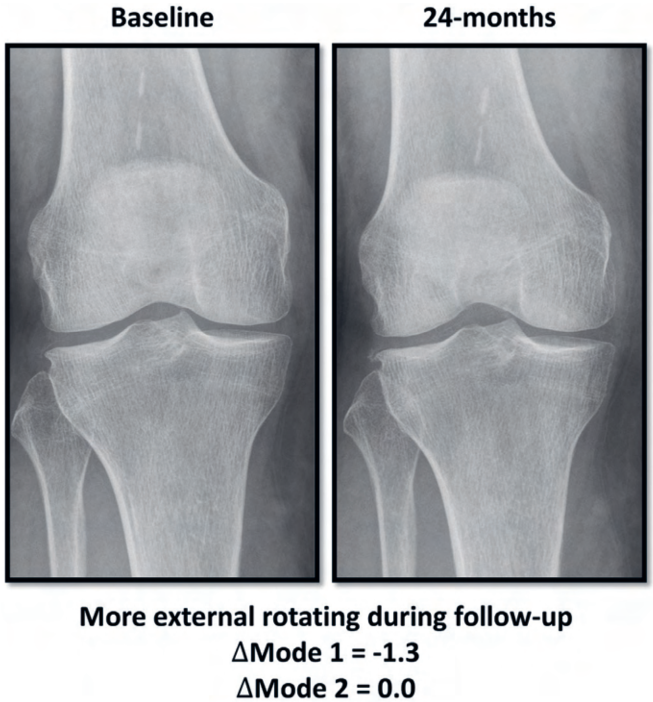

Figure 1 - Example of knee radiographs of the same patient at baseline (left) and 24-month follow-up (right). At follow-up, the knee is positioned in greater external rotation, as indicated by a change in shape mode 1 (ΔMode 1 = –1.3), while the degree of flexion/extension remains unchanged (ΔMode 2 = 0.0). SSMs allow for the quantification of such subtle differences in knee positioning, which are often not visually apparent.

2.5 Design of the study

This study consists of two phases, using patients from the IMI-APPROACH cohort. In the first phase, a cross-sectional analysis assessed whether differences between mJSW and MRI-based cartilage thickness can be attributed to knee flexion and rotation during acquisition, with the MRI-based meniscus status considered. All patients with baseline radiographs and MRI scans of the index knee were included. In the second phase, a longitudinal analysis was performed, calculating the difference in knee flexion and rotation over 24 months (ΔMode 1 and ΔMode 2) and the changes in mJSW (ΔmJSW) and MRI cartilage thickness (ΔCartilage thickness) over 24 months, incorporating MRI-based meniscus status as a parameter. The longitudinal Δdifference was determined by subtracting ΔmJSW from ΔCartilage thickness, which provided the difference in MRI-based and radiographical-based change in mJSW. Patients with both baseline and 24-month radiographs and MRI scans were included. For the longitudinal analysis, baseline meniscal extrusion and meniscal damage were used.

2.6 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 27.0 software (IBM, Armonk, New York). Descriptive statistics, displaying means and standard deviations (SDs), or numbers and percentages, were provided. Histograms were assessed for normal distribution. Univariable linear regression was employed to assess the impact of Mode 1 (internal/external rotation), Mode 2 (flexion/extension), meniscal extrusion, and meniscal tears on the difference between MRI-based cartilage thickness and minimal joint space width (mJSW) independently. Moreover, multivariable linear regression was used to analyze the impact of Mode 1 (internal/external rotation), Mode 2 (flexion/extension), meniscal extrusion, and meniscal tears on the difference between MRI-based cartilage thickness and mJSW. The degree of underestimation and overestimation of ΔmJSW relative to ΔMRI-based cartilage thickness was determined using the β coefficients from the multivariable regression analysis in patients without meniscal extrusion or meniscal damage. Furthermore, the change in mJSW is often used as the surrogate measure of cartilage degeneration over a specific time. Therefore, our methodology was also applied to examine how changes between baseline and follow-up in Mode 1 and Mode 2 (ΔMode 1, ΔMode 2), as well as meniscal extrusion and meniscal tears, influenced the change in mJSW compared to the change in MRI-based cartilage thickness (ΔDifference). Statistical significance was defined as a p-value < 0.05.

3. Results

3.1 Patients and data assessment

A total of 297 IMI-APPROACH patients Were initially considered for the study. However, 15 patients had missing MRI scan parameters (MOAKS and/or cartilage thickness), and 17 patients had incomplete, radiographic parameters (either ODIA software measurements or SSM were missing). As a result, a total of 265 patients were included in the first phase of the study. Every patient participated with one (index) knee. The characteristics of the patients included in the cross-sectional study are detailed in Table 1.

Table 1 – The characteristics of the included IMI-APPROACH cohort patients.

	Baseline (N=265)
Age (years)	66.6 (7.2)
Sex, no. (%) women	206 (77.7%)
Body Mass Index (kg/m^2)	27.9 (5.1)
mJSW medial compartment (mm)	3.6 (1.4)
Cartilage thickness medial compartment (mm)	3.5 (1.1)
Medial extrusion of the medial meniscus, no. (%)	
No meniscal extrusion	179 (67.5%)
Meniscal extrusion	79 (29.8%)
Unscorable	7 (2.6%)
Lateral extrusion of the lateral meniscus, no. (%)	
No meniscal extrusion	236 (89.1%)
Meniscal extrusion	27 (10.2%)
Unscorable	2 (0.8%)
K&L grade, no. (%)	
Grade 0	47 (17.7%)
Grade 1	72 (27.2%)
Grade 2	60 (22.6%)
Grade 3	72 (27.2%)
Grade 4	11 (4.2%)
Missing	3 (1.1%)

Mean (standard deviation (SD) are depicted, unless stated otherwise.; no., number; mJSW, minimum joint space width; K&L, Kellgren and Lawrence

The longitudinal analysis included 162 participants (77.8% women) with a baseline mean age of 66.0 years (SD 7.5) and BMI of 28.1 kg/m^2 (SD 5.2). The follow-up of the IMI-APPROACH patients occurred during the COVID-19 pandemic, which contributed to the missing follow-up data. Over 24 months, mean age increased by two years to 68.0 years, BMI remained stable at 27.9 kg/m^2, and mean mJSW of the medial compartment decreased from 3.8 mm (SD 1.3) to 3.7 mm (SD 1.4). The mean cartilage thickness of the medial compartment decreased from 3.0 mm (SD 0.7) to 2.9 mm (SD 0.7). Most participants remained within KL grades 2-4 (54%) at both baseline and 24 months follow-up. The absolute Δdifference between ΔMRI-cartilage thickness and ΔmJSW is 0.37 ± 0.36 mm. For patients with a 0 SD for rotation (mean rotation) (N = 24), this Δdifference between ΔMRI-cartilage thickness and ΔmJSW is 0.35 ± 0.37 mm. For patients with a 0 SD for flexion (mean knee flexion) (N = 29), this Δdifference is 0.5 ± 0.4 mm.

3.2 Statistical shape modes

24 shape modes were created to describe 90% of the shape variation. Shape mode 1, the primary mode of variation, represented knee rotation and accounted for 33.6% of total variation in shape. The positioning of both the patella and medial femoral condyles

played a crucial role in discerning knee rotation (Figure 2). A positive ΔMode 1 denoted an increase in internal rotation at follow-up (24 months) relative to baseline. Shape mode 2, reflecting knee flexion/extension accounts for 25.4% of total variation in shape. The location of the patella and medial tibial plateau indicated an important part of recognizing knee flexion (Figure 2). A positive ΔMode2 denoted an increase in flexion.

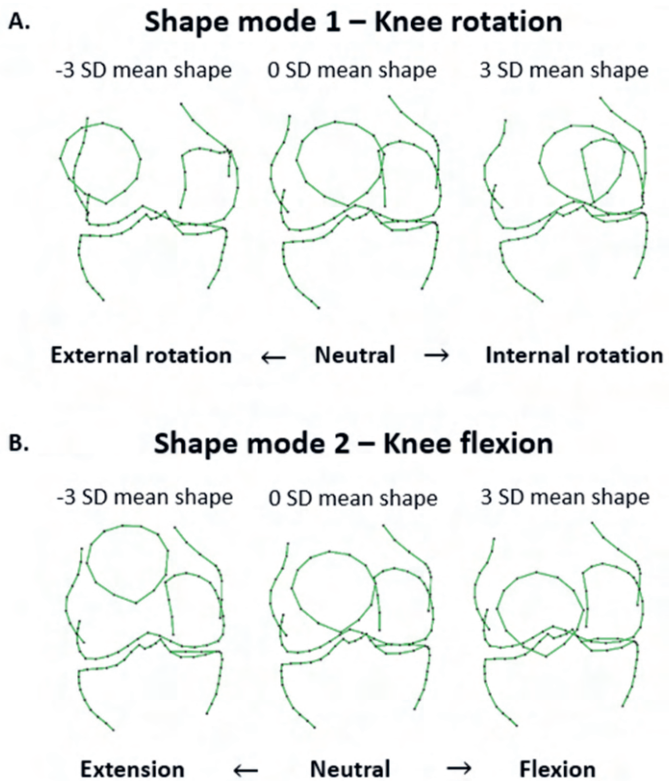

Figure 2 - Positioning Mode 1 and Mode 2 of the IMI-APPROACH cohort. A) Shape mode 1 (knee rotation). The mean knee rotation (0 standard deviation (SD)) and the +3/-3 SD are shown. B) Shape mode 2 (knee flexion). The mean knee flexion (0 standard deviation (SD)) and the +3/-3 SD are shown.

3.3 Statistical shape modes and joint space width measurements

Univariable regression revealed that knee rotation (P = 0.01, β = -0.12) and flexion (P = 0.026, β = 0.11) significantly influenced cross-sectional differences between MRI cartilage thickness and mJSW. Medial (P = 0.002, β = 0.30) and lateral meniscal damage (P = 0.003, β = -0.36) were also significant, while meniscus extrusion showed no significant effects (Medial: P = 0.93, β = 0.00; Lateral: P = 0.65, β = -0.03).

Using multivariable regression, knee rotation (mode 1) significantly influenced the cross-sectional difference between MRI cartilage thickness and mJSW ($P < 0.001$, $\beta = -0.18$) (Figure 3). In Figure 3, mode 1 is plotted against the difference between MRI cartilage thickness and mJSW. Internal rotation was associated with an overestimation of mJSW compared to MRI cartilage thickness (mJSW > MRI-based cartilage thickness), whereas external rotation caused an underestimation (mJSW < MRI-based cartilage thickness). In contrast, knee flexion (mode 2) showed no significant relationship with the cross-sectional difference ($P = 0.20$, $\beta = 0.06$) (Figure 3). Medially extrusion of the medial meniscus and laterally extrusion of the lateral meniscus showed no significant relationship with the cross-sectional difference (Medial: $P = 0.98$, $\beta = -0.00$; Lateral: $P = 0.91$, $\beta = 0.01$). Finally, medial and lateral meniscal damage resulted in a significant difference between MRI cartilage thickness and mJSW (Medial: $P < 0.001$, $\beta = 0.33$; Lateral: $P = 0.003$, $\beta = -0.38$).

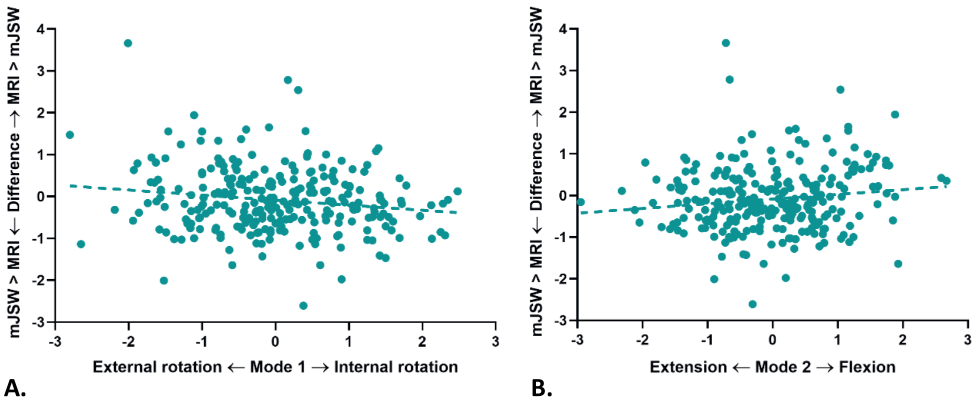

Figure 3 - Relationship between the standard deviation of shape modes for rotation (A) and flexion/extension (B) and the difference between mJSW and cartilage thickness. The shape modes are represented by their standard deviations within this population, where 0 corresponds to the average shape mode (i.e., the average knee rotation and flexion/extension of the cohort). On the vertical axis the difference is provided by MRI-cartilage thickness – mJSW.

In the multivariable analysis of longitudinal changes, more internal rotation at follow-up compared to baseline, indicated here as positive ΔKnee rotation (Δmode 1), showed no significant effects with the difference over time ($P = 0.72$, $\beta = 0.02$) (Figure 4). In Figure 4, Δmode 1 is plotted against the Δdifference between MRI cartilage thickness and mJSW. ΔKnee flexion (Δmode 2) was significantly associated with longitudinal differences ($P = 0.002$, $\beta = 0.19$) (Figure 4), where more knee flexion at follow-up results in a reduction in mJSW that does not represent an actual decrease in mJSW, while more extension at follow-up can create a false impression of mJSW increase. Medially extrusion of the medial meniscus and laterally extrusion of the lateral meniscus showed a significant relationship with the longitudinal difference (Medial: $P < 0.001$, β

= 0.16; Lateral: P < 0.001, β = -0.21). Meniscal damage showed no significant associations with the longitudinal difference (Medial: P = 0.39, β = 0.07; Lateral: P = 0.08, β = -0.17).

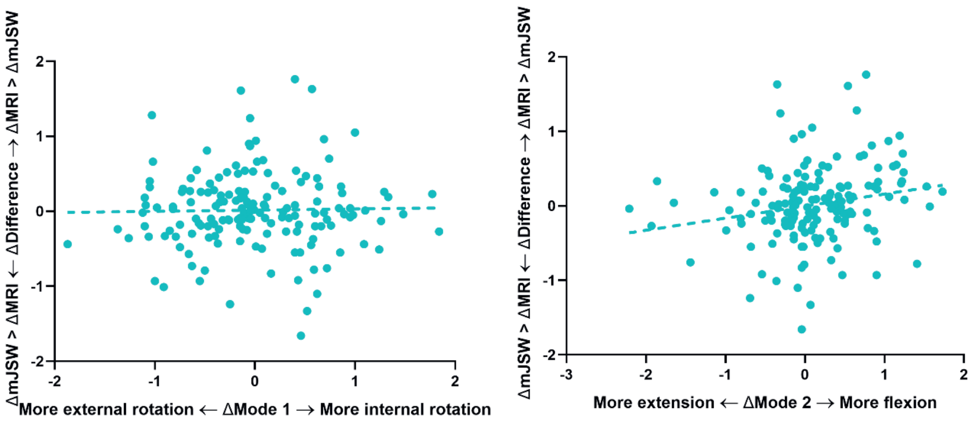

Figure 4 - Relationship between differences in standard deviation of shape modes for rotation (A) and flexion/extension (B) and the Δdifference between changes of mJSW during follow-up and the changes in cartilage thickness found in MRI. The shape modes are represented by their standard deviations within this population, where 0 corresponds to the average shape mode (i.e., the average knee rotation and flexion/extension of the cohort). On the vertical axis the Δdifference is provided by ΔMRI-thickness -ΔmJSW. Thus, a loss or gain in mJSW found during follow-up is skewed relative to the cartilage thickness measurements on MRI, dependent on the positioning differences of the knee during the two acquisitions of the radiographs.

We determined the degree of underestimation (mJSW < MRI-based cartilage thickness) and overestimation (mJSW > MRI-based cartilage thickness) of ΔmJSW compared to ΔMRI-based cartilage thickness for patients without meniscal extrusion and meniscal damage, as this represents the largest group in our study population. A one SD increase in internal rotation causes a 0.02 mm overestimation of mJSW compared to MRI-based cartilage thickness, while a similar increase in flexion results in a 0.2 mm underestimation. When both parameters increase by one SD, mJSW is underestimated by 0.2 mm. These effects become more pronounced with a two SD increase. A two SD increase in internal rotation and a two SD increase in knee extension result in an overestimation of mJSW by 0.43 mm.

4. Discussion

In this study, we investigated whether differences between surrogate cartilage thickness (mJSW) from knee radiographs and cartilage thickness from knee MRI could be (at least partially) attributed to positioning during radiographical acquisition. This was determined at a single time point (cross-sectional) and over a two-year follow-up period (longitudinal). Our findings showed that knee rotation (determined by SSM mode 1) significantly affected the cross-sectional difference between the mJSW and the cartilage thickness from MRI when meniscal status was not considered. It was shown that internal rotation caused an overestimation and external rotation an underestimation of mJSW compared to MRI cartilage thickness. Knee flexion (SSM mode 2) had also a significant effect on the cross-sectional difference when meniscal status was not considered, where knee flexion caused an underestimation and knee extension an overestimation of mJSW compared to MRI-cartilage thickness. When examining the multivariable model, we observed that meniscal damage and knee rotation have a significant effect on the difference between the mJSW and the cartilage thickness from MRI. Knee flexion and meniscal extrusion did not have a significant effect.

Longitudinally, knee rotation showed no significant effect on the Δdifference between ΔmJSW and ΔMRI cartilage thickness. Knee flexion differences (Δmode 2) showed a significant effect on the Δdifference. More specifically, knee flexion resulted in an underestimation, while knee extension led to an overestimation of changes in mJSW. Thus, increased flexion at follow-up may result in a false conclusion of cartilage loss based on mJSW, while increased extension may lead to undetected cartilage thinning or even a falsely detected increase in cartilage (surrogate) thickness. Meniscal extrusion at baseline showed a significant effect on the longitudinal differences, and meniscal damage showed no significant effect on the Δdifference. Notably, a 2 SD increase in internal rotation and a 2 SD increase in knee extension resulted in a false increase of mJSW by 0.43 mm. These findings underscore the critical role of knee positioning during radiographic acquisition in contributing to the differences between mJSW and MRI-based cartilage thickness.

Knee rotation and flexion biases are well-known limitations in measuring KOA progression using radiographs[50,129,130,137,138]. Studies have shown that variations in knee positioning can significantly affect JSW measurements, leading to inconsistencies in assessing cartilage degeneration. Kan *et al.*[129] found that medial JSW was significantly smaller in flexion view compared to the extended view, while Kinds *et al.*[130] concluded that leg extension increases JSW measurements. Our research demonstrates that these positioning effects may contribute to the differences between MRI-based cartilage thickness and radiographic mJSW measurements. Despite using the standardized Buckland-Wright protocol[36] in our study, the shape modes with the largest variation were those related to knee positioning, specifically rotation and flexion. We employed SSMs due to their ability to capture and quantify these variations in shape in a rigorous mathematical approach, expressing the variation in terms of standard deviation within the measured population. One of the key strengths of this method is its ability to make even small variations in knee positioning visible and measurable. In the study by Haverkamp *et al.* [142], SSMs were also used to assess the effect of knee flexion, concluding that OA knees were more extended compared with control knees. It is possible that the patient's positioning may be influenced by the thickness of the MRI cartilage and thus the severity of KOA. Additionally, patients experiencing high levels of pain may have limited knee extension. Ultimately, various factors could contribute to the positioning of the patient. In our study, we compare mJSW measurements with the reference, MRI-based cartilage thickness, and examined the effect of positioning over time, providing us more sensitive measurements per patients and offering a deeper understanding of how positioning influences the difference between cartilage thickness and mJSW.

In addition to the variability in knee positioning, we observed a considerable variability in the difference between the mJSW and MRI-based cartilage thickness, as revealed in Figure 3 and Figure 4. The mJSW measurements are influenced by multiple factors, including the measurement technique, and the specific radiographic protocol used[151]. Notably, automatic measurement of mJSW resulted in more consistent outcomes than the manual measurement method, highlighting the potential benefits of automated techniques for improving measurement accuracy[152]. Previous research has extensively compared radiographic JSW measurements with cartilage thickness from non-weight-bearing MRI scans. While cross-sectional studies show strong correlations between these methods[131,132], longitudinal analyses often reveal weak or no significant correlations between changes in JSW and cartilage thickness [133–135], possibly due to factors such as meniscal extrusion, cartilage quality, loading effects, and positioning[136]. Meniscal extrusion does contribute to these differences over time. More specifically, the longitudinal difference between mJSW and MRI-based cartilage thickness was smaller in patients with medial or lateral meniscus extrusion compared to those without meniscal extrusion. However, it is important to note that most patients (89.1%) had no meniscal extrusion at baseline. Our study demonstrates that differences between cartilage thickness and mJSW can be partially explained by changes in radiographic positioning (knee rotation and flexion), with meniscal extrusion also contributing to these differences. This highlights the importance of considering positioning and technical aspects when interpreting mJSW measurements in both research and clinical settings.

Changes in mJSW serve as a primary outcome in numerous clinical investigations. Moreover, mJSW often serves as an inclusion criterion in OA studies, such as in the case of IMI-APPROACH cohort. In this cohort, mJSW was utilized as a parameter in a machine-learning model to predict the probability of increased or sustained knee pain and structural OA progression during the 24-month follow-up [143]. In addition to mJSW, other joint space width (JSW) measures exist, such as mean JSW and fixed location JSW[135,153]. However, mJSW is the most used measure in OA studies and clinical investigations. Our research highlights that, despite the standardized Buckland Wright radiograph acquisition protocol[36], knee rotation accounts for 33.6% and knee flexion for 25.4% of the total variation of 2D presented shape on the radiographs. It seems that there is a substantial influence of knee rotation and flexion on the truthfulness of classified progressors and non-progressors. This may result in falsely included patients into research cohorts based on their disease severity. Moreover, this method of mJSW analyses on radiographs may induce noise when categorizing patients into progressors and non-progressors in a research cohort, for instance for the assessment of treatment effectiveness. These insights emphasize the critical role of knee positioning during radiographical acquisition when mJSW is utilized as a primary endpoint or inclusion criterion in OA research. Even with the use of standardized radiograph acquisition protocols, we still observe the effect of knee positioning. Therefore, it is crucial to account for the influence of knee positioning when interpreting mJSW results. Looking ahead, it may be necessary to investigate alternative OA measures on radiographs that exhibit reduced sensitivity to positioning variations.

Our current study had several limitations. Firstly, we used cartilage thickness on MRI scans for comparison to mJSW. However, mJSW reflects both cartilage and meniscus and is measured in a weight-bearing position, whereas MRI-based cartilage thickness exclusively represents cartilage and is obtained in a non-weight-bearing position. Additionally, an increased cartilage thickness over time can be caused by cartilage swelling due to increased water content from collagen cleavage[154–157]. However, this type of cartilage is likely more flexible and leads to a decrease in mJSW under loading such as occurs during the weight bearing radiographical acquisition, while simultaneously showing an increase in cartilage thickness on MRI performed without loading conditions[136]. In such case the MRI-based cartilage thickness does not serve as best representative of cartilage status and its ground truth becomes questionable. Secondly, potential measurement errors in mJSW measurements could influence the outcomes of this study. In most studies, mJSW is measured using specialized software such as e.g. Knee Imaging Digital Analysis[31]. However, we opted for fully automated software (ODIA) that automatically selects the anterior edge of both the lateral and medial tibial plateau and provides validated reproducible results[144] of mJSW over a specific region of the medial and lateral joint space. Thirdly, while our study primarily addresses the positioning of the patient's knee in terms of flexion and rotation, it is important to note that the position of the X-ray tube above or below the knee joint can also affect mJSW measurements[50]. Fourthly, we only examined the effect of positioning on the differences in the medial compartment. This limitation means that potential effects on the lateral compartment were not assessed, which could provide a more comprehensive understanding of the impact of positioning on knee joint morphology. Fifthly, although this study demonstrates that positioning contributes to the differences between mJSW and actual cartilage thickness, the translation to clinically relevant differences remain an open question. This aspect requires further investigation in a larger study population to better understand how these variations impact clinical interpretation and decision-making. Moreover, our study does not clarify whether the change in mJSW due to positioning is explained by a different viewing angle of the joint or by an inherent change in JSW. This can be determined in future research. Finally, the timing during the day of the MRI-scan has the potential to impact cartilage thickness measurements. Both gravity and physical activity can affect cartilage thickness in the knee[158]. A study by Danieli *et al.*[158] demonstrated that after 60 minutes of running, cartilage thickness decreased significantly, ranging from 0.02 to 0.19 mm depending on the location.

5. Conclusion

In conclusion, our study highlights the significant impact of knee positioning on differences between weight-bearing mJSW and non-weight-bearing MRI cartilage thickness. Cross-sectional analyses revealed that knee rotation notably influenced these differences, with internal rotation overestimating and external rotation underestimating mJSW. Longitudinal analyses indicated that knee flexion played a role in longitudinal differences, where increased flexion at follow-up results in a reduction in mJSW that does not represent an actual decrease in mJSW. When both internal rotation and extension increased by 2 standard deviations from average in the current population, the combined effect resulted in a 0.4 mm false finding of surrogate cartilage change on radiographs. These findings underscore the critical role of knee positioning during radiographic acquisition in contributing to the differences between mJSW and MRI-based cartilage thickness.

03

Chapter 3

Unicompartmental versus Bicompartmental Joint Space Width measures: Which Reflect Whole Joint Structural Damage Better? Data From IMI-APPROACH

Eva A. Bax, Roel J.H. Custers, Nienke van Egmond, Moyo C. Kruyt, Hassan Rayegan, Margreet Kloppenburg, Francisco J Blanco, Ida K. Haugen, Francis Berenbaum, Frank W. Roemer, Harrie Weinans, Simon C. Mastbergen, Mylène P. Jansen

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Abstract

Objective: To investigate the associations between whole joint cartilage and meniscal morphology on MRI and radiographic joint space width (JSW) measures and in knee osteoarthritis (KOA), to determine whether bicompartmental measures demonstrate stronger associations than unicompartmental ones, and to evaluate their correlations with Kellgren and Lawrence grading.

Methods: A cross-sectional analysis of baseline radiographs and MRIs from 262 KOA participants in the prospective, multicenter IMI-APPROACH cohort was conducted. Radiographic measures included minimum joint space width (mJSW), fixed location JSW (JSW(x)), mean JSW, and joint line convergence angle (JLCA), assessed using fully automated software. JSW was evaluated both unicompartmentally and bicompartmentally. Cartilage morphology, full-thickness cartilage loss, meniscal extrusion, tears, and maceration were assessed using the semi-quantitative MRI Osteoarthritis Knee Score to summarize whole-joint cartilage and meniscal morphology. Associations of radiographic measures with MRI outcomes were assessed using multivariable linear regression; Spearman correlations with Kellgren and Lawrence (KL) were also evaluated.

Results: MRI-defined meniscal maceration was associated with unicompartmental and bicompartmental JSW measures. Full-thickness cartilage loss was associated with unicompartmental (95% CI [-0.16; -0.02]) and bicompartmental mJSW (95% CI [-0.14; -0.02]), and JLCA (95% CI [0.04; 0.22]). Models explained 32–39% of variance for unicompartmental and 23–45% for bicompartmental measures (R^2). Bicompartmental measures showed stronger correlations with KL grading than unicompartmental measures (95% CI: –0.31 to –0.02).

Conclusions: Associations between whole-joint cartilage and meniscal degeneration are similar for uni- and bicompartmental JSW, with bicompartmental JSW showing stronger correlations with KL grades. These findings support including both compartments in radiographic assessment to improve structural evaluation in KOA.

1. Introduction

For radiographic assessment of knee osteoarthritis (KOA), key parameters include joint space width (JSW), Kellgren and Lawrence (KL) grading, and joint line convergence angle (JLCA). JSW is often the primary outcome in clinical trials and a common inclusion criterion in OA cohort studies[38,143]. JSW can be measured as minimum JSW (mJSW), fixed location JSW (JSW(x)), or mean JSW[153]. These JSW measures are typically applied unicompartmentally, most often the medial compartment, or are used without specifying the compartment[38,153].

Since KOA is considered a whole joint disease, assessing both the medial and lateral compartments provides a more accurate representation of disease progression. The KL grading system offers a joint-wide score based mainly on osteophytes and joint space narrowing, but its categorical nature limits sensitivity to subtle changes[31], and may have lower reproducibility Therefore, continuous variables, such as JSW and JLCA, offer an alternative to superiorly assess progression. The JSW can be expressed as a bicompartmental average, considering both the medial and lateral compartments. The JLCA is defined as the angle between the femoral and tibial joint lines[31]. It reflects cartilage loss, meniscal damage, and extrusion within one compartment relative to the contralateral compartment[159].

Despite the widespread use of these measures, the relationship between unicompartmental JSW and whole joint cartilage and meniscal morphology remains unclear, and the potential of bicompartmental measures is insufficiently explored. Because of the higher prevalence of medial compartment OA, most observational cohorts and clinical trials have focused primarily on the medial tibiofemoral compartment[160,161], and the majority of published studies restrict JSW measurement to this location[153,162,163]. Furthermore, it is common practice to compare such unicompartmental JSW measures with the whole-joint KL score[135,163,164]. To address these gaps, this study investigates three key research questions. First, we assess the cross-sectional correlation between whole joint cartilage and meniscal morphology assessed on MRI-scans and unicompartmental JSW; second, we examine whether bicompartmental measures yield stronger associations than unicompartmental ones; third, we evaluate the correlations of uni- and bicompartmental JSW measures with KL grading We hypothesized that whole-joint cartilage and meniscal morphology would be more strongly associated with bicompartmental JSW measures than with unicompartmental measures, and that bicompartmental JSW would show stronger correlations with KL grading compared to unicompartmental JSW.

2. Methods

2.1 Participants

In the prospective Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) cohort, 297 participants with femorotibial OA were included in five European centers and followed for 2 years[143].Recruitment was based on the clinical criteria from the American College of Rheumatology (ACR) and predictive models using radiographs, demographic, and clinical data from the screening visit to identify OA patients most likely to experience pain or structural progression over two-years[143,165]. Additional inclusion criteria included the ability to walk unassisted, primarily tibiofemoral KOA, and meeting the ACR clinical classification criteria for KOA[143]. At baseline, participants had weight-bearing radiographs and MRI of the index knee. Those without baseline radiographs or MRI were excluded in this study.

The study was approved by Institutional Review Boards, followed ethical and legal guidelines, including Good Clinical Practice and the Declaration of Helsinki. It was registered (NCT03883568), and all participants gave informed consent.

2.2. Radiographic Imaging Assessment

The radiographs were obtained following the Buckland-Wright protocol, with a posteroanterior view of the knee in semi-flexed position (7° - 10°) and under weight-bearing conditions[36,166]. Standard exposure parameters were applied (55 kV, 5 mAs) with a focal film distance of 1.2 m, the knee positioned against the detector, and the feet fixed in 7.5° external rotation. All radiographs were evaluated using the KL grading system by a blinded rheumatologist trained for KL scoring without specific prior experience. For four patients (1.5%), the baseline KL grade from this observer was unavailable; given the high interobserver reliability (quadratic weighted kappa = 0.9), the corresponding KL grades from the second trained observer were used, resulting in a complete dataset. In addition, all knee radiographs were automatically analyzed using Orthopedic Digital Image Analysis (ODIA)[144] software to determine the mJSW, JSW(x), mean JSW, and JLCA in the medial and lateral compartments (Figure 1). ODIA calculates mean JSW by fitting 30 intra-articular circles within the joint, with circle diameters representing JSW per compartment[144]. The smallest diameter per compartment defined the medial and lateral mJSW[144], while JSW(x) was measured at 0.275 (medial) and 0.725 (lateral) along the joint line, where 0 represents the most medial and 1 the most lateral point[153]. For unicompartmental measures, the medial compartment was used; bicompartmental values were calculated as the average of medial and lateral JSW. JLCA was defined as the angle between the distal femoral and proximal tibial joint lines[144], with neutral ranging from 0°–2°, varus as ≥2°, and valgus as ≤0°[51].

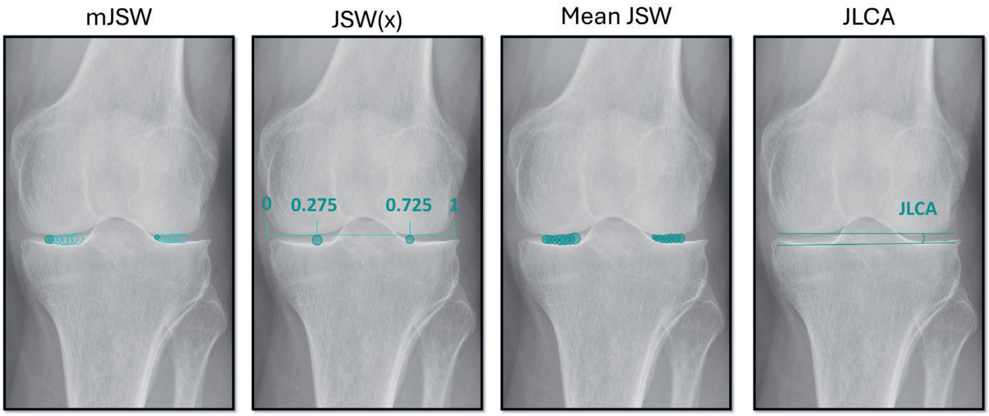

Figure 1 - Radiographic Imaging Assessment. Measurements include the mJSW in the medial and lateral compartments, the fixed joint space width (JSW(x)), the mean JSW, and the joint line convergence angle (JLCA).

2.3 Magnetic Resonance Imaging Assessment

MRI of the index knee was performed across five participating clinical sites. Two centers utilized 1.5 Tesla scanners (A Coruña: Ingenia CX, Philips Medical Systems, Netherlands; Oslo: Aera, Siemens Healthcare, Germany), while the remaining three centers employed 3 Tesla systems (Utrecht: Ingenia or Achieva, Philips Medical Systems, Netherlands; Leiden: Ingenia, Philips Medical Systems, Netherlands; Paris: Skyra, Siemens Healthcare, Germany). The standardized imaging protocol included axial, sagittal, and coronal intermediate-weighted fat-suppressed sequences, along with a coronal T1-weighted turbo spin-echo sequence, all of which were applied for semi-quantitative assessment. All MRI examinations were performed without contrast administration. Whole joint cartilage and meniscal morphology was assessed using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS)[146], scored by an experienced radiologist with 17 years of experience at the time of reading, who was blinded to clinical data. The whole joint health evaluation included cartilage morphology, meniscal extrusion, and tears.

2.3.1 Cartilage morphology

Cartilage loss was categorized based on a real extent of partial cartilage loss and on percentage of full-thickness cartilage loss within that subregion (Figure 2A and 2B). Area extent involvement was graded from 0 to 3 (< 10%, 10-75%, >75%) and full-thickness cartilage loss represents the percentage of complete loss in a given subregion and was also graded from 0-3[146]. Grading was performed in femoral (posterior, central) and tibial (anterior, central, posterior) subregions of both compartments. Whole joint cartilage loss was defined as the sum of scores across 10 subregions, ranging from 0 to 30. The same method was applied to full-thickness cartilage loss.

2.3.2 Meniscal extrusion

Whole joint meniscal extrusion was calculated as the sum of medial extrusion of the medial meniscus and lateral extrusion of the lateral meniscus (Figure 2C). Each extrusion was graded from 0 to 3: Grade 0: <2 mm, Grade 1: 2–2.9 mm, Grade 2: 3–4.9 mm, and Grade 3: >5 mm[146]. The total score ranged from 0 to 6.

2.3.3 Meniscal tears

Meniscal tears were assessed in the anterior horn, body, and posterior horn of both the medial and lateral meniscus[146]. Grade 0 indicated an intact meniscus, while Grades 2 to 4 reflected varying tear types, and Grades 6 to 8 indicated different degrees of maceration (Figure 2D). Patients were categorized into any tear (yes/no), and any maceration (yes/no).

2.4 Statistical analysis

All statistical analyses were performed using SPSS Version 29.0. Descriptive statistics (means, SD, frequencies, percentages) were calculated. Multivariable linear regression examined the association of partial cartilage loss, full-thickness cartilage loss, meniscal extrusion, and tears (independent variable) with unicompartmental and bicompartmental JSW measures and JLCA (dependent variables). Standardized beta coefficients were reported, representing the change in the outcome per 1 standard deviation increase in the exposure. Diagnostic checks were performed for all linear regression models. Normality of residuals was assessed using QQ plots, homoscedasticity was evaluated via plots of standardized residuals versus standardized predicted values, and multicollinearity was checked with VIF (<5 for all predictors). Spearman's rho (ρ) correlations assessed the relationships between KL grading, unicompartmental and bicompartmental JSW measures, and JLCA (Figure 1), with the absolute JLCA value used. Statistical tests (Steiger's Z-test) were used to compare the significance of correlations sharing one variable in common (KL-grading), with Z_H representing the test statistic for the difference between dependent correlations. A p-value < 0.05 was considered statistically significant.

In addition, sensitivity analyses were conducted to evaluate the robustness of the findings. Two models were specified: Model 1 included full-thickness cartilage loss, partial cartilage loss, meniscal extrusion, horizontal meniscal tear, vertical meniscal tear, complex meniscal tear, and meniscal maceration; Model 2 additionally adjusted for age, gender, weight, and height.

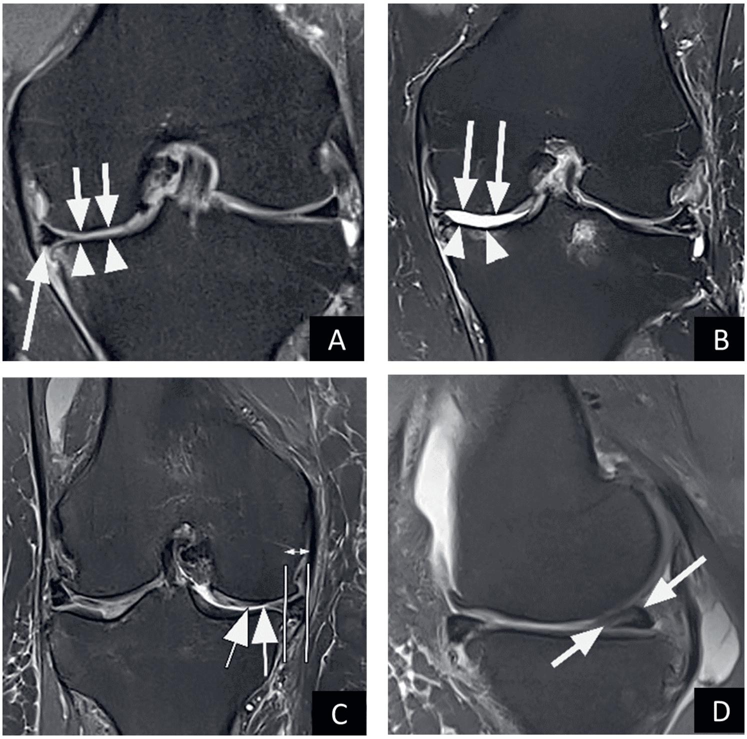

Figure 2 - MOAKS assessment of MRI features contributing to joint space width and narrowing. A) Coronal intermediate-weighted fat suppressed 3 T MRI shows diffuse superficial cartilage damage in the central subregion of the medial femur (short arrows) corresponding to grade 3.0 MOAKS. In addition, there is wide-spread superficial thinning (grade 3.0) of cartilage at the central subregion of the medial tibia (arrowheads). There is grade 1 extrusion of the medial meniscus (long arrow). B) Another coronal image obtained at a 3 T system shows wide-spread full thickness cartilage loss (MOAKS grade 3.3) at the central medial femur (arrows) and tibia (arrowheads). C) Coronal MRI acquired at 3 T shows a grade 3 extrusion of the medial meniscus protruding 6 mm medially of the edge of the medial tibial plateau (vertical lines and double-headed arrow). In addition, there is superficial cartilage damage (MOAKS 2.0) at the central subregion of the medial femur. D) Sagittal intermediate-weighted fat suppressed MRI obtained at 1.5 T shows a classic degenerative horizontal-oblique tear of the posterior horn of the medial meniscus (arrows).

3. Results

3.1 Participants

Of the 297 participants in the IMI-APPROACH cohort, 262 participants were included with the required baseline data. The average age was 66.6 ± 7.2 years, and most participants were female (76.7%). A detailed description of the participants can be found in Appendix A.

3.2 Association of MRI whole joint cartilage and meniscal morphology with unicompartmental JSW measures

MRI-defined full-thickness cartilage loss was associated with mJSW (beta = -0.29, 95% CI [-0.16; -0.02]). Partial cartilage loss, meniscal extrusion, and meniscal tears were not associated with mJSW, JSW(x), and mean JSW. Meniscal maceration was associated with a reduction of mJSW (beta = –0.33, 95% CI [–1.29; –0.48]), JSW(X) (beta = –0.23, 95% CI [–1.03; –0.20], and mean JSW (beta = –0.27, 95% CI [–1.10; -0.31]). The models explained 22%, 13%, and 15% of the variance for mJSW, JSW(x), and mean JSW, respectively (R^2 values). These results are shown in Table 1. The results of the sensitivity analyses are presented in Appendix C.

3.3 Association of MRI whole joint cartilage and meniscal morphology with bicompartmental JSW measures and JLCA

Full-thickness cartilage loss was associated with bicompartmental mJSW (beta = -0.26, 95% CI [-0.14; -0.02]) and JLCA beta = 0.29, 95% CI [-0.4;0.22]). Partial cartilage loss, meniscal extrusion, and meniscal tears were not associated with average mJSW, average JSW(x), average mean JSW, and JLCA. Meniscal maceration was associated with a reduction of average mJSW (beta = –4.19, 95% CI [–1.00;–0.36]), average JSW(X) (beta = –0.25, 95% CI [–0.84;–0.23], average mean JSW (beta = –0.26, 95% CI [–1.00;–0.28]), and JLCA (beta = 0.23, 95% CI [0.31;1.32]).The models explained 25%, 34%, 25%, and 23% of the variance for bicompartmental JLCA, mJSW, JSW(x), and mean JSW, respectively (R^2 values), which seems higher than for unicompartmental measures. Results are summarized in Table 1. The results of the sensitivity analyses are presented in Appendix C.

3.4 Correlation with Kellgren and Lawrence Score

The unicompartmental JSW measures (mJSW, JSW(X), mean JSW) showed weak correlations with KL grading, with Spearman's ρ = -0.3 (95% CI: -0.44 to -0.21 for mJSW; -0.40 to -0.17 for JSW(X); -0.40 to -0.18 for mean JSW). Bicompartmental JSW measures were also correlated with KL grading, with ρ values of -0.5 (95% CI: -0.54 to -0.35) for average mJSW, -0.4 (95% CI: -0.48 to -0.27) for average JSW(X), and -0.4 (95% CI: -0.47 to -0.25) for average mean JSW. The JLCA showed a moderate correlation with KL (ρ = 0.5, 95% CI: 0.35 to 0.55).

Bicompartmental JSW measures showed stronger correlations with KL grading than the corresponding unicompartmental measures (mJSW: Z_H = -5.6, 95% CI [-0.31; -0.16]; JSW(X): Z_H = -2.7, 95% CI [-0.19; -0.04]; mean JSW: Z_H = -2.24, 95% CI [-0.21; -0.02]). JLCA was more strongly correlated with KL grading than all unicompartmental JSW measures (Z_H = 3.3, 95% CI [0.11;0.36]). These results, including confidence intervals and the KL 2–4 subanalysis, are summarized in Appendix B.

4. Discussion

This study examined whether unicompartmental JSW measures were associated with MRI-assessed whole joint cartilage and meniscal morphology and if bicompartmental measures show stronger associations. Bicompartmental measures show similar associations with advanced structural damage, including full-thickness cartilage loss, partial cartilage loss, meniscal extrusion, tears, and maceration, as unicompartmental measures. Bi-compartmental JSW showed stronger correlations with KL grades than unicompartmental JSW, indicating that bicompartmental measures may better reflect overall radiographic disease severity. The absence of association with partial cartilage loss suggests that JSW measures primarily reflect more severe cartilage degeneration rather than diffuse joint changes. Moreover, the lack of associations with meniscal extrusion and meniscal tears indicates that JSW predominantly reflects meniscal maceration rather than extrusion or tears. Taken together, these findings support the use of bicompartmental measures as more sensitive indicators of joint structural damage in radiographic assessment.

Our findings also showed that full-thickness cartilage loss had a higher regression coefficient with JSW measures than partial cartilage loss. While cartilage loss includes both partial and full-thickness loss, full-thickness loss refers to complete cartilage loss within a specific subregion. Although prior research indicated that both partial and full-thickness cartilage defects contribute to the development of KOA[167], no previous studies have clearly shown that full-thickness cartilage loss has a stronger association with JSW than partial cartilage loss. This emphasizes that full-thickness loss is fundamentally different from superficial cartilage loss, a distinction that is not fully captured by commonly used measures such as average cartilage thickness or cartilage volume. Therefore, including full-thickness loss, for example quantified as denuded bone area, as a continuous measure is important to more accurately reflect its effect on JSW.

Table 1 – Associations between radiographic measures and whole joint health on MRI. The table presents regression coefficients (β), confidence intervals, and explained variance (R^2) for each radiographic parameter. The R^2 values indicate the proportion of variance in each radiographic measure explained by the set of MRI-assessed MOAKS parameters included in the model. Unicompartmental (medial compartment) and bicompartmental joint space width (JSW) measures, as well as joint line convergence angle (JLCA), were analyzed in relation to MRI-assessed full-thickness cartilage loss, partial cartilage loss, meniscal extrusion, and meniscal tears, and meniscal maceration. Significant associations are indicated with an asterisk (*).

	mJSW	JSW(x)	Mean JSW	JLCA
Unicompartmental				
Full-thickness cartilage loss	β = -0.26 **[-0.16;-0.02]***	β = -0.17 [-0.13;0.02]	β = -0.21 [-0.14;0.00]	
Partial cartilage loss	β = 0.08 [-0.04;0.08]	β = -0.06 [-0.08;0.05]	β = -0.01 [-0.05;0.06]	
Meniscal extrusion	β = 0.02 [-0.14;0.19]	β = 0.08 [-0.09;0.25]	β = -0.06 [-0.11;0.22]	
Meniscal tears	β = 0.01 [-0.27;0.34]	β = 0.08 [-0.11;0.51]	β = 0.04 [-0.20;0.39]	
Meniscal maceration	β = -0.33 **[-1.29;-0.48]***	β = -0.23 **[-1.03;-0.20]***	β = -0.27 **[-1.10;-0.31]***	
R^2	22%	13%	15%	
Bicompartmental				
Full-thickness cartilage loss	β = -0.26 **[-0.14;-0.02]***	β = -0.16 [-0.10;0.10]	β = -0.15 [-0.11;0.02]	β = 0.29 **[0.04;0.22]***
Partial cartilage loss	β = -0.10 [-0.07;0.02]	β = -0.18 [-0.08;0.01]	β = -0.16 [-0.09;0.02]	β = -0.05 [-0.09;0.06]
Meniscal extrusion	β = -0.00 [-0.13;0.13]	β = 0.04 [-0.09;0.15]	β = 0.04 [-0.11;0.18]	β = 0.10 [-0.08;0.33]
Meniscal tears	β = -0.00 [-0.23;0.25]	β = -0.00 [-0.23;0.23]	β = 0.05 [-0.16;0.38]	β = 0.01 [-0.35;0.42]
Meniscal maceration	β = -0.29 **[-1.00;-0.36]***	β = -0.25 **[-0.84;-0.23]***	β = -0.26 **[-1.00;-0.28]***	β = 0.23 **[0.31;1.32]***
R^2	34%	25%	23%	25%

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

Additionally, meniscal maceration showed higher regression coefficient with JSW than meniscal extrusion or tears. The sensitivity analysis, in which distinctions were made according to tear type, did not result in higher R-squared values. Notably, the contribution of meniscal extrusion to JLCA also appeared to be higher than that of other bicompartmental measures. This finding can be explained by the more frequent medial extrusion of the medial meniscus compared to lateral extrusion of the lateral meniscus in the IMI-APPROACH[168]. The same trend of more involvement of the medial meniscus was observed for anterior extrusion. Since JLCA reflects the angle between the distal femur and proximal tibia[51,144], this usually asymmetrical meniscal extrusion likely explains its stronger association with JLCA compared to other bicompartmental JSW measures.

Our study highlights the importance of evaluating both the medial and lateral compartments in radiographic assessments of KOA. When focusing on a single compartment, it is essential to explicitly report the compartment from which JSW measurements are derived—a detail that is frequently omitted in the literature[135,169]. The reliability of JSW measurements has improved with computerized analysis[152]; however, the smallest detectable difference (SDD) ranges between 0.5–1.5 mm with semi-automated methods[31] but decreases to 0.30–0.68 mm with fully automated software[144]. The JLCA, although not yet widely included as a radiographic measure in KOA assessments, showed stronger correlations with KL grading than unicompartmental JSW measures. JLCA is relatively simple to measure manually and has shown high inter- and intra-observer reliability[159], with a SDD of 0.48°[144]. In addition, it does not require radiograph calibration.

This study has several limitations. First, the cross-sectional design limits conclusions on KOA progression, longitudinal studies are needed to assess the added value of bicompartmental measures. Second, measurement and positional errors in JSW may have influenced results[170]. We used fully automated software, which is reproducible, but minor inaccuracies in landmark detection may still occur[31]. Third, we selected specific cartilage and meniscal parameters from the MOAKS. Including additional parameters may enhance the associations observed and offer a more comprehensive assessment of whole joint health. Fourth, simultaneous medial narrowing and lateral widening may offset each other, potentially obscuring true changes in bicompartmental JSW measures. Fifth, in this study we focused on mJSW, mean JSW, and JSW(X) as our JSW measures. However, a previous publication by Cheung *et al.*[171] concluded that measurement of multiple JSWs across the tibial plateau yields superior predictive performance for KOA compared with mJSW. This multiple JSWs measure was not included in this study, although the mean JSW can be considered a measure of JSWs across the tibial plateau. Finally, in this study we focused on the MOAKS score as a measure of whole-joint cartilage and meniscal morphology. However, for future research it would be valuable to also include T2 mapping in order to draw conclusions whether changes in compositional measures of cartilage may have an impact on radiographic JSW measures longitudinally[136,172].

5. Conclusion

This study highlights that MRI-based measures of cartilage degeneration and meniscal pathology show similar associations with uni- and bicompartmental radiographic JSW measures, while bicompartmental JSW measures show stronger correlations with KL grades. These findings emphasize the importance of incorporating both compartments in KOA assessments, as reliance on unicompartmental measures alone may not fully capture whole joint cartilage and meniscal morphology.

Appendix A – Participants

Figure A1 shows the flowchart of included participants from IMI-APROACH. Table A1 presents baseline characteristics, categorized into patient characteristics, unicompartmental and bicompartmental radiographic assessments, and whole joint health on MRI. Figure A2 illustrates the distribution of whole joint health by parameter.

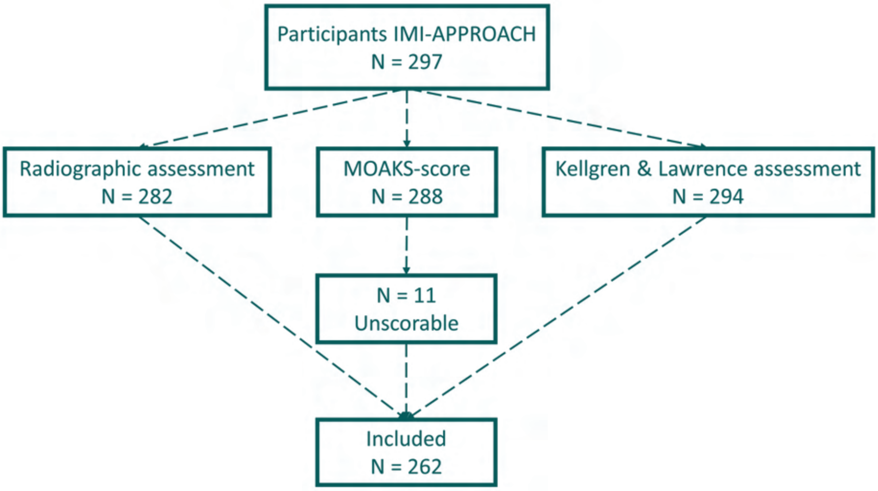

Figure A1 – Flowchart of participants inclusion in the study.

Table A1 - Baseline characteristics of the included participants n= 262.

Patient characteristics	
Age (years), mean ± SD	66.6 ± 7.2
Sex (female), n (%)	201 (76.7)
Kellgren and Lawrence, n (%)	
Grade 0	47 (17.9)
Grade 1	74 (28.2)
Grade 2	61 (23.3)
Grade 3	71 (27.1)
Grade 4	9 (3.4)
Radiographic assessment medial compartment	
mJSW (mm), mean ± SD	3.6 ± 1.3
Mean JSW (mm), mean ± SD	4.3 ± 1.3
JSW(x) (mm), mean ± SD	5.0 ± 1.3
Radiographic assessment lateral compartment	
mJSW (mm), mean ± SD	3.7 ± 1.5
Mean JSW (mm), mean ± SD	5.4 ± 1.4
JSW(x) (mm), mean ± SD	5.4 ± 1.6
Radiographic assessment bicompartmental	

Average mJSW (mm), mean ± SD	3.7 ± 1.2
Average mean JSW (mm), mean ± SD	4.9 ± 1.0
Average JSW(x) (mm), mean ± SD	5.2 ± 1.2
JLCA (degrees), mean ± SD	1.6 ± 2.3
Whole joint health, MRI	
Full-thickness cartilage loss, mean ± SD	2.3 ± 3.7
Partial cartilage loss, mean ± SD	6.6 ± 5.5
Meniscal extrusion, mean ± SD	1.3 ± 1.3

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

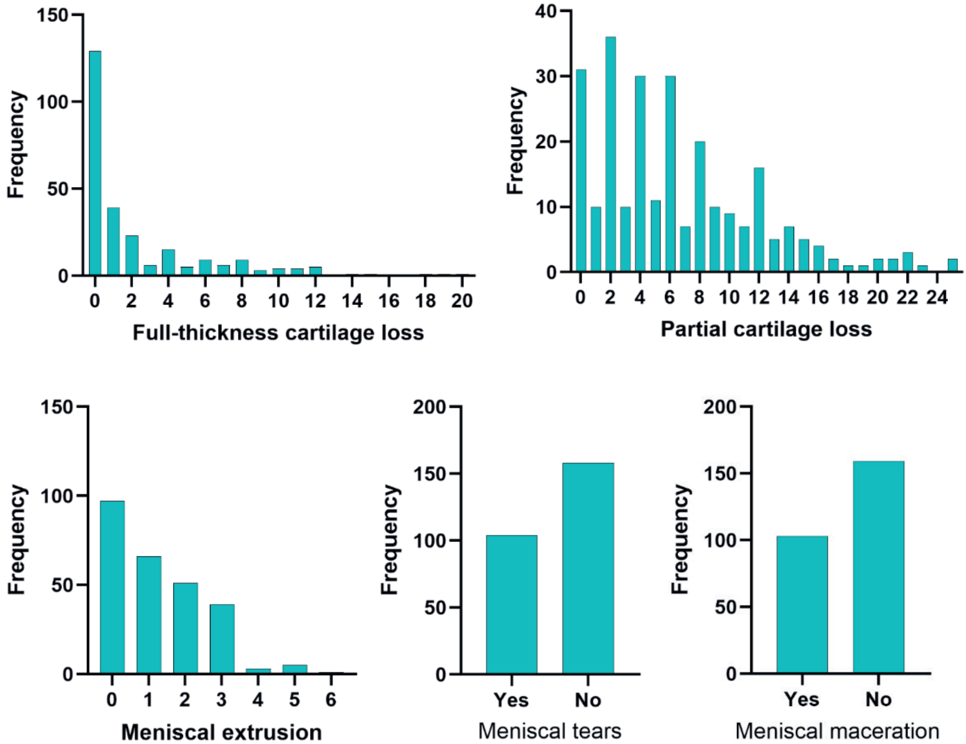

Figure A2 - Distribution of whole joint health measured on MRI using the MOAKS, stratified by full-thickness cartilage loss, partial cartilage loss, meniscal extrusion, meniscal tears, and meniscal maceration.

Appendix B – Correlations Kellgren and Lawrence

Table B1 - Correlations between unicompartmental JSW measures, bicompartmental JSW measures and JLCA with the Kellgren and Lawrence score, as well as correlations between unicompartmental and bicompartmental JSW measures.

	Spearman's rho	Confidence interval	P-value
Unicompartmental			
mJSW	-0.3	[-0.44; -0.21]	< 0.001
JSW(x)	-0.3	[-0.40; -0.17]	< 0.001
Mean JSW	-0.3	[-0.40; -0.18]	< 0.001
Bicompartmental			
Average mJSW	-0.5	[-0.54; -0.35]	< 0.001
Average JSW(x)	-0.4	[-0.48; -0.27]	< 0.001
Average mean JSW	-0.4	[-0.47; -0.25]	< 0.001
JLCA	0.5	[0.35;0.55]	< 0.001
Unicompartmental versus bicompartmental			
mJSW	0.8	[0.69; 0.80]	< 0.001
JSW(x)	0.8	[0.70; 0.81]	< 0.001
Mean JSW	0.7	[0.68; 0.80]	< 0.001

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

Table B2 - Comparison of correlations of unicompartmental versus bicompartmental JSW measures, with KL grading as the variable in common, using Steiger's Z-test.

	Z_H	95% CI	P-value
Unicompartmental versus bicompartmental			
mJSW	-5.6	[-0.31; -0.16]	< 0.001
JSW(x)	-2.7	[-0.19; -0.04]	< 0.01
Mean JSW	-2.2	[-0.21; -0.02]	0.03
JLCA versus unicompartmental JSW measures			
JLCA versus unicompartmental mJSW	3.3	[0.11; 0.36]	< 0.001
JLCA versus unicompartmental JSW(x)	3.3	[0.11; 0.36]	< 0.001
JLCA versus unicompartmental mean JSW	3.3	[0.11; 0.36]	< 0.001

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

Table B3 – Subanalysis of correlations between unicompartmental JSW measures, bicompartmental JSW measures, and JLCA in patients with Kellgren and Lawrence (KL) grades 2–4.

	Spearman's rho	Confidence interval	P-value
Unicompartmental			
mJSW	-0.3	[-0.42; -0.10]	0.002
JSW(x)	-0.2	[-0.40; -0.08]	0.003
Mean JSW	-0.3	[-0.41; -0.09]	0.003
Bicompartmental			
Average mJSW	-0.4	[-0.50; -0.20]	< 0.001
Average JSW(x)	-0.3	[-0.42; -0.10]	0.001
Average mean JSW	-0.3	[-0.45; -0.13]	< 0.001
JLCA	0.3	[0.15; 0.46]	< 0.001

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

Appendix C – Sensitivity analysis

The results of the sensitivity analyses are presented in Table C1 and Table C2.

When analyzing meniscal tears separately, vertical tears occasionally contributed significantly to the models; however, these findings did not alter the overall conclusions (Table C1). For unicompartmental measures, the explained variance (R^2) was 21% for mJSW, 14% for JSW(x), and 15% for mean JSW. For bicompartmental measures, R^2 values were higher, with 35% for mJSW, 25% for JSW(x), 27% for mean JSW, and 24% for JLCA. These R^2 values are comparable to those observed in the simplified models, in which meniscal tears were included as a binary variable (yes/no).

Similarly, adjusting for age, sex, height, and weight identified some additional significant associations—such as height and weight contributing to certain bicompartmental measures—but the overall pattern of associations remained unchanged. For unicompartmental measures, the explained variance (R^2) was 25% across mJSW, JSW(x), and mean JSW. For bicompartmental measures, R^2 values seems higher, with 43% for mJSW, 40% for JSW(x), 42% for mean JSW, and 27% for JLCA (Table C2). These R^2 values appear higher than those observed in the simplified models, in which this variable was not included.

Table C1 – Associations between radiographic measures and whole joint health on MRI. The table presents regression coefficients (β), confidence intervals, and explained variance (R^2) for each radiographic parameter. The R^2 values indicate the proportion of variance in each radiographic measure explained by the set of MRI-assessed MOAKS parameters included in the model. Unicompartmental (medial compartment) and bicompartmental joint space width (JSW) measures, as well as joint line convergence angle (JLCA), were analyzed in relation to MRI-assessed full-thickness cartilage loss, partial cartilage loss, meniscal extrusion, horizontal meniscal tear, vertical meniscal tear, complex meniscal tear, and meniscal maceration. Significant associations are indicated with an asterisk (*).

	mJSW	JSW(x)	Mean JSW	JLCA
Unicompartmental				
Full-thickness cartilage loss	**β = -0.26 [-0.16;-0.02]***	β = -0.18 [-0.14;0.01]	**β = -0.21 [-0.14;0.00]***	
Partial cartilage loss	β = 0.07 [-0.04;0.08]	β = -0.05 [-0.07;0.05]	β = 0.02 [-0.05;0.06]	
Meniscal extrusion	β = 0.05 [-0.11;0.22]	β = 0.10 [-0.07;0.28]	β = 0.08 [-0.83;0.24]	
Horizontal meniscal tear	β = 0.06 [-0.15;0.50]	β = 0.04 [-0.22;0.46]	β = 0.04 [-0.22;0.43]	
Vertical meniscal tear	β = 0.01 [-0.56;0.62]	β = 0.09 [-0.13;1.09]	β = 0.01 [-0.35;0.82]	
Complex meniscal tear	β = -0.09 [-0.85;0.09]	β = -0.04 [-0.66;0.31]	β = -0.07 [-0.72;0.20]	
Meniscal maceration	**β = -0.35 [-1.35;-0.53]***	**β = -0.24 [-1.06;-0.21]***	**β = -0.29 [-1.14;-0.34]***	
R^2	21%	14%	15%	
Bicompartmental				
Full-thickness cartilage loss	**β = -0.27 [-0.14;-0.03]***	β = -0.17 [-0.12;0.01]	β = -0.17 [-0.10;0.01]	**β = 0.29 [0.04;0.22]***
Partial cartilage loss	β = -0.09 [-0.07;0.03]	β = -0.13 [-0.08;0.02]	β = -0.16 [-0.07;0.01]	β = -0.04 [-0.09;0.06]
Meniscal extrusion	β = 0.02 [-0.12;0.15]	β = 0.05 [-0.10;0.19]	β = 0.06 [-0.08;0.17]	β = 0.09 [-0.09;0.33]
Horizontal meniscal tear	β = -0.01 [-0.29;0.23]	β = -0.04 [-0.40;0.18]	β = -0.04 [-0.33;0.16]	β = -0.01 [-0.44;0.39]
Vertical meniscal tear	β = 0.09 [-0.07;0.87]	**β = 0.15 [0.20;1.25]***	**β = 0.13 [0.08;0.96]***	β = 0.08 [-0.20;1.30]
Complex meniscal tear	β = -0.07 [-0.61;0.13]	β = -0.02 [-0.50;0.33]	β = -0.06 [-0.55;0.15]	β = 0.02 [-0.49;0.69]
Meniscal maceration	**β = -0.30 [-1.03;-0.38]***	**β = -0.26 [-1.01;-0.28]***	**β = -0.26 [-0.86;-0.25]***	**β = 0.24 [0.33;1.37]***
R^2	35%	25%	27%	24%

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

Chapter 3

Table C2 – Associations between radiographic measures and whole joint health on MRI. The table presents regression coefficients (β), confidence intervals, and explained variance (R^2) for each radiographic parameter. The R^2 values indicate the proportion of variance in each radiographic measure explained by the set of MRI-assessed MOAKS parameters included in the model. Unicompartmental (medial compartment) and bicompartmental joint space width (JSW) measures, as well as joint line convergence angle (JLCA), were analyzed in relation to MRI-assessed full-thickness cartilage loss, partial cartilage loss, meniscal extrusion, meniscal tears, meniscal maceration, age, gender, weight, and height. Significant associations are indicated with an asterisk (*).

	mJSW	JSW(x)	Mean JSW	JLCA
Unicompartmental				
Full-thickness cartilage loss	**β = -0.30 [-0.18;-0.03]***	**β = -0.23 [-0.15;-0.01]***	**β = -0.27 [-0.16;-0.02]***	
Partial cartilage loss	β = 0.07 [-0.04;0.08]	β = -0.09 [-0.08;0.04]	β = -0.00 [-0.06;0.06]	
Meniscal extrusion	β = 0.04 [-0.12;0.20]	β = 0.10 [-0.06;0.26]	β = 0.08 [-0.08;0.23]	
Meniscal tears	β = -0.01 [-0.34;0.27]	β = 0.02 [-0.24;0.36]	β = -0.01 [-0.31;0.27]	
Meniscal maceration	**β = -0.30 [-1.20;-0.40]***	**β = -0.18 [-0.86;-0.08]***	**β = -0.23 [-0.96;-0.20]***	
Age	β = -0.06 [-0.03;0.01]	β = 0.01 [-0.02;0.02]	β = -0.03 [-0.02;0.02]	
Gender	β = -0.02 [-0.50;0.37]	β = 0.03 [-0.35;0.52]	β = 0.02 [-0.37;0.46]	
Weight	β = -0.01 [-0.01;0.01]	β = 0.05 [-0.01;0.01]	β = 0.03 [-0.01;0.01]	
Height	**β = 0.24 [0.01;0.05]***	**β = 0.31 [0.02;0.06]***	**β = 0.30 [-0.02;0.05]***	
R^2	25%	25%	25%	
Bicompartmental				
Full-thickness cartilage loss	**β = -0.28 [-0.14;-0.03]***	**β = -0.21 [-0.13;-0.01]***	**β = -0.21 [-0.11;-0.01]***	**β = 0.30 [0.04;0.23]***
Partial cartilage loss	β = -0.15 [-0.08;0.01]	β = -0.21 [-0.09;0.00]	**β = -0.23 [-0.08;-0.00]***	β = -0.06 [-0.09;0.06]
Meniscal extrusion	β = 0.01 [-0.11;0.13]	β = 0.06 [-0.08;0.18]	β = 0.06 [-0.06;0.16]	β = 0.10 [-0.07;0.35]
Meniscal tears	β = -0.04 [-0.32;0.14]	β = -0.03 [-0.31;0.18]	β = -0.07 [-0.36;0.06]	β = 0.02 [-0.33;0.45]
Meniscal maceration	**β = -0.25 [-0.90;-0.29]***	**β = -0.20 [-0.81;-0.17]***	**β = -0.19 [-0.68;-0.14]***	**β = 0.23 [0.30;1.31]***
Age	β = -0.00 [-0.02;0.02]	β = 0.05 [-0.01;0.03]	β = 0.05 [-0.01;0.02]	β = -0.08 [-0.05;0.01]
Gender	β = 0.06 [-0.16;0.51]	β = 0.04 [-0.26;0.45]	β = 0.10 [-0.07;0.53]	β = 0.08 [-0.26;0.86]
Weight	**β = 0.19 [-0.01;0.02]***	**β = 0.12 [0.00;0.02]***	**β = 0.16 [0.00;0.02]***	**β = 0.14 [0.00;0.03]***
Height	β = 0.13 [0.00;0.03]	**β = 0.34 [0.03;0.06]***	**β = 0.26 [0.01;0.04]***	β = -0.12 [-0.04;0.00]
R^2	43%	40%	42%	27%

mJSW, minimum joint space width; JSW(x), fixed location joint space width; JSW, joint space width; JLCA, Joint Line Convergence Angle

Part II

Impact of Lower Limb Alignment

04

Chapter 4

Tibial Genu Varum and Primary Cam Morphology in Healthy Young Adults: A Cross-Sectional Study Uncovering the Double Threat to Joint Health

Eva A. Bax, William Colyn, Johan Bellemans, Harrie Weinans, Rintje Agricola, Fleur Boel

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Abstract

Objectives: This study investigated the association between alpha angles of the hip and tibial genu varum in a healthy population with equal male-to-female distribution. It also examined sex-based differences, explored the impact of sports participation, and assessed the interplay between these conditions.

Methods: Tibial, femoral, intra-articular knee deformities, and the alpha angle of the hip were analyzed in 200 healthy volunteers (400 legs) aged 20-27 years using weight-bearing radiographs. The Tegner score was retrospectively collected and used to distinguish between high and low sports activity. Generalized estimating equations were used to examine the association between lower limb malalignment and alpha angle, accounting for side and gender.

Results: Tibial alignment was associated with the alpha angle (β=-0.02, P=0.002); tibial genu varum was associated with a higher alpha angle. Other deformities and their interaction with sports activity had no association with the alpha angle. Males exhibited a higher alpha angle (β=0.19, P<0.001, Δ=9.0°) and more tibial genu varum (β=-0.95, P=0.002, Δ=1.1°) than females. High sports activity was associated with increased tibial genu varum (β=-0.75, P=0.02) compared to low sports activity.

Conclusion: This study found a significant association between alpha angle and tibial genu varum. Males exhibited higher alpha angles and more tibial genu varum than females. While higher sports activity was associated with tibial genu varum, no differences in alpha angle were seen across activity levels. These findings urge for future research to further explore mechanical load adjustments that prevent genu varum and primary cam morphology, reducing osteoarthritis risk.

1. Introduction

Cam morphology, characterized by an aspherical shape of the femoral head due to abnormal bone formation at the anterolateral head-neck junction[173], significantly increases the risk of developing hip osteoarthritis[174–176]. Cam morphology mostly develops gradually during adolescence, particularly in young male athletes engaged in high impact sports and is then referred to as primary cam morphology[177,178]. This morphology is believed to emerge in response to repetitive mechanical loading, which redistributes stress and stimulates extra bone growth[179,180], and stabilizes after closure of the proximal femoral growth plate [179].

The same phenomenon is recognized in the tibia, where genu varum is more commonly observed in high impact athletes than in non-athletes[63,64,66,181]. Genu varum increases medial knee load and is a predictive factor for the development of knee osteoarthritis[21,22,182]. High sports participation during youth have been linked to the development of genu varum in the proximal tibia by the end of growth[66].

While the effects of primary cam morphology and lower limb malalignment have been studied independently, their interplay has not yet been investigated. Therefore, the primary objective of this study was to investigate the association between alpha angles of the hip and tibial genu varum in a healthy population with equal male-to-female distribution. We hypothesize that alpha angle is associated with tibial genu varum, as both cam morphology and genu varum appear to develop in response to mechanical loading during late skeletal growth, just before physeal closure[66,179]. The secondary objectives were to examine sex-based differences in alpha angle and genu varum, and to explore the potential influence of sports participation on these variations. Clinically, both cam morphology and genu varum are associated with an increased risk of developing hip and knee osteoarthritis, respectively. Demonstrating a significant association between these conditions would provide important insights into possible shared developmental mechanisms and suggest that modifying mechanical load during skeletal growth could help prevent these structural changes[66,179], ultimately contributing to the prevention of hip and knee joint pathologies, which is increasingly important given the rising incidence and prevalence of osteoarthritis[183].

2. Methods

2.1 Participants

A total of 200 healthy young adults, aged between 20 and 27 years, participated in this cross-sectional study[66]. The study was conducted from October 2009 to March 2010. Participants were recruited as volunteers from movie theatres, technical high school and university campuses, and job recruitment bureaus. Eligibility criteria required no prior history of orthopedic issues or trauma. The study group consisted of 100 males and 100 females. Participants were retrospectively surveyed regarding their sports activities during their growth period. All participants provided written informed consent, and the study protocol was reviewed and approved by the institutional ethics committee of the University of Leuven, Belgium (B32220097076) prior to commencement.

2.2 Radiographic Imaging Protocol

All participants underwent weight-bearing full-leg radiography following the protocol outlined by Paley[51]. Radiographs were obtained with participants standing barefoot, feet together in the "stand at attention" position, and patellae facing forward. The X-ray beam was aligned with the knee, and the radiography tube was positioned 305 cm away. Radiographic parameters were set to 500 mA and 75 kV, with individual adjustments made when necessary. All radiographs were calibrated, and a blinded examiner (WC) conducted all measurements of lower limb alignment using the AGFA PACS software (Agfa-Gevaert).

2.3 Radiographic measurements

Radiological lower limb malalignment consists of three components: the mechanical medial proximal tibial angle (mMPTA), the mechanical lateral distal femoral angle (mLDFA), and the joint line convergence angle (JLCA) (Figure 1). The mMPTA quantifies tibial plateau alignment and was defined as the angle between the mechanical axis of the tibia and the proximal tibial joint line[51] (Figure 1). A neutral mMPTA ranges from 85° and 90°, with tibial genu varum alignment $< 85°$ and tibial genu varum alignment as $>$ 90°. The mLDFA measures femoral alignment and is defined as the angle between the mechanical axis of the femur and the distal femoral joint line[51] (Figure 1). A neutral mLDFA ranges from 85° and 90°, with femoral genu varum alignment $> 90°$ and femoral genu valgum alignment as $< 85°$. The JLCA evaluated knee joint congruity and was defined as the angle between the femoral and tibial joint lines[51] (Figure 1). Normal JLCA values range between 0° and 2°, with values > 2° indicating an intra-articular genu varum alignment and values < 0° indicating an intra-articular genu valgum alignment. All radiographs were calibrated, and a blinded examiner conducted all measurements of lower limb alignment using the AGFA PACS software (Agfa-Gevaert).

The alpha angle quantifies femoral head sphericity (Figure 1). It is defined by the intersection of the femoral head-neck axis and a line from the femoral head center to the alpha point—the first deviation of the femoral head-neck junction from the best-fitting circle. The alpha angle was automatically determined on the weight-bearing full-leg radiograph using a validated method[184]. Primary cam morphology was quantified using an alpha angle ≥ 60°[185].

2.4 Athletic activity during adolescence

Participants were retrospectively surveyed about their sports activities during childhood and adolescence, categorized into three age groups. These age groups account for sex-specific growth stages: 10–12, 13–14, and 15–17 years for males, and 8–10, 11–12, and 13–15 years for females. Sports activities were quantified using the Tegner activity scale[186], a validated instrument ranging from 0 (disability due to knee problems) to 10 (participation in competitive elite-level sports). Scores of 7 or higher were classified as high-activity athletes, whereas scores below 7 indicated low-activity athletes.

Participants were then grouped based on time-varying covariates[187], which is a method that accounts for changes in activity levels over time. They were categorized into four exposure patterns: high sport activity throughout childhood, low sport activity throughout childhood, high sport activity transitioning to low sport activity, and low sport activity transitioning to high sport activity. Additionally, participants were asked whether they played soccer. For this specific group of soccer players, radiographic measurements—including the mMPTA, mLDFA, JLCA, and alpha angle —were compared to those of non-soccer players and non-soccer players with high levels of sports activity.

2.5 Statistical analysis

All statistical analyses were performed using SPSS version 27.0 (IBM, Armonk, NY) in accordance with the Checklist for Statistical Assessment of Medical Papers22. Variables were assed for normality using histograms. Descriptive statistics, including means and standard deviations (SDs) for normally distributed data, and medians with interquartile ranges (IQR) for non-normally distributed data, were provided. A generalized estimating equation model with a gamma distribution was used to analyze the alpha angle (dependent variable), considering mMPTA, mLDFA, JLCA, gender, and sports activity as independent variables. Side was included in the model to adjust for correlations in within subject variables, using an unstructured working correlation matrix. Additionally, the effect of gender and sport activity on alpha angle and mMPTA was examined, with side included to account for correlations between repeated measurements. Statistical significance was defined as a p-value < 0.05.

Chapter 4

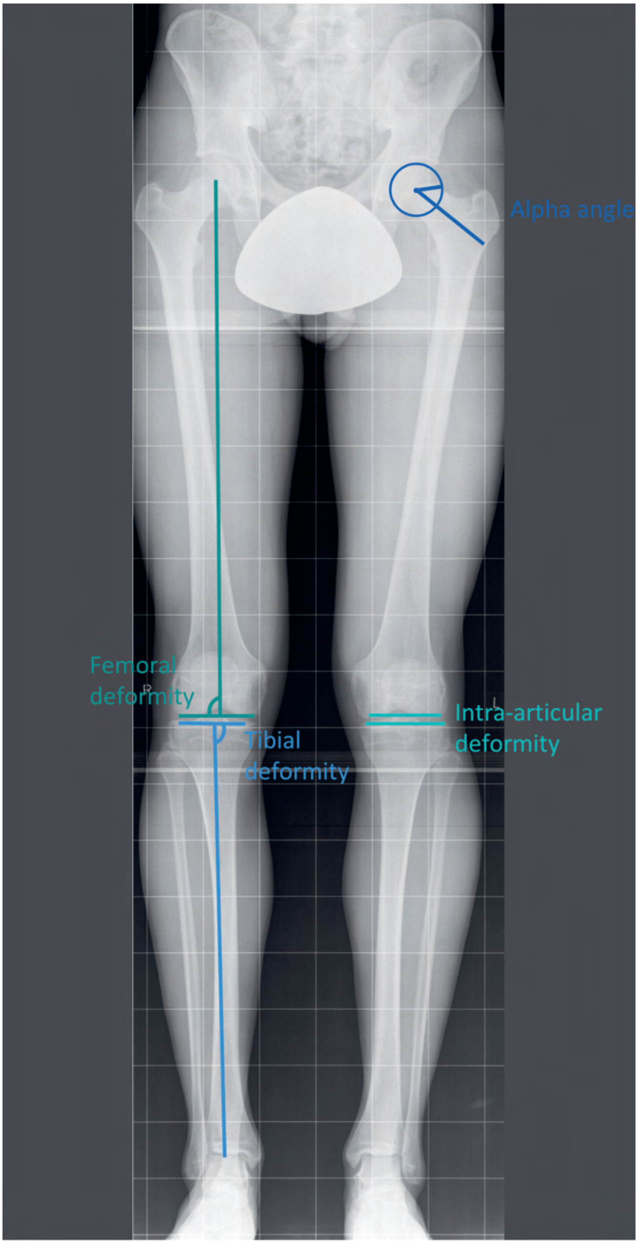

Figure 1 - Measurements of tibial, femoral, and intra-articular knee deformities, along with the alpha angle of the knee, on weight-bearing full-leg radiographs.

3. Results

3.1 Patient characteristics

The study included 100 males and 100 females. The mean BMI was 22.1 ± 3.1 kg/m^2. The median alpha angle was 46.1° (IQR 10.4°). Of the participants, 54 legs (13.5%) had an alpha angle ≥ 60° (median alpha angle 67.2°, IQR 12.8°). The mean mMPTA was 84.1 ± 2.1°, mLDFA was 88.0 ± 1.8°, and JLCA was 0.3 ± 1.1°. Of the participants, 66 had tibial genu varum (mean mMPTA 83.8 ± 1.0°), and 26 legs had tibial genu valgum (mean mMPTA 91.0 ± 0.9°). Femoral genu valgum was present in 19 legs (mean mLDFA 84.1 ± 0.7°), while femoral genu varum was found in 42 legs (mean mLDFA 91.0 ± 1.6°). Additionally, 21 legs showed intra-articular genu varum (mean JLCA 2.5 ± 0.5°), and 117 legs had intra-articular genu valgum (mean JLCA -1.1 ± 0.8°).

3.2 Sport activity

Regarding sport activity levels, the mean Tegner score during the second decade of life was 6.3 ± 2.3 for males and 4.8 ± 1.8 for females. Of the participants, 92 (46.0%) had low sport activity, 68 (34.2%) had high sport activity, 23 (11.6%) switched from high to low activity, and 17 (8.5%) increased their activity levels during childhood. Among males, 54 (108 legs) (54.0%) did not play soccer during childhood, with 12 (24 legs) (12.0%) having high activity based on the Tegner score. 31 males (62 legs) (31.0%) played soccer throughout this period, all with high activity, except for one. Ten males (10.0%) discontinued playing soccer during childhood, while five (5.0%) started. Soccer players showed a lower mMPTA, when compared to non-soccer players and male non-soccer players with a high level of sports activity during childhood (Table 1). Furthermore, soccer players exhibit a higher alpha angle of the hip than both non-soccer players and male non-soccer players with a high sports activity level during childhood (Table 1). Female soccer players were excluded from these analyses due to the limited sample size, as only two women had played soccer during childhood.

Table 1 - Radiological measurements for male soccer players (N = 31, 62 legs), male non-soccer players (N = 54, 108 legs), and male non-soccer players with a high sports activity level (N = 12, 24 legs). mMPTA, mLDFA, and JLCA are presented as mean ± SD. Alpha angle is presented as median (IQR).

	mMPTA	**mLDFA**	**JLCA**	**Alpha Angle**
Male soccer players	85.4° ± 2.2°	87.9° ± 1.8°	0.14° ± 1.2°	52.4° (16.0°)
Male non-soccer players	87.0° ± 1.7°	87.9° ± 2.2°	0.38° ± 1.1°	50.7° (9.3°)
Male non-soccer players high sport activity level	86.7° ± 2.7°	88.3° ± 1.2°	0.3° ± 1.2°	49.1° (6.2°)

mMPTA, mechanical medial proximal tibial angle; mLDFA, mechanical lateral distal femoral angle; JLCA, joint line convergence angle

3.3 Association between gender, sport activity, and radiographic measurements

The generalized estimating equation analysis, accounting for side, revealed that the mMPTA had a significant association with alpha angle (β = -0.02, 95% CI [-0.03, -0.01], P = 0.002) (Figure 2A). This indicates that a lower mMPTA, representing increased tibial genu varum, was associated with a higher alpha angle. The same trend was observed when comparing the three tibia groups, with tibial genu varum mMPTA showing higher alpha angles than the neutral group (Figure 2B). In contrast, neither the mLDFA (β = -0.01, CI [-0.02, 0.00], P = 0.21) nor the JLCA (β = 0.01, CI [-0.01, 0.02], P = 0.48) showed a significant relationship with the alpha angle. Furthermore, the interaction terms between exposure patterns of sport activity and mMPTA, mLDFA, and JLCA were not statistically significant.

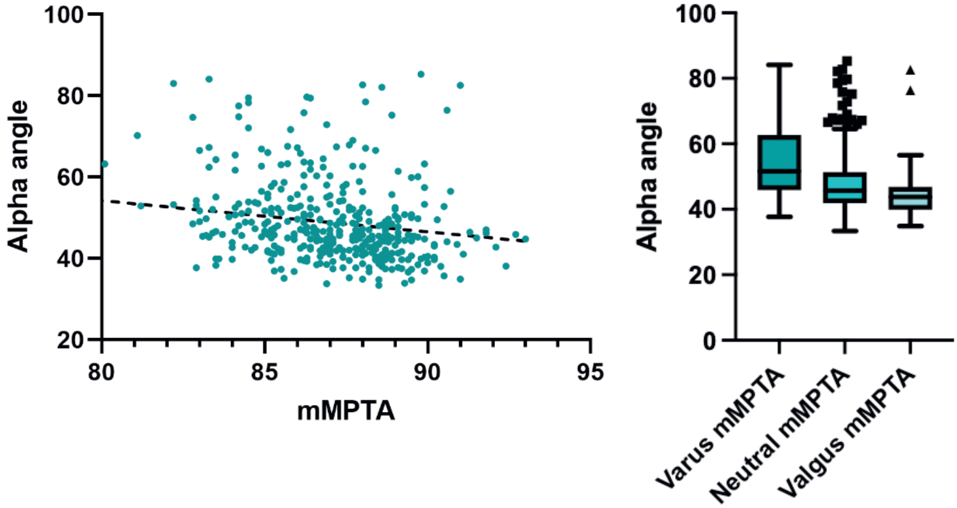

Figure 2 – Relationship between medial proximal tibial angle (mMPTA) and the alpha angle. A) Scatter plot showing the relationship between the mMPTA and the alpha angle, demonstrating a significant association. B) Boxplot of alpha angles for the three tibia groups: genu varum (66 lower limbs), neutral (308 lower limbs), and genu valgum (26 lower limbs).

Males show a significantly lower mMPTA than females (β = -0.95, CI [-1.56, -0.34], P = 0.002), accounting for side and sport activity (Figure 3A). Males also have a significantly higher alpha angle than females (β = 0.19, CI [0.14, 0.23], P < 0.001) (Figure 3B). High sports activity was associated with a lower mMPTA compared to low sport activity (β = -0.75, CI [-1.37, -0.13], P = 0.02), accounting for gender and side (Figure 3C). No statistically significant difference in alpha angle and sports activity was found (β = -0.01, CI [-0.05, 0.04], P = 0.79) (Figure 3D).

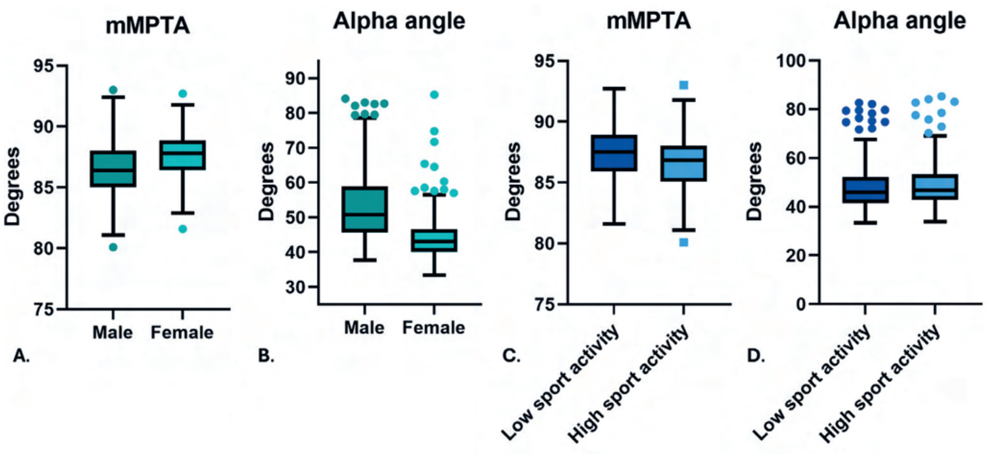

Figure 3 - Differences in radiographic measurements between males and females, as well as between low and high sport activity groups. A) mMPTA comparison between males and females. B) Alpha angle comparison between males and females. C) mMPTA comparison between low- and high-activity athletes. D) Alpha angle comparison between low- and high-activity athletes.

4. Discussion

This study investigated the association between hip alpha angles and tibial genu varum in a healthy population with an equal male-to-female distribution. The most important finding of this study was the significant association between alpha angle and tibial deformity, with a lower mMPTA linked to a higher alpha angle. No statistically significant interaction with sport activity was detected, suggesting that mMPTA's influence on alpha angle is not affected by activity level. Both primary cam morphology and tibial genu varum are associated with an increased risk of hip and knee osteoarthritis[174–176,182], respectively, indicating the potential clinical importance of their association. Additionally, males had significantly higher alpha angle values and lower mMPTA compared to females, reinforcing that primary cam morphology and tibial varus are more common in males[55,57,58,177,188–190].

Current literature highlights the association between primary cam morphology and high-impact sports, particularly soccer, likely due to the repetitive mechanical stress on the hip during adolescence[174,177,179,180,191]. Our study found no significant differences in alpha angle between high and low sport activity levels during childhood. However, male soccer players had a higher alpha angle compared to male non-soccer players and male non-soccer players with high sport activity levels. The literature further supports the association between involvement in sports, and greater tibial varus, emphasizing the role of physical activity in shaping lower leg alignment [21,63,64,66,181]. Notably, lower leg alignment has been widely acknowledged as a contributing factor to the risk of sports injuries[192]. Our study also showed that participants with high sport activity during childhood had a significantly lower mMPTA compared to those with low sport activity, while accounting for gender in a balanced male and female population. Male soccer players had a lower mMPTA compared to male non-soccer players and male non-soccer players with high sport activity. Despite these findings, the direct relationship between tibial deformity and alpha angle has been underexplored. Our research addresses this gap by demonstrating a significant association between tibial deformity and a cam shaped femoral head.

Our study demonstrates an association, not a causal relationship, between alpha angle and tibial deformity. While causality implies direct cause-and-effect, our findings show a statistical connection without confirming direct causality. Klij *et al.*[193] suggested that there is no causal relationship between cam morphology and varus orientation, as these features appear to develop simultaneously at the last phase of growth. It has been suggested that children with bowlegs may have a functional advantage in sports like soccer, potentially due to natural selection[66]. Mechanical studies, for example Hueter-Volkmann's law, explain how loading affects knee growth[69–71,194]. Primary cam morphology typically develops gradually during skeletal maturation in response to repetitive mechanical loading, stabilizing after the closure of the proximal femoral growth plate[177,179]. In young soccer players, the primary cam morphology becomes apparent once the growth plate closes[177], emphasizing the role of sport-specific loading. In addition, previous studies suggest that lower-limb alignment and hip morphology are interconnected within the kinetic chain. Frontal knee alignment has been associated with hip morphology and hip pain[195], and alterations in frontal knee alignment may also lead to changes in frontal hip alignment[196]. Furthermore, hip shape has been linked to knee osteoarthritis, and femoral morphology has been associated with the development of knee pain[197], highlighting the complex biomechanical relationship between hip structure and knee joint pathology[198].

Our findings suggest that both cam morphology and genu varum alignment may develop through similar adaptive mechanisms of the growth plates in response to mechanical loading. Consequently, the observed association may partly reflect shared developmental factors rather than a direct biological link. Clinically, both cam morphology and genu varum have been associated with increased risks of hip and knee osteoarthritis, respectively. Understanding their relationship may provide insight into these shared mechanisms and help guide strategies to modify mechanical load during growth, potentially reducing the risk of future joint pathology[183]. Further research is needed to explore how mechanical load adjustments during growth might prevent the development of tibial genu varum and cam morphology, potentially reducing the future risk of osteoarthritis.

Primary cam morphology and tibial genu varum are associated with an increased risk of hip[174–176] and knee osteoarthritis[21–23,199], posing a significant threat to joint health. Osteoarthritis is a major global health burden with rising healthcare costs[7,183]. Aging and obesity, key risk factors[200,201], are increasing, with obesity expected to reach 50% by 2030[202,203] and the elderly population continuing to grow[5]. As a result, osteoarthritis prevalence will rise further[183]. Targeted prevention strategies during skeletal growth could potentially reduce osteoarthritis incidence. Adjusting mechanical loads on the knees in males may help prevent varus alignment and its associated pathologies[66,179]. Similarly, modifying athletic activities during critical growth periods could influence the development of primary cam morphology[179], which may contribute to reducing osteoarthritis prevalence. Therefore, future research should focus on investigating the effects of mechanical load adjustments in individuals at risk for developing primary cam morphology and varus alignment. Such preventive strategies could play a pivotal role in reducing the incidence of both hip and knee osteoarthritis in athletes, contributing to the long-term joint health and reducing healthcare burdens.

This study has several limitations. Its retrospective design may have introduced recall bias, particularly regarding self-reported sports participation during adolescence. Furthermore, the radiographic assessments of lower limb alignment were conducted by a single observer who was blinded to additional information. The accuracy of the observer may influence these measurements, potentially leading to systematic bias. However, previous studies have shown that both intra- and interobserver reliability are excellent, with reported values exceeding 0.85 for these measurements[49,204]. The alpha angle measurement accuracy depends on accurate landmark placement. The automatic search model was trained on a different dataset consisting of primarily anteroposterior pelvic radiographs. However, the training set of the automatic search model also contained long-limb radiographs like those used in the current study. Therefore, we think that the automated method could be used appropriately on the weight-bearing full-leg radiograph. Another limitation is the use of weight-bearing radiographs, where knee positioning may affect the reliability of the measurements[50,205,206]. We mitigated this by standardizing limb rotation to ensure forward facing patellae[51]. However, detection of primary cam morphology on weight-bearing full-leg radiographs is limited by projection: cam morphology is typically located anterolaterally on the femoral head-neck junction and is best visualized with the hip in slight internal rotation or on dedicated lateral views. Since weight-bearing full-leg radiographs are taken in a neutral position and no lateral hip views were available, the prevalence of primary cam morphology in this cohort is likely underestimated. In addition, the cross-sectional study design precludes any causal inference, and the study cohort consisted of healthy young adults, which may limit generalizability to symptomatic populations with femoroacetabular impingement. Finally, no power calculation was performed for the current study objectives.

5. Conclusion

In conclusion, this study investigated the association between lower limb malalignment and alpha angle in a healthy participant population with an equal male-to-female distribution. We found a significant association between alpha angle and tibial genu varum, with genu varum linked to a higher alpha angle. Males exhibited higher alpha angles and more tibial varus than females. While higher sports activity was associated with a tibial genu varum, alpha angle and femoral or intra-articular knee deformities showed no difference across activity levels. Future research should focus on mechanical load adjustments in at-risk individuals to potentially prevent leg malalignment and cam morphology, which may help reduce the incidence of knee and hip osteoarthritis and improving long-term joint health.

05

Chapter 5

Progression of Bone and Joint Space Deformity in Patients with Mild Knee Osteoarthritis: Data from the IMI-APPROACH Cohort

H. Chien Nguyen, Eva A. Bax, Roel J.H. Custers, Nienke van Egmond, Ruurd J.A. Kuiper, Vahid Arbabi, Hassan Rayegan, Willem Paul Gielis, Ralph J.B. Sakkers, Margreet Kloppenburg, Francisco J Blanco, Ida K Haugen, Francis Berenbaum, Mylène P. Jansen, Simon C. Mastbergen, Claudia Lindner, Tim F. Cootes, Harrie Weinans

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Abstract

Objective: This study aimed to divide leg malalignment into different categories of valgus and varus of the femur, tibia, and intra-articular knee joint and investigates whether knee osteoarthritis (OA) patients are susceptible for changes of such leg deformities over time.

Methods: This study included 317 radiographs and CT-images on baseline and 24 months of 169 patients (median age 67, 78.2% female) of the prospective European IMI-APPROACH cohort, enrolled for knee OA. Femoral, tibial, and intra-articular geometry was determined. Different categories were analyzed based on varus or valgus in the femur, in the tibia, or within the intra-articular joint. Changes of these variables over time and their correlations were determined with mixed model analysis.

Results: Femurs tended to become more varus-like over the two-year follow up (0.3°, 95% CI 0.6°–0.1°, p=0.02), bony valgus femurs became more varus shaped (1.1°, 95% CI:1.7°–0.5°, p<0.001). Patients with bone varus and a normal joint line convergence angle (JLCA) showed a significant increase in intra-articular joint varus, with a mean JLCA increase of 1.1° (95% CI:0.4°–1.7°, p=0.005). By two years, they reached the threshold for defining intra-articular joint varus deformity, with a JLCA of 2.0°.

Conclusions: Substantial intra-articular joint and bone varus progression was observed within two years. This study shows that bone deformity is to some extent a dynamic process and there is a growing varus malalignment in the intra-articular knee joint and bones. Thereby this study emphasizes the importance of leg malalignment for progression of intra-articular knee joint changes in early OA.

1. Introduction

Osteoarthritis (OA) is a major healthcare burden with an estimated 595 million people worldwide affected in 2020[207]. The knee is the most affected joint, and the disease is characterized as multifactorial, involving structural alterations in the subchondral bone, hyaline cartilage, ligaments, capsule, synovium, and periarticular muscles[7]. The doctrine of OA as a passive wear-and-tear degenerative disease is changing to a much more complex pathogenesis, which involves metabolic, inflammatory, and mechanical factors[7]. Given this complexity, OA healthcare could benefit from more refined disease frameworks derived from phenotypes to provide more personalized treatments at an early stage of the disease process[208–212].

One of the investigated OA phenotypes is a biomechanically malaligned leg, with a varus or valgus overall leg shape. In general, a deviation of ±2° from neutral hip knee ankle angle (HKA) is considered pathological, although many people with a malalignment are not aware of their deformity[58,213]. Varus and valgus malalignment shift the mechanical leg axis from the middle to respectively the medial or lateral compartment of the knee resulting in potential excessive loading with a higher risk of cartilage and meniscus degeneration in one of these compartments[7,16,23,208,212]. The correlation between malalignment of the leg and knee OA initiation or progression is not straightforward[21,23,182,212,214–219]. Only radiological progression and not clinical progression has been correlated to malalignment, but this correlation is difficult to predict in the individual patient [21,23,182,212,214–219].

Malalignment of the leg can be the result of three aspects: i) deformity in the tibia; ii) deformity in the femur; and/or iii) non equally distributed cartilage loss in the knee joint, potential surrounding soft tissue laxity, and meniscal abnormalities which leads to an intra-articular joint deformity[220,221].

This study aimed to investigate three potential sources of lower limb deformity—femoral, tibial, and intra-articular knee joint —to assess how bony and intra-articular joint geometry changes over time in patients with knee OA. Our hypotheses are that bone deformities drive intra-articular joint change over time, with valgus bones towards more valgus intra-articular joint progression and varus bones towards more varus intra-articular joint progression[7,16,21,23,208,212,222–224].

2. Methods

2.1 Patients

This study included 297 knee radiographs and whole-body Computed Tomography (CT)-images of the IMI-APPROACH cohort. IMI-APPROACH is a two-year European cohort study to describe, validate, and predict phenotypes of OA using clinical, imaging, and biochemical markers[143]. Recruitment relied on positive clinical American College of Rheumatology (ACR) criteria for knee OA[41,143] and machine-learning models that guide patient inclusion to predict the probability of increased or sustained knee pain and structural OA progression during the two-years follow-up period. The elaborate selection process and the included patients have been described by van Helvoort et al.[143]

2.2 Imaging acquisition

Weight bearing knee radiographs (Buckland-Wright protocol)[36,143] and supine whole-body Computed Tomography (CT) images of 297 patients were available of the index and contralateral side on baseline and after 24 months follow-up, resulting in a total of 594 knees available for analysis[143]. CT images were used for the femoral and tibial analyses of varus and/or valgus. The knee radiographs were used to measure the intra-articular joint varus or valgus.

2.3 Image analyses

The mechanical lateral distal femoral angle (mLDFA) and mechanical medial proximal tibial angle (mMPTA), both indicators for femoral/tibial varus and/or valgus deformity, were automatically measured on both CT timepoints with validated software (Figure 1)[225,226]. The intra-articular joint varus or valgus deformity was quantified as the joint line convergence angle (JLCA) on knee radiographs at both time points, using the Osteoarthritis Digital Image Analysis (ODIA) tool[144]. Mean error of automated JLCA measurements when compared to manually checked ODIA measurements was defined in a previous study as 0.4°[144].

The hip knee angle (HKA) reflects the amount of varus or valgus in the leg by measuring the angle between the mechanical axes of the femur and tibia (Figure 1D) on standardized whole leg radiographs[49,50]. The arithmetic hip-knee-ankle angle (aHKA) is a surrogate for the HKA and represents the mechanical axis deviation attributable solely to the bony deformities of the femur and tibia. The aHKA was calculated by subtracting the mLDFA from the mMPTA, resulting in negative values for a bony varus and positive values for a bony valgus (Figure 1E)[211].

The change over the 24 months follow-up in femoral and tibial geometry was measured for different categories, by dividing the knees into bony and intra-articular space induced deformities based on the JLCA, mLDFA, and mMPTA at baseline (Table 1). The change over 24 months in intra-articular space geometry was also measured for different categories, based on bony and intra-articular space deformities, defined by the JLCA and aHKA on baseline (Table 1). The normal values for mMPTA, mLDFA, aHKA, and JLCA as proposed by Paley were used to differentiate between normal and pathological deformities[213,227]. The change in knee geometry of the tibia (mMTPA), femur (mLDFA), and intra-articular joint (JLCA) between baseline and 24 months was analyzed for each alignment category.

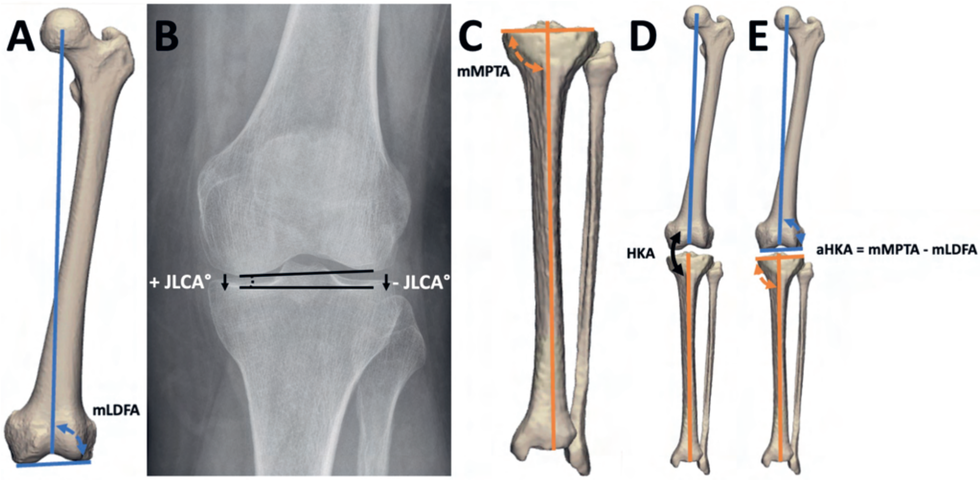

Figure 1 – A) Measurement of the mechanical lateral distal femoral angle (mLDFA), B) joint line convergence angle (JLCA), and C) mechanical medial proximal tibial angle (mMPTA). Normal range of mLDFA and mMPTA is between 85° and 90°, while normal range of JLCA is between 0° and 2°[550]. Varus progression has a positive effect on the JLCA and valgus progression a negative effect. D)The hip knee angle (HKA) is measured as the angle between the mechanical axes of the femur and the tibia, E) The arithmetic hip knee ankle angle (aHKA) representing the bony valgus/varus was calculated by subtracting the mLDFA from the mMPTA, a deviation of ±2° from neutral aHKA is considered pathological.

2.4 Statistical analyses

Descriptive statistics were computed using means with the standard deviation (SD) or medians with range, where appropriate. Changes in knee morphology (mMPTA, mLDFA, and JLCA) from baseline to 24 months were analyzed using a mixed model analysis, correcting for the possible influence of the inclusion of patients' left and right knees. The possible difference between changes in the diseased index and contralateral knee was tested using the same mixed model analyses. P values < 0.05 were considered statistically significant. All analyses were performed in IBM SPSS Statistics v26.0.0.1 (Armonk, New York, United States).

Table 1 - Selection criteria for the groups' normal alignment, intra-articular joint valgus or varus deformity, bone valgus or varus deformity, and both bone and intra-articular joint valgus or varus deformity. The selection was based on JLCA measurements on knee radiographs, and mechanical lateral distal femoral angle (mLDFA) mechanical medial proximal tibial angle (mMPTA) on rendered 3D models of the CT-scans. The arithmetic hip knee ankle angle (aHKA) was calculated by subtracting the mLDFA from the mMPTA, representing the bony overall leg alignment.

	JLCA Intra-articular joint space varus/valgus	**mLDFA Femur varus/valgus**	**mMPTA Tibia varus/valgus**	**aHKA Bone varus/valgus**
Normal	0° - 2°	85° - 90°	85° - 90°	-2° - 2°
JLCA varus	> 2°	85° - 90°	85° - 90°	-2° - 2°
Bone varus	0° - 2°	> 90°	< 85°	< -2°
Bone and JLCA varus	> 2°	> 90°	< 85°	< -2°
JLCA valgus	< 0°	85° - 90°	85° - 90°	-2° - 2°
Bone valgus	0° - 2°	< 85°	> 90°	> 2°
Bone and JLCA valgus	< 0°	< 85°	> 90°	> 2°

JLCA, Joint Line Convergence Angle; mLDFA, mechanical Lateral Distal Femoral Angle; mMPTA, mechanical Medial Proximal Tibial Angle; aHKA, Arithmetic Hip–Knee–Ankle Angle

3. Results

This study included 317 knees of 160 patients with available baseline and 24 months knee radiograph and CT-scan. Table 2 summarizes the baseline and 24 months characteristics of all included knees.

Table 2 - Baseline and 24 months characteristics of 160 patients with knee osteoarthritis and 317 included knees. BMI = body mass index, KL = Kellgren and Lawrence, mMPTA = mechanical medial proximal tibial angle, mLDFA = mechanical lateral distal femoral angle, JLCA = joint line convergence angle, aHKA = arithmetic hip knee ankle angle.

	Baseline	**24 months**
Knee joint side, n (%)	Left = 160 (*50.5%*) Right = 157 (*49.5%*)	
Gender, n (%)	Male = 35 (*21.8%*) Female = 125 (*78.2%*)	
BMI (kg/m^2) at baseline, mean (SD)	27.7 (*SD 5.0*)	
Age at baseline, median (range)	67 (*range 48 – 82*)	
KL grade of index knee at baseline, n (%)		
Grade 0	84 (*26.5%*)	
Grade 1	94 (*29.7%*)	
Grade 2	67 (*21.1%*)	
Grade 3	62 (*19.6%*)	
Grade 4	10 (*3.2%*)	
mMPTA°, mean (SD)	87.0° (*SD 2.1°*)	86.9° (*SD 2.2°*)
mLDFA°, mean (SD)	86.0° (*SD 2.1°*)	86.3° (*SD 2.1°*)
JLCA°, mean (SD)	1.4° (*SD 2.0°*)	1.6° (*SD 2.1°*)
aHKA°, mean (SD)	1.0° (*SD 2.7°*)	0.6° (*SD 2.6°*)

BMI, Body Mass Index; KL, Kellgren–Lawrence; mMPTA, mechanical Medial Proximal Tibial Angle; mLDFA, mechanical Lateral Distal Femoral Angle; JLCA, Joint Line Convergence Angle; aHKA, Arithmetic Hip–Knee–Ankle Angle

3.1 Femoral and tibial varus or valgus changes over time

All 317 included femurs tended to become significantly more varus-like (on average 0.3°, 95% CI 0.6° – 0.1°, p = 0.02) over the two years follow-up period. Valgus femurs with normal intra-articular joint geometry (n = 44) had a significant progression towards varus of 1.1° (95% CI 1.7° – 0.5°, p < 0.001) (Figure 2A, red line). Valgus femurs with intra-articular joint varus (n = 26) revealed a significant progression towards varus too, with on average 1.0° (95% CI 1.8° – 0.3°, p = 0.009) (Figure 2A, brown line).

Overall, valgus tibias (n = 25) tended to become more varus-like with an average decrease in mMPTA of 0.5° (Figure 2B, green (p = 0.579), brown (p = 0.181) and red lines (p = 0.303)). This phenomenon was not statistically significant. There was a significant change in mMPTA observed in knees with normal intra-articular joint geometry and mMPTA on baseline (Figure 2B, yellow line), albeit not relevant as the mean was 0.1° (95% CI 0.0° – 0.2°, p = 0.026) and below the measurement accuracy.

The combined femur-tibia geometry showed a mean shift toward varus of 1.2° (95% CI 0.8 – 1.2°, $p < 0.001$) in patients presenting with valgus deformity at baseline, indicating progressive varisation of the aHKA over the two-year follow-up (Figure 3).

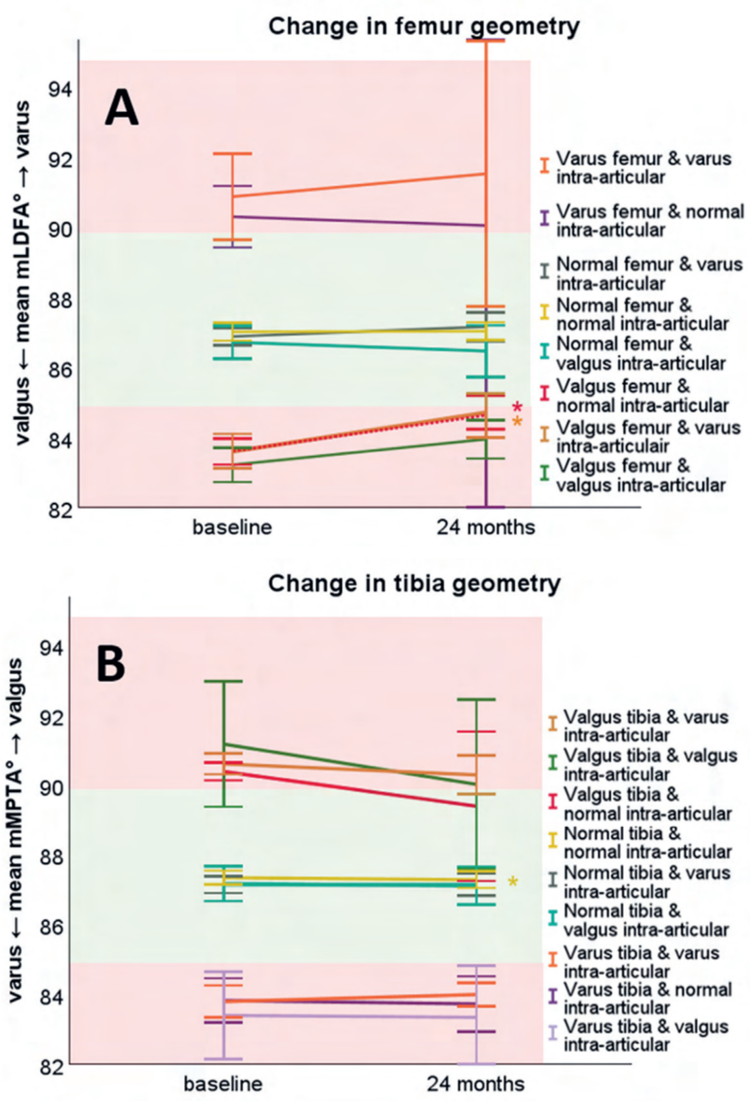

Figure 2 - Mean graphs with the 95% confidence interval (CI) of the change in femur geometry expressed as mechanical lateral distal femoral angle (mLDFA)(A) and tibia geometry expressed as mechanical medial proximal tibial angle (mMPTA) (B) between baseline and 24 months. Significant ($P \leq 0.05$) changes are marked with "*" and tested through a mixed model analysis.

There were no significant differences between the index and contralateral knees when analyzing the changes in femur and tibia geometry, p = 0.719 for mLDFA and p = 0.746 for mMPTA respectively.

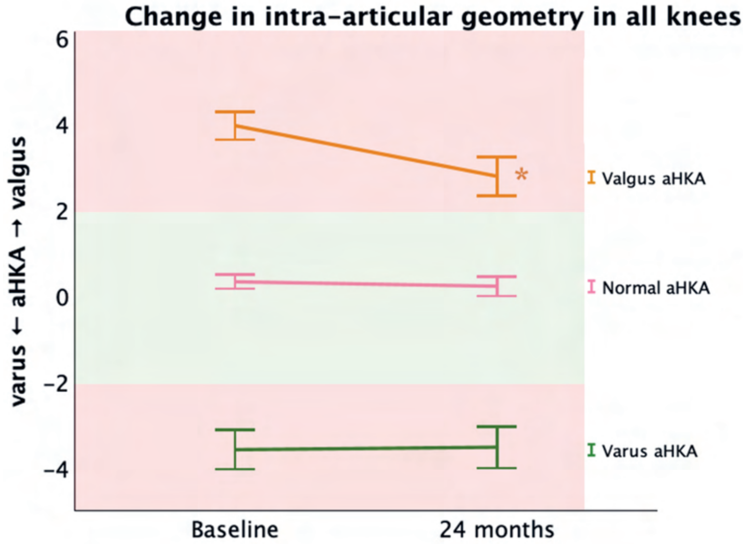

Figure 3 - Mean graphs with the 95% confidence interval (CI) of the change in arithmetic hip-knee-ankle angle (aHKA) between baseline and 24 months. The green surface indicates the normal aHKA value between -2° and 2°, while the red surfaces indicate aHKA values. Significant ($P \leq 0.05$) changes are marked with "*" and tested through a mixed model analysis.

3.2 Intra-articular joint varus or valgus changes over time

In general, intra-articular spaces tended to also become more varus like over the two years follow up, meaning an increase in JLCA. Most of these changes towards varus and valgus were non-significant except for the group with bone varus and normal intra-articular joint geometry on baseline. These patients (n = 15) showed a significant increase in intra-articular joint varus after two years, with a mean JLCA increase of 1.1° (95% CI 0.4°–1.7°, p = 0.005). By two years, they reached the threshold for defining intra-articular joint varus deformity, with a JLCA of 2.0° (Figure 4, yellow line).

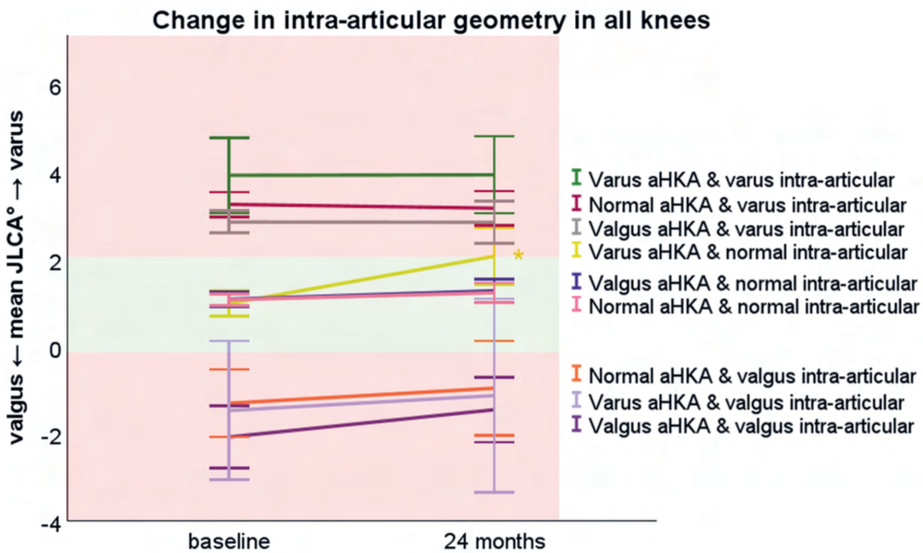

Figure 4 - Mean graphs with the 95% confidence interval (CI) of the change in calculated joint line convergence angle (JLCA) between baseline and 24 months. The green surface indicates the normal JLCA value between 0° and 2°, while the red surfaces indicate abnormal JLCA values. Varus and valgus arithmetic hip knee ankle angle (aHKA) were calculated as surrogate for the bony alignment, by subtracting the mechanical lateral femoral angle from the mechanical medial proximal tibial angle. Significant ($P \leq 0.05$) changes are marked with "*".

4. Discussion

This study aimed to measure the bony and intra-articular joint varus and/or valgus geometry in a knee OA cohort, to classify them into specific categories, and measure the possible changes in geometries over time. Surprisingly, against our expectation, this study observed small changes in femur and tibia geometries even within the two-year follow-up period, with a tendency to become more varus-like during this period. This was mostly pronounced in valgus femurs (on average 1.1°) and valgus tibias (on average 0.5°) on baseline. All intra-articular joint geometries had the tendency to progress towards a more varus shape, except for the knees with an already intra-articular joint varus at baseline. This effect was observed over a relatively short two-year period, and the progression toward varus is expected to continue until it stabilizes. The intra-articular joint progression towards varus was most significant for knees with a normal intra-articular joint geometry and bone varus deformity, which indicates continuous overload at the medial compartment making cartilage tissue susceptible for cartilage degeneration within the medial compartment (Figure 4 yellow line). Specifically, cartilage degeneration in one knee compartment might further the overall varus or valgus malalignment, thereby creating positive feedback that drives OA progression.

In a recent study by Palmer *et al.*[214], conducted to explore the potential for clinical and structural progression of OA because of leg malalignment, patient inclusion was determined based on their susceptibility to cartilage degeneration. Patients with joint space widths below 1 mm were excluded, which revealed that varus tibial alignment was associated with increased odds of structural progression in knee osteoarthritis. In agreement, the results of our current study revealed that mainly patients with bone varus and normal intra-articular joint were susceptible for structural radiographical OA progression. The relation between cartilage thickness and change in intra-articular joint space geometry was also observed by Colyn *et al.*[228], with a correlation between Kellgren and Lawrence (KL) grades and JLCA progression. So, it seems likely that changes in intra-articular joint geometry are mainly observed in knee joints with mild to moderate OA, and therefore cartilage tissue susceptible for (further) degeneration. Our current study did not include KL grades to test their potential effect on geometry changes over time, which should be considered for future research.

In the study of Colyn *et al.*[228] the JLCA was measured on standing whole leg radiographs, which also provided the complete varus/valgus stance of the leg. They concluded that the knee progression towards varus was mostly the result of an increased varus shape in the tibia (mMPTA < 85°) and increase in intra-articular joint space deformity (JLCA > 2°)[228]. In our current study, a bony change in both femur and tibia tends to change towards a varus shape. Strangely, this progression happened mostly in the valgus knees and not in the varus knees. Valgus knees may still predominantly load the medial compartment of the knee joint. It should be realized that in normal leg alignment the medial compartment takes significantly more load than the lateral compartment, on average 60% - 70% of the total load[229]. Hence, even in a slightly valgus shaped leg still most of the loading will pass through the medial side.

Albeit somewhat unexpected, the femoral geometry progression towards varus in valgus knees is worth exploration in future studies. We hypothesize that the change in morphology could possibly be the result of two theories. The first theory comes from gait explorations, in which several studies demonstrated a difference in gait between OA affected and healthy knees[230–232]. This principle of altered gait in patients with knee OA has even been translated into targeted gait alterations as a treatment to achieve pain relief[233]. These alterations in gait support our hypothesis that it is plausible for knee OA patients to develop unique coping mechanisms for pain relief through alterations in their walking patterns. Over time, an altered gait pattern possibly affects the morphology of a bone as a result of different loads. The second theory is that bone morphology only changes at the knee joint ends of the bones due to possible flattening of one compartment and simultaneous formation of osteophytes because of knee OA. These could potentially affect our calculation of varus and valgus parameters (mLDFA and mMPTA).

Both research and clinical care of knee OA could benefit from further phenotyping of different varus/valgus types as suggested previously[213,234,235]. The result of the current study indicates to differentiate malalignment categories based on the presence of an intra-articular joint space varus/valgus or varus/valgus in the bone structures. The normal range of intra-articular joint space geometry is 2° in JLCA, therefore an increase in varus shape of 1.1° within a short period of 2 years is relevant. With this knowledge future studies could attempt to determine more exactly why some patients become progressors, while others are not[21,182,214–219]. This could help in more exact predictions for OA progression and patient indication for therapies.

Patients included in our current study were selected via an algorithm designed by the IMI-APPROACH consortium, based on pain among other things using the ACR criteria[143]. From a surgical perspective, one might justify performing a knee osteotomy in the femur and/or tibia specifically in patients that present a varus malformation. Patient cases presenting knee OA related symptoms and mild radiographical structural manifestations might favor from such an intervention to prevent increases (1.1° in JLCA withing two years) in the overall varus shape, which furthers to progression of cartilage loss in a positive feedback loop. On the contrary, in cases of femoral valgus and normal intra-articular joint space geometry a possible delay in surgical intervention might be considered since our data revealed a decrease in valgus shapes even within this relatively short two-year period. The timing of an osteotomy to prevent further OA progression can be challenging, but current data, such as from the IMI-APPROACH cohort, can help guide the optimal timing for this surgery.

Our current study had limitations. First, the formation of osteophytes and bone remodeling due to OA progression could also influence knee geometry measurements, in particular the joint line angles[228,236]. Future research could delve into the possibility of osteophyte formations and the influence on bone geometry measurements. Second, the selection process of the patients led to a skewed distribution between males and females for analyses, since females are predominantly present in the IMI-APPROACH cohort[143]. This potentially led to a more valgus distributed cohort[237]. Third, all measurements were performed fully automatically, which may introduce measurement error. However, this automated method has been extensively validated and shows excellent agreement with manual measurements. Fourth, no clinical outcomes were included in the present study. Future research should evaluate whether changes in leg geometry translate into clinically relevant outcomes. Fifth, the 24 month follow up period may be insufficient to fully capture the natural course of OA progression. Nevertheless, even within this relatively short timeframe, we observed significant changes, indicating that meaningful disease progression can occur over such a period. Sixth, intra-articular joint progression may be influenced by meniscal pathology or meniscectomy, which was not captured in our dataset and should be investigated in future research. This potential contributor should be examined in future studies. Lastly, the IMI-APPROACH cohort included patients based on their likelihood of OA progression. The result of the current study is therefore not representative for healthy patients without clinical symptoms and having varus/valgus deformities.

5. Conclusion

Most bones show a trend to become more varus shaped in time, even femurs with a strong valgus shape showed a trend to normalize. Substantial intra-articular joint varus progression was observed within two years, in particular within patients that had bone varus at baseline. This study shows that bone deformity is to some extent a dynamic process and there is a growing varus malalignment in the intra-articular knee joint as well as in the bones. Thereby this study emphasizes the importance of leg malalignment for progression of intra-articular knee joint changes in early OA.

06

Chapter 6

The Impact of Varus and Valgus Alignment on Knee Cartilage Quality Assessed by Magnetic Resonance Imaging: Insights from the IMI-APPROACH Cohort

Eva A. Bax, Joost A.J. Kerkhof, Nienke van Egmond, Ruurd J.A. Kuiper, Hassan Rayegan, Margreet Kloppenburg, Francisco J Blanco, Ida K. Haugen, Francis Berenbaum, Simon C. Mastbergen, Felix Eckstein, Wolfgang Wirth, Frank W. Roemer, Moyo C. Kruyt, Harrie Weinans, Roel J.H. Custers

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Abstract

Background: Lower limb malalignment increases the risk of unicompartmental knee osteoarthritis (KOA). This study investigates the association between knee cartilage quality, assessed via MRI-based T2 mapping, and lower limb malalignment. It also examines whether cartilage quality is more influenced by bony or intra-articular malalignment.

Methods: In this cross-sectional analysis of 156 knees from the IMI-APPROACH cohort, tibiofemoral cartilage T2 values were measured using high-resolution MRI, distinguishing superficial and deep layers. Malalignment was categorized into entire leg, bony, and intra-articular malalignment (via the Joint Line Convergence Angle). Correlations between T2 values and alignment were assessed using Spearman's rho. A subgroup analysis evaluated cartilage quality in constitutional malalignment (malalignment without intra-articular deviation).

Results: Cartilage T2 values were significantly associated with alignment. Varus knees showed significantly longer T2 in the superficial medial cartilage ($\rho = -0.2$, $p = 0.04$), and valgus knees in the lateral compartment ($\rho = 0.1$, $p = 0.35$). Associations were strongest for intra-articular malalignment ($\rho = 0.3$, $p < 0.01$). In constitutional varus, a non-significant medial T2 prolongation was observed ($\rho = -0.2$, $p = 0.28$); no changes were found in constitutional valgus.

Conclusion: Lower limb malalignment, particularly intra-articular malalignment, is associated with compartment-specific lower cartilage quality, as reflected by longer T2 values. Distinguishing between bony and intra-articular malalignment, rather than overall limb alignment, should be a focus of future studies on malalignment. Future research should explore whether constitutional malalignment and early cartilage alterations may trigger cartilage degeneration and KOA progression.

1. Introduction

Knee osteoarthritis (KOA) is the most common progressive joint disease worldwide[183]. The prevalence of KOA in individuals aged over 40 years is 22.9% worldwide, posing a significant health issue[183]. With aging and an increasingly obese population, it is becoming even more prevalent than in previous decades[183]. KOA is characterized by the gradual breakdown of the protective cartilage in the joint, accompanied by inflammation and changes in surrounding tissues, which contribute to pain, stiffness, and a diminished range of motion[238].

The radiological diagnosis of KOA is often made at a late stage, as radiographs reveal KOA changes at a relatively late stage[239]. T2 mapping using Magnetic Resonance Imaging (MRI) scans is a powerful tool for assessing cartilage composition, as it reveals water content and collagen fiber orientation[136,240], with prolonged T2 indicative of poorer cartilage quality[172,241]. T2 mapping, highly sensitive to changes in collagen concentration and fragmentation of the collagen matrix, has proven to be a valuable tool for assessing cartilage degeneration, with histological studies suggesting its reliability and providing critical insights into in vivo cartilage degeneration[242,243].

Individuals with lower limb joint malalignment are at increased risk of developing unicompartmental KOA[23,182], as the asymmetric loading of a single tibiofemoral compartment causes cartilage degeneration[22]. Lower limb malalignment encompasses both bony malalignment and intra-articular knee joint malalignment[244]. Bony alignment refers to the alignment of the tibial and/or femoral bones. Intra-articular malalignment, in contrast, refers to structural abnormalities within the knee joint itself, including cartilage degeneration, meniscal damage, and meniscal extrusion[159,245]. Some individuals exhibit constitutional varus, which means that only bony malalignment is present, without intra-articular knee joint malalignment[58]. As a result, these individuals do not show radiological evidence of KOA, but they do have lower limb malalignment. However, these individuals are at an increased risk of developing KOA over time[246]. MRI T2 mapping may offer a valuable tool for assessing cartilage quality in these individuals, potentially identifying those at elevated risk for developing unicompartmental KOA. By enabling timely interventions, this technique could play a critical role in mitigating disease progression and reducing long-term joint damage.

Sharma *et al.*[22] investigated the relationship between KOA progression based on MRI and lower limb malalignment. Their study showed that varus knee malalignment was associated with the development of cartilage damage in the medial compartment and demonstrated reduced risk of cartilage damage in the less-loaded compartment in either varus or valgus knees. However, the study did not utilize T2 mapping and did not distinguish between malalignment attributable to bony and intra-articular knee joint malalignment. Identifying this difference is important, as intra-articular knee joint malalignment reflects unicompartmental cartilage and/or meniscal loss, which are part of the joint degeneration process[159].

Therefore, this cross-sectional study in participants with KOA examines the association between knee cartilage quality (T2) and lower limb malalignment, focusing on whether the association of the entire leg malalignment is primarily influenced by intra-articular or bony malalignment. We hypothesized that bony varus alignment is associated with lower cartilage quality reflected by longer T2 in the medial compartment. Conversely, bony valgus alignment was expected to be associated with lower cartilage quality (longer T2) in the lateral compartment, reflecting the isolated effects of lower limb malalignment on T2 related cartilage quality.

2. Methods

2.1 Participants

In the prospective Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) cohort, 297 KOA participants from five European centers were followed for 2 years[143]. Participants aged 18 years and older were selected based on the likelihood of experiencing structural and/or knee pain progression over a two-year period. The index knee was selected based on American College of Rheumatology (ACR) criteria. In case of equal symptoms in both knees, the right knee was chosen. The inclusion and exclusion criteria for the IMI-APPROACH cohort have been previously published[143]. Participants underwent low dose whole body computed tomography (CT) scan, weight-bearing posteroanterior radiographs according to the Buckland-Wright protocol and 1.5 or 3.0 T MRI scans of the index knee at baseline [143,145]. Participants with available baseline CT scans, radiographs, and 3T MRI scans, including T2-mapping, were included in this study.

The study was approved by the Institutional Review Boards, following protocols, Good Clinical Practice, the Declaration of Helsinki, and all ethical and legal regulations. The study was registered under clinicaltrials.gov nr: NCT03883568 and informed consent was obtained.

2.2 Imaging assessment

The Kellgren and Lawrence (K&L) score was determined by one experienced observer on knee radiographs with good reliability[247]. Based on these scores, participants were categorized into two groups: those with no or doubtful radiographic OA (K&L 0–1) and those with mild to severe radiographic OA (K&L 2–4). Furthermore, all weight-bearing knee radiographs were reproducibly and automatically analyzed using the Osteoarthritis Digital Image Analysis (ODIA) to determine the Joint Line Convergence Angle (JLCA) in weight-bearing position (Table 1) (Figure 1)[144]. The JLCA obtained from radiographs served as a measure of intra-articular alignment and can be considered a unicompartmental (non-symmetrical) loss of cartilage and/or meniscus of the knee, while JLCA alterations may also be influenced by soft tissue tension or laxity[159,245]. A JLCA between 0-2° is considered as healthy (Table 1), while a JLCA outside this normal range is considered pathological and a visible sign of KOA[51].

Table 1 - The alignment classification for normal, varus and valgus alignment. The alignment was determined for JLCA on standing knee radiographs, and bone morphology on rendered 3D models of the CT-scans.

		JLCA	Bony alignment
Normal		|0° - 2°|	|178° - 182°|
Varus	Intra-articular	> 2°	|178° - 182°|
	Bones	|0° - 2°|	< 178°
Valgus	Intra-articular	< 0°	|178° - 182°|
	Bones	|0° - 2°|	> 182°

JLCA, joint line convergence angle;

The femur and tibia were automatically segmented from the low dose whole body Computed Tomography (CT) using a deep learning approach[225]. Bony deformities in the individual bones of the tibia (mechanical medial proximal tibial angle (mMPTA)) and femur (mechanical lateral distal femoral angle (mLDFA)) were automatically determined from CT-scan as proposed by Paley[51,226] (See Figure 1). The bony alignment was determined by mMPTA – mLDFA + 180°, as proposed by MacDessi *et al.*[244] and represents the alignment of the tibial and femoral bones. A bony varus alignment was defined as 178° or less, and a bony valgus alignment as 182° or more[248] (Table 1). The deformity of the entire leg (mechanical hip-knee-ankle angle (mHKAA)) reflects both bony deformity and intra-articular knee joint deformity (JLCA) and can be calculated using the formula mMPTA - mLDFA - JLCA + 180°. The mMPTA and mLDFA were obtained from CT imaging, which is independent of patient positioning, whereas the weight-bearing JLCA was assessed using weight-bearing radiographs. A neutral mHKAA ranges from 178° to 182°, with varus alignment defined as 177° or less, and valgus alignment as 183° or more[51]. Coronal lower limb malalignment was classified into three categories: entire leg alignment (1), bony alignment in femur and/or tibia (2), and intra-articular alignment (3).

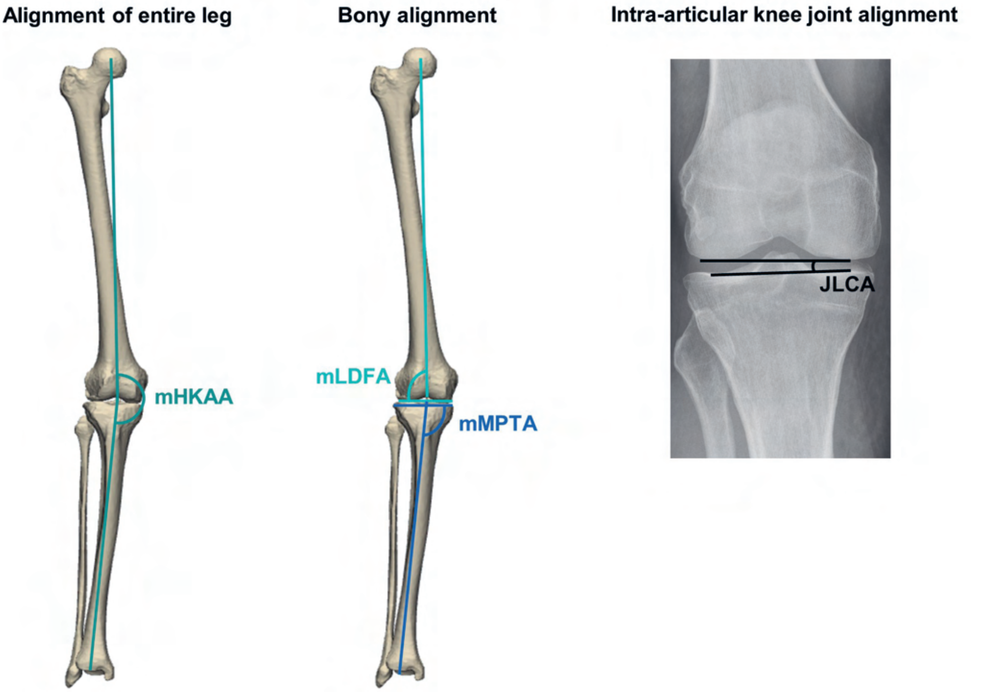

Figure 1 - Illustration of coronal lower limb malalignment: Entire leg alignment (mechanical hip-knee-ankle angle (mHKAA)), bony alignment (mechanical medial proximal tibial angle (mMPTA)), mechanical lateral distal femoral angle (mLDFA)), and intra-articular knee joint alignment (joint line convergence angle (JLCA)).

Cartilage T2 times, reflecting cartilage matrix quality, were determined using high-resolution MRI for both tibial and femoral cartilage. T2 times were obtained by manual, quality-controlled cartilage segmentation (Chondrometrics GmbH, Freilassing, Germany)[249,250]. Due to the recognized spatial variation of cartilage T2 with tissue depth[251], the cartilage was divided into the top 50% (superficial) and bottom 50% (deep)[251], based on the local distance between the segmented cartilage surface and bone interface[249] and the superficial and deep layer T2 times were calculated for both the medial and lateral compartment[252] (Figure 2).

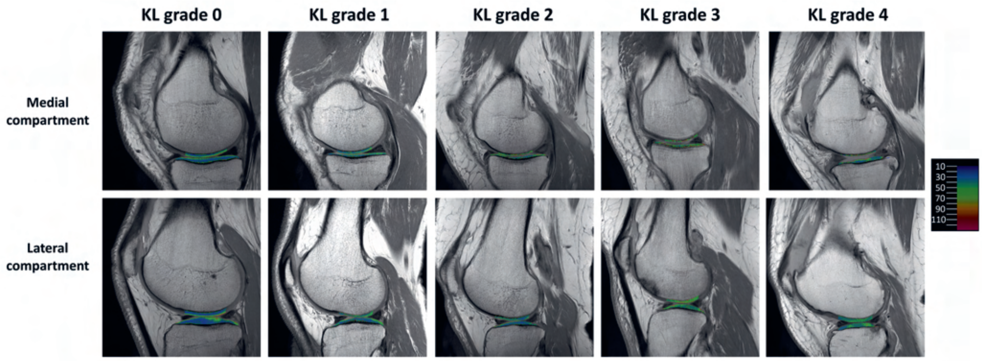

Figure 2 - Representative T2 mapping images of the medial (top row) and lateral (bottom row) compartments across Kellgren-Lawrence (KL) grades 0–4. Color-coded overlays indicate T2 relaxation times, with higher values (warmer colors) reflecting lower cartilage quality.

2.3 Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 29.0 software. Descriptive statistics, including means and standard deviations (SD) were computed. The Shapiro-Wilk test was used to assess the normality of the data. Spearman's rho (ρ) was used to assess correlations between cartilage T2 in medial and lateral knee compartments and the three alignment parameters: entire leg alignment (1), bony alignment (2), and intra-articular alignment knee joint alignment (3) (Figure 1). Spearman's rho between 0.00 and 0.19 was considered very weak, 0.20–0.39 weak, 0.40–0.59 moderate, 0.60–0.79 strong, 0.80–1.00 very strong[253]. Furthermore, Spearman's rho (ρ) were conducted for the subset of participants with constitutional joint malalignment without any intra-articular knee joint deformity (non-pathological JLCA of 0-2°). The latter subset may strengthen the pure effects of valgus or varus on T2 related cartilage quality. Finally, a Mann-Whitney U test was performed to determine whether T2 times differed significantly between K&L scores.

The False Discovery Rate (FDR) (the rate of Type I errors due to multiple testing) was controlled at 5% through the Benjamini-Hochberg method[254]. The obtained p-values were sorted in ascending order and corrected using the Benjamini-Hochberg method. With m tests and $p(n)$ as the smallest obtained p-value, the corrected p-value was determined as $p(n) \cdot \frac{m}{n}$.

A priori power analysis was conducted using G*Power version 3.1 to determine the required sample size for detecting a statistically significant correlation[255]. Assuming a significance level (α) of 0.05 and a desired power (1 − β) of 0.80, with a medium effect size (r = 0.30) based on Cohen's conventions, the analysis indicated that a minimum of 84 participants would be needed. With this sample size, the actual statistical power to detect the specified correlation was 80%.

3. Results

3.1 Participants

Of the 297 participants of the IMI-APPROACH cohort, 152 participants had the required baseline data (knee radiographs, T2-mapping on 3T MRI, and CT scans) and were included. Average age was 66.7 ± 7.0 years and the participants were predominantly female (81.4%). 79 participants (50.6%) had a K&L score of 0 or 1, while 70 participants (49.4%) had a K&L score between 2 and 4. See Table 2.

The mean mHKAA (providing the total alignment of the entire leg including the intra-articular portion) was 179.8 ± 3.0°, with 29.5% exhibiting varus and 18.6% exhibiting valgus alignment. The mean bony alignment was 180.0 ± 2.7°. A total of 71 participants (45.5%) exhibited a bony malalignment without any intra-articular knee joint deformity. Of these participants, 26.8% exhibiting a varus bony alignment and 73.2% a valgus bony alignment. Finally, the mean JLCA was 1.5± 2.1°. A total of 71 participants (45.5%) had a JLCA within the normal range, 57 (36.5%) demonstrated a varus JLCA, and 28 (17.9%) exhibited a valgus JLCA.

Table 2– Patient characteristics of the included participants n= 156.

Age (years), mean ± SD	66.7 ± 7.0
Body Mass Index (kg/m^2), mean ± SD	26.8 ± 4.1
Sex (female), n (%)	127 (81.4)
Kellgren and Lawrence, n (%)	
Grade 0	38 (24.4)
Grade 1	41 (26.3%)
Grade 2	31 (19.9)
Grade 3	41 (26.3)
Grade 4	5 (3.2)

SD, Standard deviation.

3.2 Kellgren and Lawrence and T2 times

The deep layer of the medial compartment demonstrated a significantly shorter T2 time (better cartilage quality) in the K&L 0-1 group in comparison to K&L 2-4 (median 30.9 ms vs 35.8 ms) (P < 0.001) (Figure 3). Likewise, the deep layer of the lateral compartment exhibited a significantly shorter T2 time within the K&L 0-1 group when compared to the K&L 2-4 group (median 31.8 versus 33.9 ms) (P < 0.001) (Figure 3). The superficial layer of the medial and lateral compartment did not exhibit a significant difference between the groups (Medial: P = 0.12 Lateral: P = 0.86) (Figure 3). Additionally, KL grade and JLCA were moderately positively correlated (ρ = 0.43, 95% CI 0.29–0.56, P < 0.001).

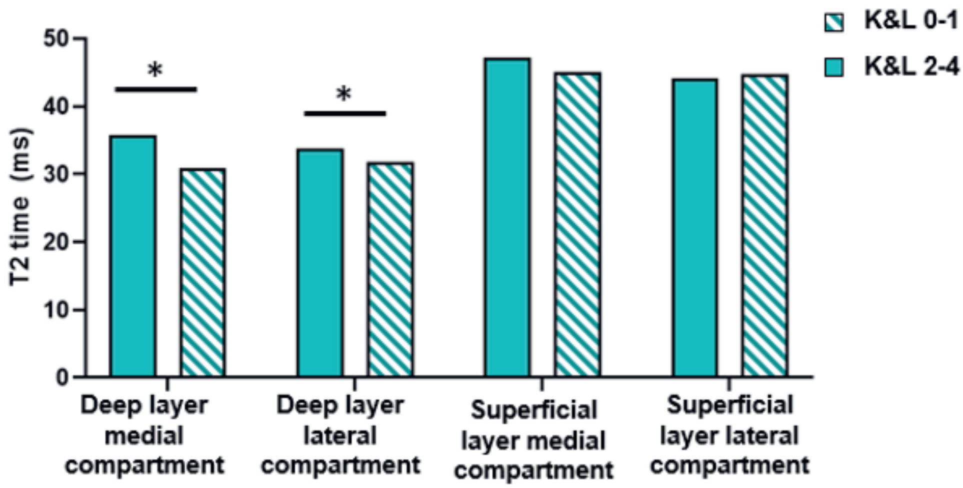

Figure 3 – Comparison of T2 time across different knee compartments and layers between two groups (K&L 0-1 and K&L 2-4). Asterisks indicate significant differences ($p < 0.05$) between the groups for the specified compartments.

3.3 Alignment and T2 times correlation in the entire group

For all three aspects of (mal)alignment it was found that varus shapes had higher T2 time (more cartilage degeneration) at the medial compartment compared to the lateral compartment. In line with this, valgus shapes had higher T2 at the lateral compartment (Figure 4).

More specifically in the superficial layer of the medial compartment, a weak but statistically significant correlation was evident between the T2 time and the entire leg (mHKAA) (ρ = -0.31, p < 0.001). Conversely, a very weak significant correlation was noted between the T2 time and bony alignment (ρ = -0.19, p = 0.04). Furthermore, a significant, weak correlation was detected between the T2 times and the JLCA derived from weight-bearing radiographs (ρ = 0.31, p < 0.001). For the superficial layer of the lateral compartment T2 showed very weak correlations with mHKAA (ρ = 0.11, p = 0.59) and bony deformity (ρ = 0.10, p = 0.35). Moreover, a correlation of very weak strength was identified between T2 time and the intra-articular alignment (JLCA) (ρ = -0.05, p = 0.62). See Figure 4 and Table 3.

For the deep layer similar significant correlations were found where again higher T2 times in the medial compartment corresponded with varus deformities for all three aspects of joint (mal)alignment. However, for the bony alignment, no statistically significant correlations were found (medial: ρ = -0.07, p = 0.49; lateral: ρ = 0.04, p = 0.58). See Figure 4 and Table 3.

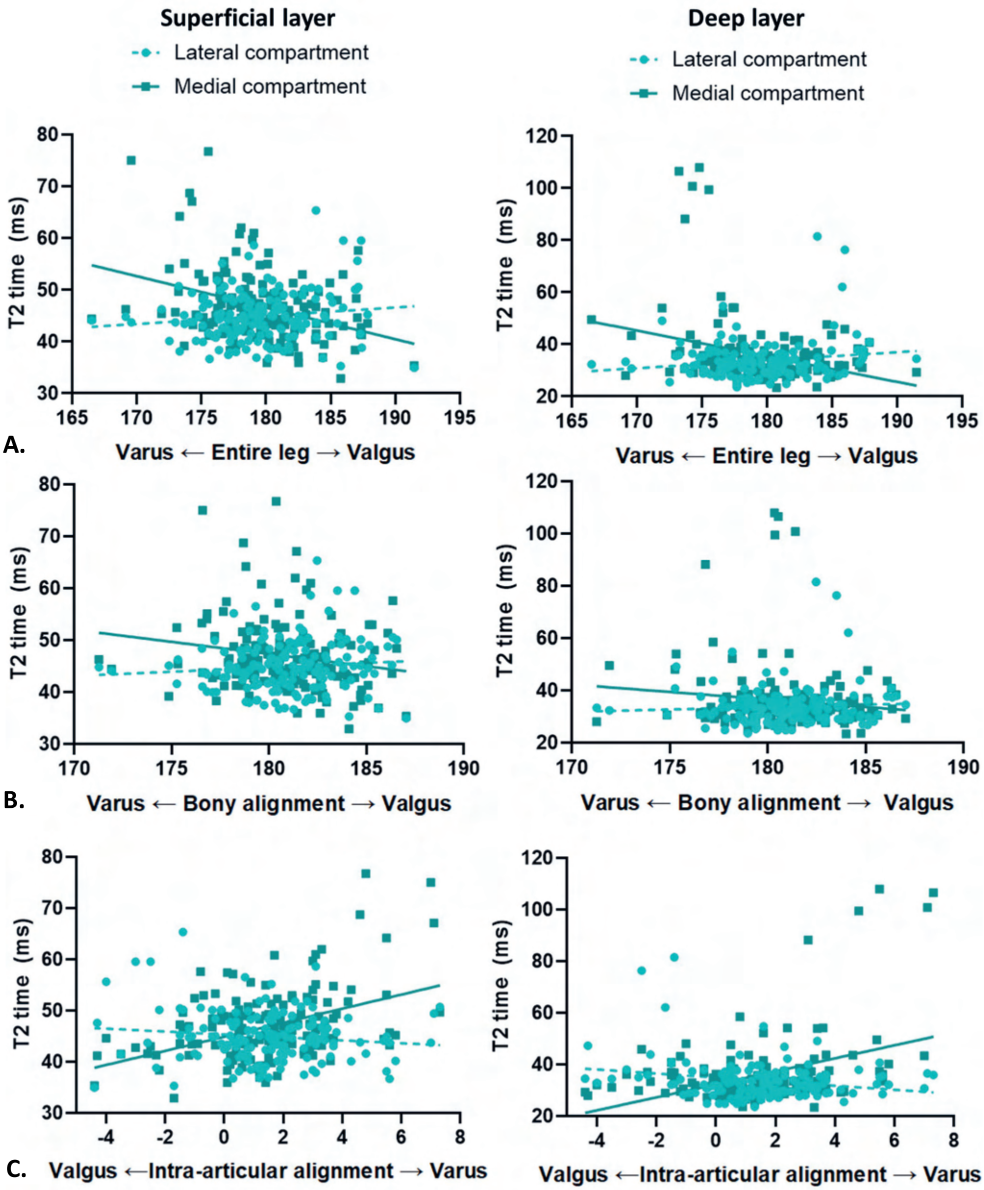

Figure 4 - Correlation between T2 time and the various aspects of alignment: entire leg alignment (mHKAA) (A), bony alignment (B), and intra-articular alignment (JLCA) (C) for the superficial layer and deep layer of the medial and lateral compartment. *Correlation is considered statistically significant.

Table 3 - T2 times correlated to the entire leg alignment, bony alignment and intra-articular alignment.

	Spearman's rho	Confidence interval	P-value[a]
Entire leg alignment			
Deep layer of lateral compartment	0.05	[-0.11; 0.21]	0.59
Superficial layer of lateral compartment	0.11	[-0.05; 0.27]	0.34
Deep layer of medial compartment	-0.23	[-0.37; -0.06]	**0.02**
Superficial layer of medial compartment	-0.31	[-0.45; -0.15]	**< 0.001**
Bony alignment			
Deep layer of lateral compartment	0.04	[-0.12; 0.21]	0.58
Superficial layer of lateral compartment	0.10	[-0.06; 0.26]	0.35
Deep layer of medial compartment	-0.07	[-0.23; 0.09]	0.49
Superficial layer of medial compartment	-0.19	[-0.35; -0.03]	**0.04**
Intra-articular alignment			
Deep layer of lateral compartment	-0.10	[-0.26; 0.06]	0.32
Superficial layer of lateral compartment	-0.05	[-0.21; 0.11]	0.62
Deep layer of medial compartment	0.26	[0.10; 0.40]	**0.004**
Superficial layer of medial compartment	0.31	[0.16; 0.45]	**< 0.001**

[a] *p* values corrected for multiple testing using the Benjamini–Hochberg
The bold *p* values were considered statistically significant.

3.4 Alignment and T2 times correlation in the JLCA-normal group

It should be realized that a malalignment of the intra-articular alignment (Figure 4C) already refers to cartilage degeneration, as a high of low JLCA represents cartilage loss in one compartment of the knee joint relative to the other. To assess the pure effects of varus or valgus alignment on T2-related cartilage quality, we examine a subset of participants without intra-articular knee joint deformity. This analysis included 71 participants with normal (straight) joint space, defined by JLCA values between 0° and 2° (Table 1). This enables to analyze the T2 times in medial and lateral compartments with respect to bony alignment only.

In the superficial layer, there was still a weak (non-significant) correlation between the T2 times and bone deformity (medial: $\rho = -0.22$; lateral $\rho = -0.04$) (Figure 5 Table 4). In the deep layer, this correlation was virtually absent and non-significant (medial: $\rho = -0.03$; lateral $\rho = -0.05$) (Figure 5 and Table 4).

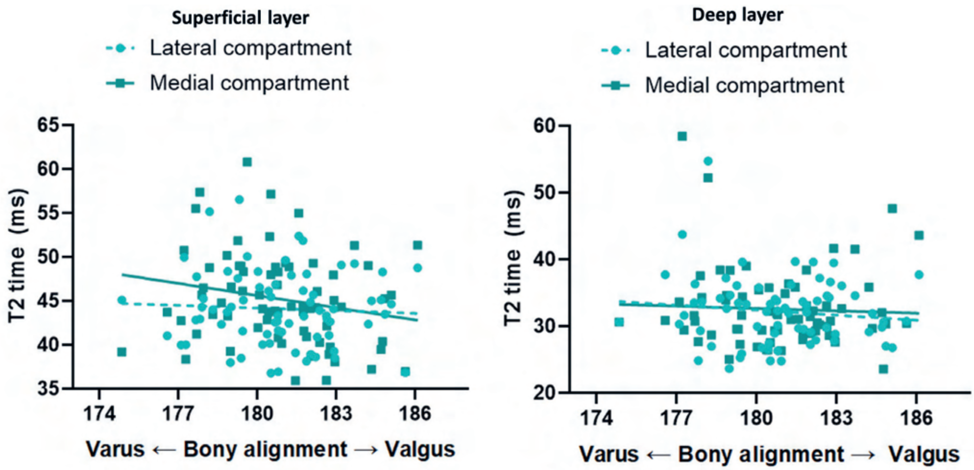

Figure 5 - Correlation between T2 time bony alignment of the 71 participants with JLCA values within the normal range for the superficial layer and deep layer of the medial and lateral compartment.

Table 4 - T2 times correlated to the bony alignment of the 71 participants with normal JLCA values.

	Spearman's rho	Confidence interval	P-value[a]
Bony alignment			
Deep layer of lateral compartment	-0.05	[-0.29; 0.19]	1.00
Superficial layer of lateral compartment	-0.04	[-0.28; 0.20]	0.97
Deep layer of medial compartment	-0.03	[-0.27; 0.21]	0.81
Superficial layer of medial compartment	-0.22	[-0.43; 0.03]	0.28

[a] *p* values corrected for multiple testing using the Benjamini–Hochberg

4. Discussion

This study examined the association between knee cartilage quality, assessed by T2 mapping, and lower limb malalignment. Prolonged T2 times, indicating lower cartilage quality, were generally observed in participants with higher K&L scores. This is a finding that confirmed previous work[172,240,256]. We evaluated entire leg alignment (mHKAA), bony alignment (reflecting tibial and femoral bowing), and intra-articular alignment (JLCA). All three measures were associated with reduced cartilage quality in the superficial layer of the medial compartment in varus knees and the lateral compartment in valgus knees. The strongest correlations with T2 values were observed for JLCA, while correlations with bony alignment were minimal. This suggests that the association between mHKAA and cartilage quality is primarily driven by intra-articular alignment, as mHKAA reflects both components. These findings highlight the need to distinguish between bony and intra-articular deformities in future osteotomy studies and clinical decision-making. In medial KOA with bony malalignment, osteotomy is generally effective. However, when malalignment is intra-articular only, surgical outcomes are less predictable[96]. Therefore, surgical planning should not rely solely on mHKAA; bony and intra-articular alignment must be assessed separately.

Furthermore, cartilage quality was also assessed in individuals with constitutional joint malalignment—defined by bony varus or valgus alignment without intra-articular deformity—to isolate the effect of limb alignment on T2 values. MRI T2 mapping was used to evaluate cartilage quality and potentially identifying those at elevated risk for unicompartmental KOA. In this subgroup, varus bone bowing was associated with higher T2 times in the medial compartment, but only in the superficial cartilage layer, while no such association was found for valgus alignment. The correlation between constitutional varus and elevated T2 times was weak and not statistically significant, likely due to insufficient statistical power (46%, $\rho = 0.22$, $\alpha = 0.05$, $N = 71$) of this subgroup analysis[255]. Nonetheless, a correlation of 0.3 is insufficient to reliably indicate reduced cartilage quality at the individual patient level. We hoped that T2 mapping could serve as a radiological biomarker to identify participants with constitutional malalignment and elevated T2 values, who may be at increased risk for developing KOA in the future. However, this hypothesis remains unconfirmed due to the absence of longitudinal T2, radiographic, and CT data in the IMI-APPROACH cohort. Moreover, the IMI-APPROACH cohort includes patients with symptomatic KOA, thereby excluding individuals with asymptomatic constitutional malalignment.

Regarding the mHKAA, a significant correlation was found only for varus malalignment in the superficial and deep layers of the medial compartment. This may be due to the fact that, in a neutral stance, approximately 70% of knee load passes through the medial compartment[22]. Varus alignment increases this load, leading to overload and cartilage degeneration, while valgus alignment distributes the load more evenly. These results align with Sharma *et al.*[22], who reported an association between malalignment and cartilage damage but did not distinguish between mHKAA, bony, and intra-articular alignment. Additionally, the higher prevalence of intra-articular varus compared to valgus (Table 2) may partly explain the observed correlation, given that mHKAA reflects both bony (mMPTA, mLDFA) and intra-articular (JLCA) deformities.

While previous studies on T2 mapping have focused on demographic and early OA indicators[172,252], our study specifically examined lower limb alignment. Our findings suggest that intra-articular malalignment may affect cartilage quality; however, due to the cross-sectional design of this study, causal interferences cannot be drawn. As abnormal JLCA can be detected on conventional radiographs, the added value of T2 mapping in symptomatic knees may be limited to a theoretical value. In participants with constitutional varus, elevated T2 values were observed in the medial compartment, though not statistically significant. This subgroup likely includes individuals with limited cartilage degeneration, as no severe bony varus or valgus deformities were present. Participants with such deformities may already exhibit cartilage loss and/or meniscal extrusion, resulting in an abnormal JLCA and their exclusion from the constitutional malalignment group. Additionally, we assessed both cartilage layers and found, consistent with previous research[257], that the superficial layer showed greater sensitivity to mechanical load, reflected by higher T2 values in participants with mild intra-articular malalignment.

Our study has several limitations. First, the additional analysis lacked statistical power due to the small number of participants with a JLCA within the normal range, which may explain the non-significant correlation between bony varus and increased medial T2 times. Only 30 participants (42.3%) showed constitutional malalignment, indicating a limited sample size of constitutional varus or valgus in our cohort. Moreover, there was a predominance of varus lower limb malalignment compared with valgus, which may further explain why no significant correlation was found between valgus malalignment and increased T2 times in the lateral compartment. Second, CT scans were acquired in a supine position rather than weight-bearing, which may have affected the accuracy of bony alignment assessment. However, Roth *et al.* [258] found minimal differences in bone deformities between weight-bearing and non-weight-bearing scans, while mHKAA and JLCA showed significant variation. Therefore, we used JLCA from weight-bearing radiographs to capture intra-articular alignment, and calculated mHKAA as the sum of non-weight-bearing bony alignment (from CT) and weight-bearing JLCA (from radiographs). Future improvements may include weight-bearing CT scanning[259], EOS imaging [260], or simulated standing CT reconstructions[261]. Third, interobserver variability of the K&L score is another limitation[262]. Further research may consider utilizing the JLCA as a measure of KOA instead of the K&L score. Fourth, we assessed only superficial and deep cartilage layers using T2 mapping and did not evaluate the subchondral bone that may also contribute to early cartilage pathology[263,264]. Lastly, although JLCA reflects intra-articular KOA severity through compartmental differences in cartilage loss or meniscal extrusion[159,245], our study did not include direct measures of these features. A varus or valgus JLCA already suggests the presence of cartilage loss and/or meniscal extrusion, both features of KOA.

5. Conclusion

This study demonstrates a significant relationship between lower limb alignment and cartilage quality, with alignment assessed in terms of whole-leg, bony, and intra-articular alignment. Our findings support the hypothesis that varus lower limb malalignment was associated with reduced cartilage quality in the medial compartment, whereas, contrary to our hypothesis, valgus lower limb malalignment was not associated with reduced cartilage quality in the lateral compartment. The strongest correlations were observed for intra-articular alignment. Therefore, future research should distinguish between bony and intra-articular malalignment when evaluating knee alignment. While varus bone bowing in our subgroup analysis showed a trend toward increased T2 values in the medial compartment, this finding was not statistically significant, likely due to the small sample size. Further studies are needed to determine whether bony malalignment plays a role in initiating cartilage degeneration and OA progression.

Part III

Optimizing Osteotomy Care in Knee Osteoarthritis

07

Chapter 7

Uncovering the Impact of Center of Rotation of Angulation Location on High Tibial Osteotomy in Knee Osteoarthritis: A Potential Pathway for Improved Outcomes

Yannick Janssen, H. Chien Nguyen, Roel J.H. Custers, Nienke van Egmond, Moyo C. Kruyt, Ralph J.B. Sakkers, Jaap Thooft, Margreet Kloppenburg, Francisco J Blanco, Ida K Haugen, Francis Berenbaum, Simon C. Mastbergen, Harrie Weinans, Eva A Bax

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Abstract

Objective: Lower limb malalignment accelerates the progression of knee osteoarthritis (KOA). Knee realignment osteotomy is a well-established treatment for unicompartmental KOA with malalignment. Traditional planning in KOA patients corrects deformities with an osteotomy at the metaphysis but overlooks Paley's approach, which targets the center of rotation angulation (CORA). Osteotomy at the metaphysis may induce secondary translational deformities, which remain unstudied in KOA patients. This study aims to identify the CORA in KOA patients with tibial malalignment.

Methods: Thirty tibiae (ten varus, ten neutral, ten valgus) from the IMI-APPROACH cohort were analyzed using CT scans. The CORA, defined as the intersection of the proximal and distal mechanical axes, was identified. Translational deformity was calculated by multiplying the CORA-to-osteotomy distance by the tangent of the correction angle.

Results: Among the varus tibiae, 9 out of 10 CORAs were located in the diaphysis, while 8 out of 10 valgus tibiae had their CORA in the diaphysis. When osteotomies were performed in the proximal metaphysis instead of the CORA location, secondary translational deformities of up to 3 cm were induced.

Conclusion: In KOA patients with tibial malalignment, the CORA is predominantly located in the diaphysis rather than in the proximal metaphysis, where osteotomies are typically performed. This discrepancy leads to iatrogenic translational deformities. Future research should investigate the clinical impact of these deformities to optimize osteotomy planning and potentially improve long-term surgical outcomes.

1. Introduction

Osteoarthritis (OA) affected 595 million people globally in 2019[4], with knee osteoarthritis (KOA) being the most common type[183]. As obesity and life expectancy rise[4,5,200,201,203], KOA prevalence increases[183]. Lower limb malalignment is a risk factor for KOA progression[23,182,265], shifting the knee's mechanical axis and accelerating cartilage degeneration[7,23,208,212]. Realignment osteotomies are a well-established treatment for younger patients to postpone knee arthroplasty[97,266,267], which is important as they have a higher risk of revision surgery[268].

Preoperative planning for knee osteotomy is essential for optimal outcomes[269]. Early methods like the Fujisawa point, Miniaci line, and Dugdale method[100], have evolved into the current planning nomenclature proposed by Paley[51]. Modern planning methods focus on calculating the desired wedge height for knee osteotomies, with corrections typically performed at the tibial and femoral metaphyseal ends[100,270,271]. Interestingly, Paley's approach extends beyond this conventional method by emphasizing the correction of deformities at their origin[51], a concept well-known in reconstructive surgery.

Building on this concept, the center of rotation angulation (CORA) is the point where the mechanical axes of a deformed bone intersect[51,227]. By correcting deformities at the CORA, the risk of introducing secondary translational deformities is minimized[51]. Tibial osteotomies for unicompartmental KOA are preferably performed at the proximal tibial end, as this region is characterized by superior bone healing due to its high trabecular density and vascularization[272–274] compared to the mid-diaphysis. Consequently, in these procedures, potential translation of the bone is often assumed and remains unaddressed. Therefore, our study aims to identify the CORA of patients diagnosed with KOA and associated tibial malalignment. This will provide crucial insights into the potential occurrence of iatrogenic deformities.

2. Methods

2.1 Patients

In the prospective Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) cohort, 297 KOA participants from five European centers were included[275–279]. Some of these participants also exhibited malalignment of the femur or tibia. Detailed inclusion and exclusion criteria have been previously published[143]. The study was approved by Institutional Review Boards, in accordance with all relevant ethical and legal regulations. The study was registered under clinicaltrials.gov number: NCT03883568, and informed consent was obtained from all participants.

2.2 Imaging assessment

All patients underwent low-dose whole-body computed tomography (CT) scans. The tibia and fibula were segmented from the CT scans using validated software (Mimics, Materialise, Leuven, Belgium). Bone geometry analyses were performed in 3-matic (Materialise, Leuven, Belgium). The analyses involved a semi-automated method as the functions were scripted in Python language (3-matc plugin).

2.2.1 3D tibial coordinate system

A patient specific 3D coordinate system was constructed per tibiae. The mechanical axis ran from the tibial eminences to the distal tibial plafond. The transversal plane had its origin at the tibial eminences, with the mechanical axis as normal vector. The sagittal plane, perpendicular to the transversal plane, crossed the posterior cruciate ligament attachment and medial tuberosity border (Akagi's line)[280]. The coronal plane, perpendicular to both transversal and sagittal planes, originated at the tibial eminences.

2.2.2 CORA calculation

The method fitted a plane to the articulating surface of the medial and lateral tibial plateaus (proximal tibial plane) and projected a line distally originating from the center of the eminence spines at an angle of 87° (coronal view) relative to the proximal tibial plane (proximal mechanical axis (PMA)) (Figure 1A). Additionally, a plane was fitted to the articulating surface of the distal tibial plafond (distal tibial plane), and a line was projected proximally at an 89° angle (coronal view) relative to the distal tibial plane (distal mechanical axis (DMA)), originating from the center of the distal tibial plafond (Figure 1A). The crossing of the two lines represented the CORA of the coronal tibial deformity, and the location of this CORA was calculated with respect to the tibial eminence center (knee joint center) (Figure 1A).

2.2.3 Bone deformity

Coronal bone deformities of the tibia, including the mechanical medial proximal tibial angle (mMPTA), was assessed using Paley's method[51]. The mMPTA was defined as the angle (coronal view) between the mechanical axis of the tibia and the tangent tot the proximal tibial plateau (Figure 1B). Neutral mMPTA ranged from 85° to 90°. A varus mMPTA was defined as <85°, while a valgus mMPTA was >90°[51]. A total of thirty tibiae were included: ten with a neutral mMPTA, ten with a varus mMPTA, and ten with a valgus mMPTA. Participants with tibial deformity were randomly selected to ensure a representative distribution of the mMPTA across the different alignment groups (neutral, varus, and valgus).

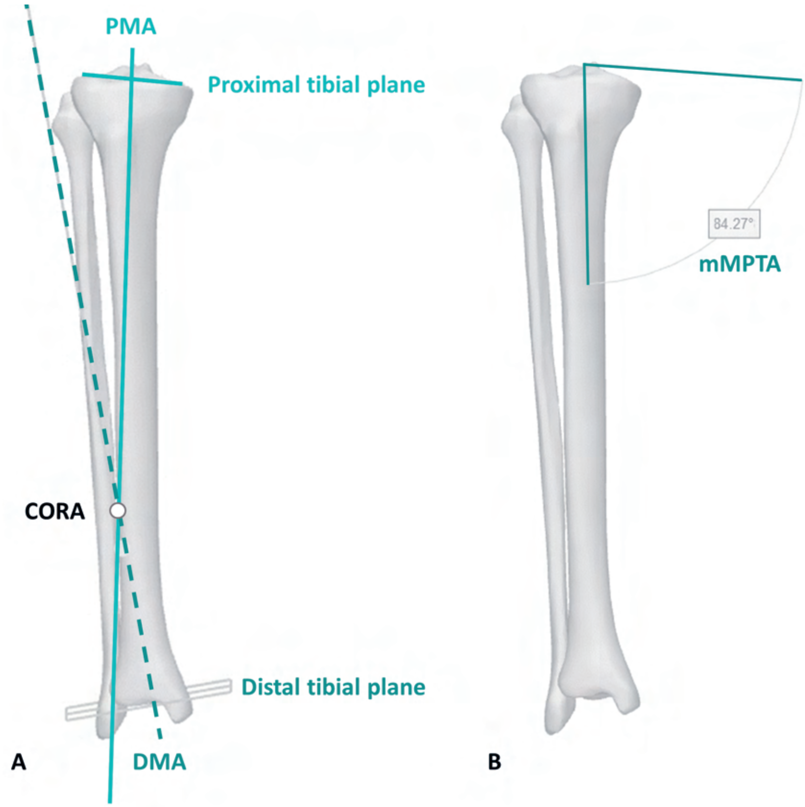

Figure 1 – Definition of the CORA and the mMPTA. A) The CORA (Center of Rotation of Angulation) is the intersection of the proximal mechanical axis (PMA, black dotted line) and the distal mechanical axis (DMA, grey line) of the tibia. B) The mMPTA (mechanical Medial Proximal Tibial Angle) is the angle formed between the mechanical axis of the tibia and the tangent of the proximal tibial plateau on the coronal plane.

2.3 The Concept of Secondary Translational Deformities in Osteotomies

In osteotomies, translation refers to the sideward displacement of the distal segment of the tibia. This occurs when the osteotomy is not performed at the CORA, which is the optimal location for performing an osteotomy without creating a secondary deformity[227]. The reason for this translation lies in the kinematics of the correction. A bone deformity creates an angular malalignment, and when an osteotomy is performed at a distance from the CORA, the bone must be corrected by rotating or angulating the distal segment to realign it with the proximal segment. This causes a sideward shift in the direction of the angular correction. Stated otherwise, when an osteotomy is performed outside the CORA, angular correction alone can render the PMA and DMA parallel while still malaligned, necessitating medial translation of the distal segment for complete alignment. See Figure 2.

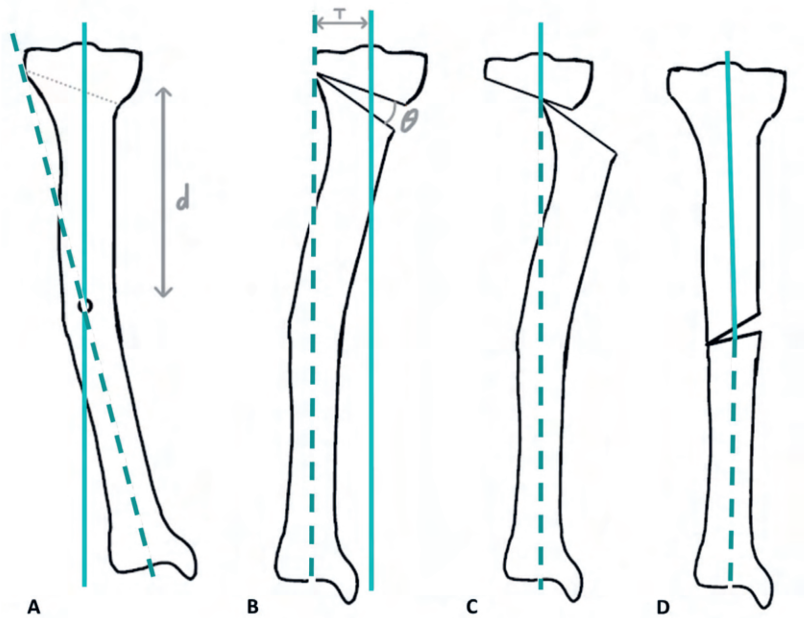

Figure 2 – The concept of iatrogenic translational deformities in osteotomies when the osteotomy is performed outside the CORA. The PMA is shown in red, the DMA in blue, and the CORA is marked by the green circle. A) The tibia with deformity. B) High tibial osteotomy performed away from the CORA leads to parallel PMA and DMA. C) Translation is required to realign the PMA and DMA. D) No translation is necessary when the osteotomy is performed at the CORA.

Translation is influenced by two factors: the distance from the CORA to the osteotomy site[281] and the correction angle[281]. Greater distance and larger correction angles increase translational displacement. The translation can be calculated by

$$T = d \times \tan(\theta) \qquad \text{(Equation 1)}$$

In this equation, T refers to the sideward displacement of the distal segment, d is the distance from the CORA to the osteotomy site, and θ is the correction angle (degrees) (Figure 2). For a varus tibia, the correction aimed to realign the mMPTA to 90°, whereas for a valgus tibia, the correction targeted an mMPTA of 85°. This aligns with clinical practice, where we apply slight overcorrection in KOA patients.

2.4 CORA location

In addition to assessing the magnitude of the secondary deformity, the location of the CORA was also evaluated. The location of the CORA on the tibia was defined as a percentage of the tibial length, with 100% representing the proximal end and 0%

representing the distal end. This method allowed for a descriptive analysis of CORA positions in tibiae with varus and valgus deformities. By comparing these positions, differences in CORA location between the two deformity groups were identified.

2.5 Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) Version 29.0 software. Descriptive statistics were computed, including means and standard deviations (SD) for continuous variables, and numbers and percentages for categorical data.

3. Results

3.1 Locations of CORA in the Tibia

A total of thirty tibiae were included in this study, consisting of ten individuals with varus alignment of the tibiae, ten with neutral alignment of the tibiae, and ten with valgus alignment, based on the mMPTA, all of whom presented with early-stage KOA. Most patients were female (73%), and the mean age was 62.9 ± 8.0 years. The mean mMPTA was 87.3 ± 3.3°.

In neutral tibial alignment, the mean mMPTA was 87.5 ± 1.4°. Since there was no deformity in these bones, the PMA and DMA (Figure 1) were nearly parallel, and no CORA was present (Figure 3A). In varus alignment, the mean mMPTA was 83.4 ± 1.0°. The CORA in the varus group was located within the proximal metaphyseal region in one case and within the diaphyseal region in nine cases (Figure 3B). In the valgus alignment group, the mean mMPTA was 91.0 ± 0.7°. The CORA of the valgus group was located within the metaphyseal region in two cases and within the diaphyseal region in eight cases (Figure 3C).

In the varus alignment group, the mean CORA was located at 54.9 ± 18.8% of the tibial length, ranging from 11.9% to 78.5% (Figure 4). In the valgus alignment group, the mean CORA was situated at 33.0 ± 15.9% of the tibial length, with a range from 4.1% to 51.6% (Figure 4). In the varus group, the CORA was located more distally than in the valgus group (Figure 4).

3.2 Secondary Translational Deformities in Osteotomies

For an angular correction of the varus mMPTA to 90°, the mean translation when performing the osteotomy on a varus tibia at the metaphysis, as opposed to at the CORA site, was 2.09 cm ± 0.85 cm, with a range from 0.17 cm to 3.04 cm. In contrast, for an angular correction of the mMPTA to 85° when correcting a valgus tibia, the mean translation was 0.96 cm ± 0.56 cm, with a range from 0.23 cm to 1.81 cm. Figure 5 illustrates the relationship between the distances from the CORA to the high tibial osteotomy plane and the corresponding calculated secondary translational deformity.

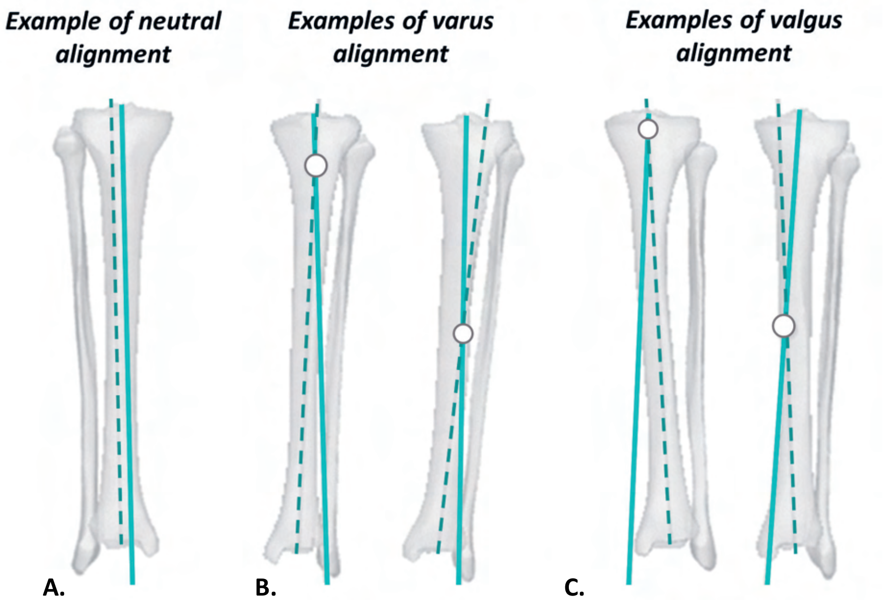

Figure 3 - Examples of CORA determinations in different tibiae. A) Neutral tibia, where the PMA (solid line) and DMA (dotted line) run nearly parallel, indicating no CORA. B) Varus tibia with an example where the CORA is in both the metaphyseal and diaphyseal regions. C) Varus tibia with another example of the CORA located in both the metaphyseal and diaphyseal regions.

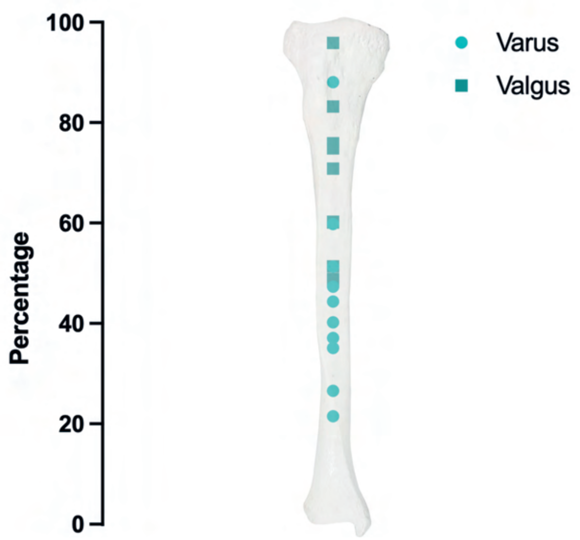

Figure 4 - CORA locations relative to tibial length, presented separately for varus and valgus tibiae, with 100% representing the proximal end and 0% representing the distal end.

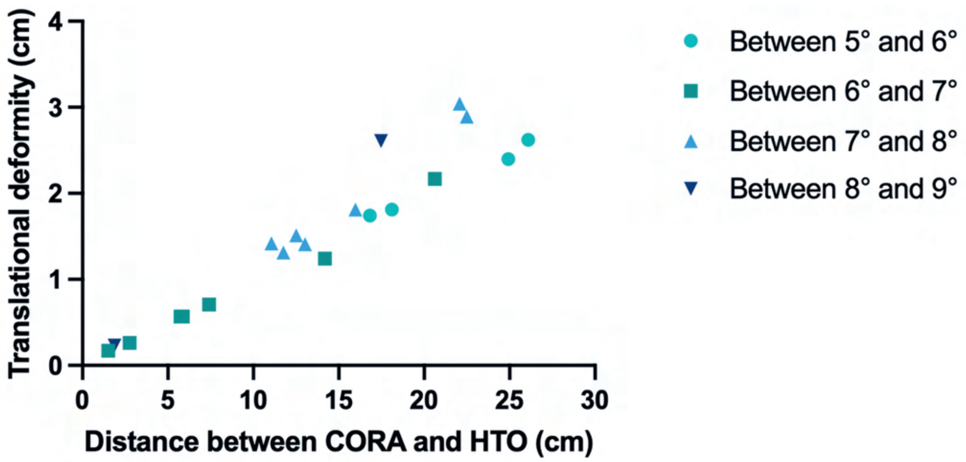

Figure 5 – Secondary translation deformity values are plotted against the distances measured between the CORA and the high tibial osteotomy plane. Distinctions were made for different correction angles, highlighting the relationship between the secondary translation and the correction magnitude.

4. Discussion

This study aimed to identify the CORA in KOA patients with tibial malalignment and explore secondary translation in tibial osteotomies not performed at the CORA, all conducted in a cohort comprising patients with KOA. A key finding was that 85% of the CORAs were in the diaphysis, leading to secondary translational deformities of up to 3 cm, a novel finding not previously reported in the knee osteotomy literature. Identifying and targeting the CORA during osteotomy planning may improve knee realignment and postoperative outcomes.

The clinical impact of these secondary translational deformities is unclear, as no studies have focused on the effect of CORA locations in KOA patients with tibial malalignment. Potential consequences may include altered gait mechanics, increased joint wear, and unfavorable force distribution within the affected compartment; however, these hypotheses require further investigation. Most existing research on osteotomies in KOA focuses on the mechanical hip-knee-ankle angle[23,282,283]. What we do know is that osteotomy is an effective treatment for relatively young KOA patients, as it can delay the need for knee arthroplasty by over 10 years[97,113,114,266]. Predictors for an increased likelihood of conversion to arthroplasty include radiographic OA severity, pain, female sex, age, and BMI, with radiographic OA severity being the strongest predictor[96,113]. While osteotomies are effective, improving long-term outcomes is crucial, especially as KOA increases in prevalence[183]. Optimizing osteotomy techniques could improve knee function and patient satisfaction, but further research is needed to validate these findings and assess their impact on clinical outcomes and the long-term effectiveness of osteotomies in KOA treatment.

In addition to the thirty tibiae analyzed, ten extra tibiae exhibited translational deformities (S-shaped) without prior osteotomy (Appendix A). These deformities can be conceptualized as a displacement in which the distal segment shifts relative to the proximal segment[51,227], which is also observed when an osteotomy is not performed at the CORA. In valgus mMPTA patients, the deformities show a varus mechanical lateral distal tibial angle. In such cases, two osteotomies with opposing corrections at each level are recommended[227]. These translational deformities, common in pediatric patients[284–286], can cause abnormal gait, joint wear, and premature OA[286]. To prevent these long-term complications, corrective osteotomies are often performed in children to align the bones properly.

Historically, osteotomies are performed in the metaphysis[100,287] due to better bone healing compared to the diaphysis[272–274]. The diaphysis consists primarily of dense cortical bone with less robust intraosseous blood supply, while the metaphysis is characterized by more metabolically active and vascular trabecular bone[272]. This difference likely contributes to higher rates of nonunion and hinge fractures in diaphyseal osteotomies[273,274]. Despite the risk of translation, the benefits of fracture healing often outweigh this concern. In practice, secondary translation is often overlooked, as the mechanical axis is shifted, which is the primary goal of the procedure.

The concept of secondary translational deformity has been described in the literature[51,227,281,286], but no studies have focused on CORA location in KOA patients with tibial malalignment. Barksfield *et al.*[281] concluded that translational deformities can be predicted by the angular correction and distance from the CORA. However, their study did not focus on KOA patients and involved smaller simulated distances. Our study shows that these distances can reach up to 3 cm, leading to larger translational deformities that require further investigation—although this was shown in a relatively small sample size. Therefore, future research is needed to evaluate CORA locations in a larger cohort of KOA patients with lower limb malalignment who are candidates for osteotomy. Future research should also assess the long-term effects of these deformities on knee function, survival rates, and patient outcomes. Moreover, the influence of these deformities on force distribution in the affected compartment should be explored, and whether performing osteotomies away from the CORA enhances or diminishes this effect.

High tibial osteotomy is indicated primarily to correct varus or valgus malalignment in unicompartmental KOA[102]. Feucht *et al.*[288] demonstrated that mild varus malalignment often results from a deformity in the joint line convergence angle (JLCA), not the bones themselves. In these cases, correcting the JLCA along with tibial realignment is recommended. Osteotomy in the proximal tibia is advantageous for JLCA deformities, but whether osteotomy is the right approach for JLCA deformities alone remains unclear. In clinical practice, during a high tibial osteotomy, correction of the JLCA is performed alongside tibial realignment. For patients undergoing osteotomy without bone deformities but with a deformity of the JLCA, performing the osteotomy in the proximal tibia is advantageous, as the CORA would lie within the knee joint for these patients. However, the question remains whether osteotomy is the appropriate indication for patients with only a deformity of the JLCA[96]. Further research is needed to better understand the optimal approach for patients with JLCA deformities.

Several limitations of this study should be acknowledged. The study included thirty tibiae, a small sample size, with the goal of raising awareness among orthopedic surgeons that the CORA in tibial malalignment is typically not always located in the proximal metaphysis. Additionally, the mean age of our cohort was higher than the typical age at which high tibial osteotomy is performed, which may affect the generalizability of our findings. Our study focused solely on patients with tibial malalignment. Future research should also examine its potential impact on femoral double-level osteotomies. Second, CORA determination was based on CT imaging, not whole-leg radiography, which remains the clinical gold standard. However, CT scans eliminate positioning factors[50], and Roth *et al.*[258] found minimal differences between weight-bearing and non-weight-bearing conditions for bony alignment. Third, in coronal alignment osteotomies for KOA patients, the osteotomy extends to the hinge point. Consequently, operating at the CORA inevitably induces minimal secondary translational deformity, as the center of rotation does not coincide with the CORA. Finally, the standardized correction angles used in this study may differ from individualized surgical planning, which could lead to different magnitudes of translational shifts and alignment outcomes. In clinical practice, surgeons increasingly avoid over-corrections, instead aiming for a more neutral alignment. Moreover, our analysis focused on secondary translation following a tibial osteotomy, whereas larger corrections in current practice are often managed with double-level osteotomies, which distribute the correction across two bones and, therefore, reduce the degree of secondary translation.

5. Conclusion

This study identified the CORA in patients with KOA and tibial malalignment, highlighting the secondary translational deformities that arise because of not performing the osteotomy at the CORA. We concluded that 85% of CORAs were in the diaphysis and not located in the proximal metaphysis, leading to secondary translational deformities of up to 3 cm after high tibial osteotomy. Future studies should focus on the clinical implications to possibly improve both its effectiveness and long-term sustainability of osteotomies.

Appendix

Figure A1 – Examples of the translational deformities in IMI-APPROACH, where the PMA and DMA run nearly parallel. The mean mMPTA and mLDTA were 91.0 ± 0.4 and 93.9± 1.6, respectively.

08

Chapter 8

What Is the Effect of a High Tibial Osteotomy on the Ankle Joint? In Most Patients, Ankle Alignment Worsens Due to a Valgus-Shaped Tibia

Sem Dorst, Roel J.H. Custers, Nienke van Egmond, Ralph J.B. Sakkers, Harrie H. Weinans, Eva A. Bax

Manuscript under review

Abstract

Purpose: Medial open-wedge high tibial osteotomy (MOW-HTO) is effective for correcting varus knee deformity but may unintentionally affect ankle joint alignment. This study investigated radiographic factors associated with postoperative ankle alignment changes following valgus-producing MOW-HTO.

Methods: Radiographic evaluation was performed on a prospective cohort of 50 knees from 49 patients who underwent MOW-HTO. Pre- and postoperative weight-bearing long-leg radiographs were analyzed to assess the bone related deformity of the tibia. Postoperative ankle alignment was classified as deviating closer to neutral or further from neutral. Correlation analyses and within- and between-group comparisons were performed, with significance set at $p < 0.05$.

Results: After MOW-HTO, all alignment parameters shifted toward valgus. Tibial deformity predominantly originated from the distal tibia, with a medial center of rotation of angulation (CORA), reflecting an overall valgus-shaped tibia. Distal tibial valgus showed a strong correlation with talar orientation relative to the ground ($\rho = 0.81$, $p < 0.001$). Patients deviating further from neutral had nearly 5° more distal tibial valgus than those deviating closer to neutral ($p < 0.001$), and more frequently showed an overall valgus-shaped tibia ($p < 0.01$). Additionally, larger correction angles were moderately associated with greater valgus shift of the ankle ($\rho = -0.44$, $p < 0.001$).

Conclusion: MOW-HTO results in a valgus shift of the talar orientation, particularly in patients with preoperative distal tibial valgus, an overall valgus-shaped tibia, and larger correction angles. Thorough preoperative assessment of tibial morphology is essential to better anticipate postoperative ankle alignment changes.

1. Introduction

Medial compartmental knee osteoarthritis (OA) is a common degenerative joint disease frequently associated with varus lower limb malalignment. Medial open-wedge high tibial osteotomy (MOW-HTO) is an effective joint-preserving treatment in which the mechanical medial proximal tibial angle (mMPTA)—the angle between the tibial plateau and mechanical axis of the tibia[227] —is corrected, thereby shifting load from the affected medial to the unaffected lateral compartment[96]. Favorable outcomes have been reported, with high patient satisfaction and improvements in pain and function[103–107,289–291]. However, MOW-HTO may also induce compensatory reorientation of the ankle joint[292–296], which can cause or increase ankle joint malalignment with concomitant ankle joint pain[293]. These changes may contribute to the development of ankle OA, ultimately leading to functional impairment and reduced quality of life[297].

In recent years, ankle joint alignment has gained increasing recognition as an important consideration in the context of MOW-HTO, although the factors contributing to postoperative ankle joint malalignment remain poorly understood[294]. A recent systematic review highlighted the need for studies that include both pre- and postoperative radiographic measurements to better identify risk factors for altered ankle joint alignment[292]. From a biomechanical perspective, several parameters are involved in postoperative ankle joint orientation. Following MOW-HTO, the mMPTA increases, shifting more toward valgus (Figure 1). Concurrently, the mechanical lateral distal tibial angle (mLDTA)—the angle between the mechanical axis of the tibia and the distal joint line1 —also typically shifts toward valgus (Figure 1). This valgus tendency is further reflected at the ankle joint, where the Ankle Joint Line Obliquity (AJLO)—defined as the angle between the talar dome and the horizontal plane[298] —generally tilts further into valgus (Figure 1). The center of rotation of angulation (CORA), defined as the intersection of the mechanical axes in a deformed bone1, indicates whether the tibia exhibits a deformity, as it reflects the relationship between the proximal and distal tibial joint lines. When the CORA is located more distally, the deformity primarily originates from the mLDTA, whereas a more proximal CORA indicates that the deformity arises from the mMPTA. In addition, the mediolateral position of the CORA provides insight into the overall alignment of the tibia: a medially located CORA is associated with an overall valgus alignment, while a laterally located CORA corresponds to an overall varus alignment. Consequently, the CORA influences changes in the AJLO; a medial CORA leads to alignment further from neutral, whereas a lateral CORA results in alignment closer to neutral.

Taken together, these observations suggest that the mLDTA, CORA location, and the degree of mMPTA correction may collectively influence postoperative AJLO, as a MOW-

HTO inherently creates a valgus alignment. Consequently, if the mLDTA or CORA already exhibit a valgus alignment preoperatively, the postoperative valgus alignment of the ankle joint may become further pronounced. To address this gap, the present study had two objectives. First, to determine the alignment of the tibiotalar in tibiae considered suitable for a valgus-producing MOW-HTO. Second, to investigate the association between the mLDTA, CORA location, and the degree of mMPTA correction with postoperative ankle joint alignment in patients undergoing MOW-HTO. A better understanding of these parameters may improve preoperative planning and reduce the risk of long-term ankle joint complications.

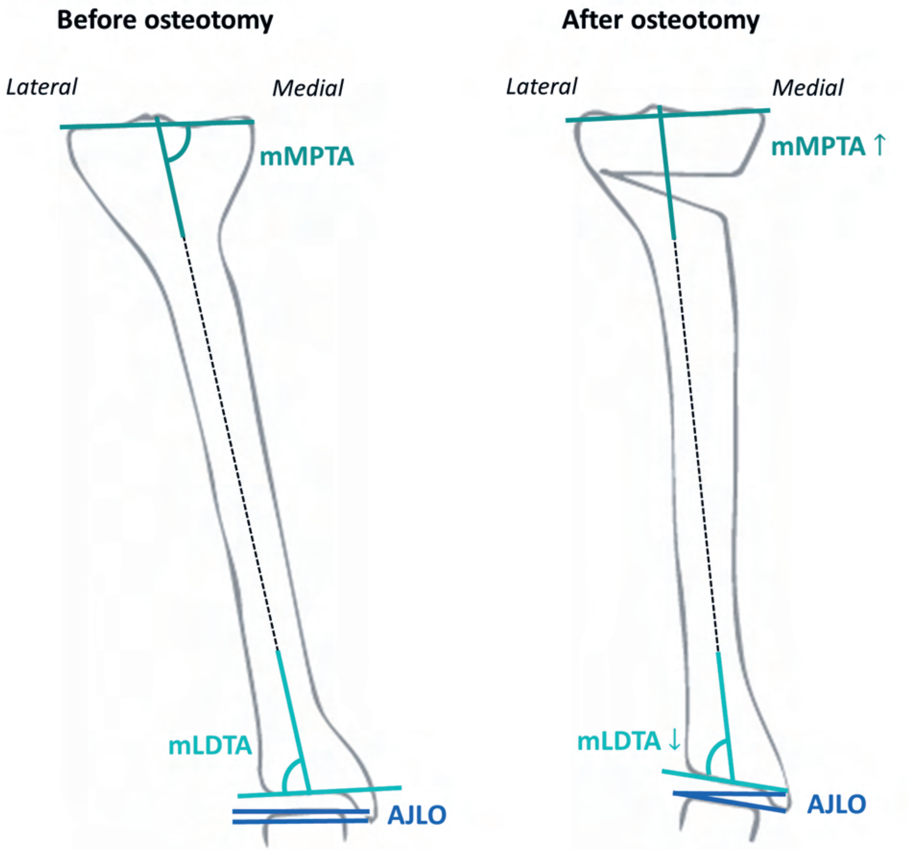

Figure 1 - Schematic representation of angular changes in lower limb alignment following MOW-HTO. The procedure results in an increase of the mMPTA, indicating a shift toward valgus alignment at the knee. Correspondingly, the mLDTA also tends to increase toward valgus. This valgus correction is further reflected at the ankle, where the AJLO typically changes from a neutral toward a more valgus alignment.

2. Methods

2.1 Study population

This study was a retrospective analysis of a prospective cohort of patients treated in a university medical center in the Netherlands. All patients who underwent MOW-HTO and were enrolled in the hospital's Knee Registry were considered for inclusion. Patients who underwent a distal femoral osteotomy or a double-level osteotomy were excluded from the study population. Demographic and clinical characteristics, including age, gender, body mass index (BMI), operated side, and degrees of correction were recorded. Patients were excluded if preoperative and/or four months postoperative weight-bearing long-leg radiographs (WLRs) were not obtained. This study does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). It therefore does not require approval from an accredited medical ethics committee in the Netherlands. However, an independent quality check has been carried out to ensure compliance with legislation and regulations (regarding informed consent procedure, data management, privacy aspects and legal aspects).

2.2 Radiographic Assessment

Pre- and postoperative WLRs were used to assess several coronal-plane radiological parameters, including the Hip-Knee-Ankle Angle (HKAA), mMPTA, Joint Line Convergence Angle (JLCA), mLDTA, CORA, and AJLO. The WLRs were acquired according to a previously published protocol[49].

The HKAA (Figure 2A) was defined as the angle between the mechanical axis of the femur and the tibia, while the mMPTA (Figure 2A) represented the angle between the mechanical axis of the tibia and the proximal tibial plateau. The JLCA (Figure 2A) was defined as the angle between the distal femoral and proximal tibial joint lines. The mLDTA (Figure 2A) indicated the angle between the mechanical axis of the tibia and the distal joint line of the tibia[227]. Normal values for these angles are presented in Table 1.

Table 1 - The alignment classification for normal, varus and valgus alignment.

	Valgus	Neutral	Varus
mMPTA	> 90°	|85° - 90°|	< 85°
JLCA	< 0°	|0° - 2°|	> 2°
mLDTA	< 86°	|86° - 92°|	> 92°

mMPTA, mechanical medial proximal tibial angle; JLCA, Joint Line Convergence Angle; mLDTA, mechanical lateral distal tibial angle

The AJLO (Figure 2B) was defined as the angle between the talar dome and the horizontal plane[298]. The change in AJLO (ΔAJLO) was calculated as the postoperative value minus the preoperative value, with negative values indicating a shift toward valgus and positive values indicating a shift toward varus. Patients were categorized into three groups based on ΔAJLO: those whose ankle joint alignment deviated closer to neutral (N = 13), those with unchanged alignment (change between −1° and +1°, N = 9), and those whose alignment deviated further from neutral (N = 28).

The CORA (Figure 2C) was defined as the intersection of the proximal and distal mechanical axes (PMA and DMA) of the tibia. The PMA, representing the mechanical axis of the proximal tibia, was drawn through the center of the proximal tibia at a medial angle of 87° relative to the proximal tibial joint line[227]. The DMA, representing the mechanical axis of the distal tibia, was drawn through the center of the distal tibia at a lateral angle of 89° relative to the distal tibial joint line[227]. Patients were categorized into two groups based on the presence or absence of a CORA. Furthermore, patients with a CORA were subcategorized according to its location—medial, lateral, or within the tibial shaft—as a medially located CORA is associated with an overall valgus alignment, whereas a lateral located CORA corresponds to an overall varus alignment. Moreover, patients were further classified based on the proximal or distal position of the CORA, with a more proximally located CORA indicating that the deformity arises from the mMPTA, whereas a more distally located CORA suggests that the deformity primarily originates from the mLDTA.

All measurements were performed by a single observer using standardized methods within the Picture Archiving and Communication System (PACS, Sectra AB, Linköping, Sweden). Measurements were recorded and subsequently verified by a second observer.

2.3 Potential Risk Factors for Ankle Joint Malalignment

Potential risk factors for postoperative ankle joint malalignment after MOW-HTO were evaluated using radiographic and geometric parameters, with the AJLO as the outcome measure. First, the mLDTA was analyzed. Second, the presence and location of the CORA were assessed and classified as medial (indicative of valgus alignment), lateral (indicative of varus alignment), or within the tibial shaft. Third, the position of the CORA was expressed as a percentage of the tibial length, with 100% corresponding to the proximal tibia and 0% to the distal tibia. Finally, the influence of the correction angle was examined.

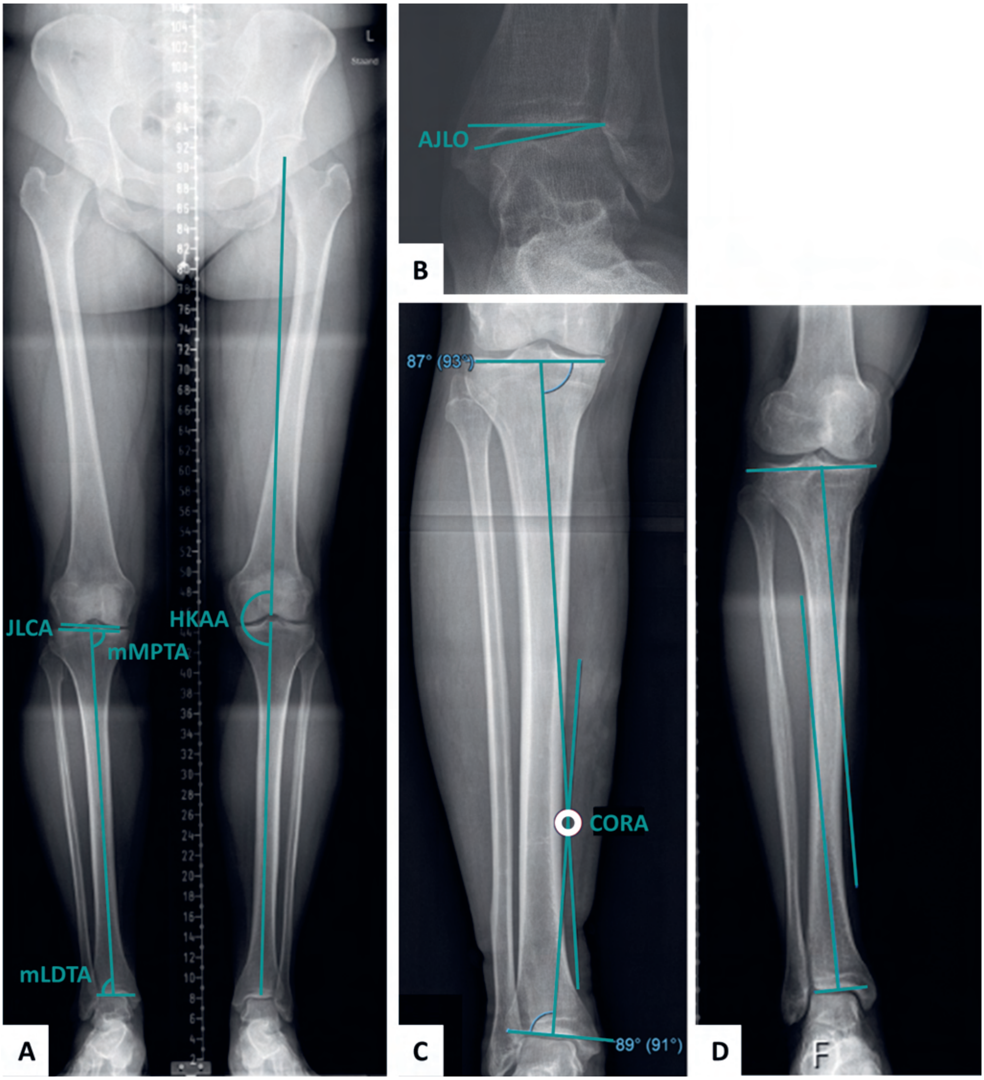

Figure 2 - Radiographic measurements on whole leg radiographs. A) Hip-Knee-Ankle Angle (HKAA), Medial Proximal Tibial Angle (mMPTA), Joint Line Convergence Angle (JLCA), and mechanical Lateral Distal Tibial Angle (mLDTA). B) Valgus Ankle Joint Line Obliquity (AJLO) C) Center of Rotation and Angulation (CORA), located medially. D) CORA absent as the lines of the mechanical axes are parallel.

2.4 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 30 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviations (SD) or median (interquartile range (IQR)), depending on normality, which was assessed using the Shapiro-Wilk test. Paired t-tests and Wilcoxon Signed Ranks tests were used for within-group comparisons, while independent t-tests and Mann-Whitney U tests were applied for between-group comparisons. Spearman's rho was used to assess correlations, and categorical variables were compared using the Chi-squared test. P-values < 0.05 were considered statistically significant.

A post hoc power analysis was performed using G*Power 3.1[255] (Heinrich-Heine-Universität, Düsseldorf, Germany). Based on an observed mean difference in AJLO of 4.8 ± 2.7°, the estimated effect size was 1.78, corresponding to a required sample size of 6 patients to detect a statistically significant difference with 90% power (α = 0.05).

3. Results

3.1 Study population

A total of 50 knees from 49 patients were included, of whom 58% were male. The mean age was 46.3 ± 8.2 years, and the mean BMI was 26.8 ± 3.2 kg/m^2. The mean interval to postoperative weight-bearing radiographs was 3.7 ± 2.5 months.

Postoperatively, the HKAA, mMPTA, mLDTA, and AJLO all shifted significantly toward valgus alignment compared with preoperative values (Table 2). Specifically, for the AJLO, two ankle joints (4.0%) remained in varus, one ankle joint (2.0%) showed no change, and 47 ankle joints (94.0%) shifted to valgus following MOW-HTO.

Table 2 – Preoperative and postoperative radiographic coronal alignment parameters following MOW-HTO.

	Preoperative	Postoperative	P-value
HKAA (mean ± SD)	184.3 ± 2.5°	178.5 ± 2.5°	< 0.001
mMPTA (mean ± SD)	86.2 ± 2.2°	91.2 ± 3.1°	< 0.001
JLCA (median (IQR))	2.0° (2.0°)	2.0° (2.0°)	0.13
mLDTA (median (IQR))	86.0° (6.0°)	85.0° (4.0°)	< 0.01
AJLO (median (IQR))	1.0° (6.0°)	−4.0° (4.0°)	< 0.001

HKAA, Hip-Knee-Ankle Angle; SD, Standard deviations; mMPTA, Mechanical medial proximal tibial angle; IQR, Interquartile range; JLCA, Joint Line Convergence Angle; mLDTA, Mechanical lateral distal tibial angle; AJLO, Ankle joint line obliquity.

3.2 Effect of mLDTA on ankle joint alignment

Preoperatively, 23 (46.0%) tibiae demonstrated a valgus mLDTA (mean 82.1 ± 2.9°), 2 (4.0%) a varus mLDTA, and 25 (50.0%) a neutral mLDTA (mean 88.5 ± 1.9°). Preoperative mLDTA was strongly and positively correlated with preoperative AJLO (ρ = 0.81, $P < 0.001$, 95% CI 0.68 to 0.89; Figure 3A). A more valgus mLDTA was associated with a more valgus orientation of the AJLO.

Analysis of AJLO changes after MOW-HTO revealed that patients whose ankle joint alignment deviated further from neutral had a statistically significantly lower preoperative mLDTA (84.5 ± 3.6°) compared with those whose alignment deviated closer to neutral (89.2 ± 3.6°; $P < 0.001$), indicating more preoperative valgus alignment in the group that deviated further from neutral (Figure 3B).

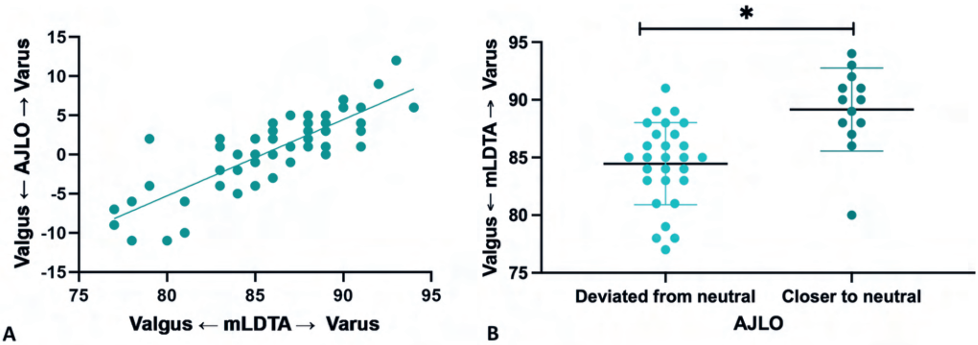

Figure 3 - Relationship between preoperative medial lateral distal tibial angle (mLDTA) and ankle joint line obliquity (AJLO). A) Scatter plot showing a strong positive correlation between preoperative mLDTA and preoperative AJLO. B) Swarm plot illustrating the preoperative mLDTA in patients whose AJLO deviated further from neutral and those whose AJLO deviated closer to neutral, showing significantly more valgus mLDTA values in patients whose alignment deviated further from neutral.

3.3 Effect of CORA on ankle joint alignment

A CORA was present in 33 knees (66.0%, Figure 2C) and absent in 17 knees (34.0%, Figure 2D). Among knees with a CORA, it was located medially (indicative of valgus alignment) in 15 knees (45.5%, Figure 2C), laterally (indicative of varus alignment) in 8 knees (24.2%), and within the tibial shaft in 10 knees (30.3%).

The median location of the CORA as a percentage of the tibial length was 20.5% (IQR 52.0), with 100% representing the proximal tibia and 0% the distal tibia (Figure 4A). This indicates that, on average, the CORA was located in the distal fifth of the tibia. There was a statistically significant moderate correlation between the location of the CORA (as a percentage of the tibial length) and the preoperative mLDTA (ρ = -0.55, $P < 0.001$, 95% CI -0.76 to -0.25). A preoperative valgus mLDTA was significantly associated with a more distally located CORA (Figure 4B).

Chapter 8

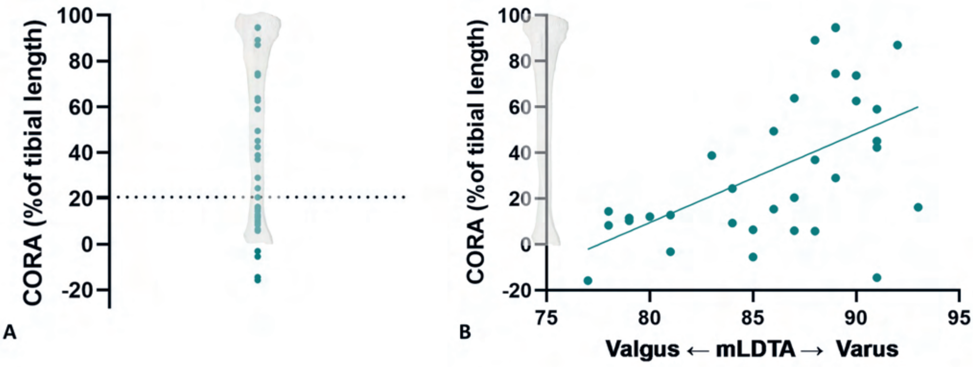

Figure 4 – CORA location expressed as a percentage of the tibial length. A) Distribution of the CORA location, with the dotted line indicating the median value at 20.5%. B) Scatter plot showing the relationship between CORA location (% of tibial length) and the preoperative mechanical lateral distal tibial angle (mLDTA). A more valgus mLDTA was associated with a more distally located CORA.

Analysis of CORA characteristics in relation to AJLO changes showed no statistically significant differences in the presence or absence of a CORA between the groups whose ankle alignment deviated closer to neutral (77% present, 23% absent) and those whose alignment deviated further from neutral (60.7% present, 39.3% absent) ($P = 0.63$) (Figure 5A). Similarly, the location of the CORA as a percentage of the tibial length did not differ significantly between the two groups (52.5% vs. 14.4%, $P = 0.22$) (Figure 5B).

In contrast, CORA location differed significantly between groups. Medial CORAs (valgus tibia) were more frequent in patients whose ankle joint alignment deviated further from neutral (42.9%) compared with those whose alignment deviated closer to neutral (7.7%) ($P < 0.01$), whereas lateral CORAs (varus tibia) were more common in patients whose alignment deviated closer to neutral (46.2%) than in those whose alignment deviated further from neutral (3.6%) ($P < 0.01$) (Figure 5C). The mean ΔAJLO was 2.7 ± 4.2° toward valgus for medial CORAs and 5.5 ± 4.4° toward valgus for lateral CORAs; this difference did not reach statistical significance ($P = 0.15$).

3.4 Effect of mMPTA correction on ankle joint alignment

The median correction angle was 7.0° (2.0°). A moderate negative correlation was observed between the correction angle and ΔAJLO ($\rho = -0.44$, $P < 0.001$; Figure 6), indicating that larger correction angles were associated with a greater shift toward valgus AJLO. However, no statistically significant difference in correction angle was found between ankles that deviated closer to neutral (7.0° (4.0°)) and those that deviated further from neutral (6.0° (3.0°); $P = 0.19$).

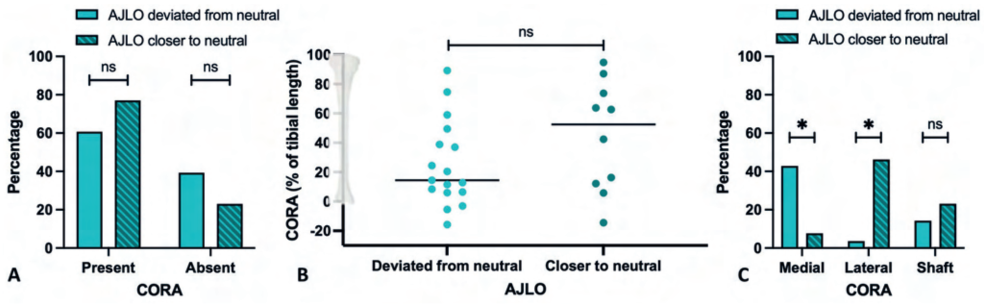

Figure 5 - Comparison of CORA characteristics between patients whose AJLO deviated further from neutral and those whose AJLO deviated closer to neutral. A) Proportion of tibiae with and without a visible CORA, showing no significant difference between groups. B) Swarm plot of CORA location as a percentage of tibial length, showing no significant difference between groups; horizontal lines indicate medians. C) Distribution of CORA location categorized as medial, lateral, or within the tibial shaft, with significantly more medial CORAs in patients whose alignment deviated further from neutral and more lateral CORAs in those whose alignment deviated closer to neutral.

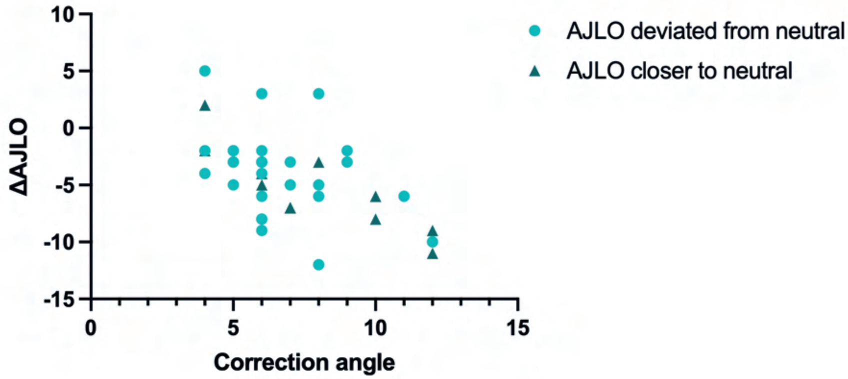

Figure 6 - Relationship between the correction angle and change in ankle joint line orientation (ΔAJLO). Data are shown according to AJLO outcome groups: deviated from neutral and closer to neutral.

4. Discussion

In this study, we aimed to evaluate the alignment of the tibiotalar joint in tibiae considered suitable for valgus-producing MOW-HTO. Preoperatively, 46.0% of tibiae demonstrated a valgus mLDTA, 50.0% a neutral mLDTA, and 4.0% a varus mLDTA. In most cases, the CORA was located medially, indicating an overall valgus tibial alignment. The CORA was located in the distal fifth of the tibia, suggesting that the deformity primarily originated from the distal tibial alignment, as reflected by the mLDTA. These findings suggest that, in these patients indicated for valgus-producing

MOW-HTO, the tibial deformity primarily originates from the distal tibia (mLDTA) rather than from the proximal tibia (mMPTA).

A secondary aim of this study was to investigate factors contributing to postoperative changes in AJLO in patients undergoing valgus-producing MOW-HTO, with specific focus on the mLDTA, the CORA, and the degree of mMPTA correction. Preoperative mLDTA was strongly correlated with preoperative AJLO, suggesting that the distal tibial alignment strongly influences the orientation of the ankle joint line preoperatively. This subgroup of patients may potentially benefit from conservative treatment options such as the use of inlays, which warrants further investigation. Patients whose ankle alignment deviated further from neutral after MOW-HTO had significantly lower (more valgus) preoperative mLDTA compared with those whose alignment deviated closer to neutral, suggesting that preexisting valgus alignment of the distal tibia predisposes to further deviation from neutral in postoperative ankle joint alignment. A moderate positive correlation was found between the preoperative mLDTA and the CORA location (as a percentage of the tibial length), with a more valgus mLDTA being associated with a more distally located CORA. Moreover, patients whose postoperative ankle joint alignment deviated further from neutral exhibited significantly more medially located CORAs—consistent with valgus alignment—than those whose alignment moved closer to neutral. In other words, when the tibial deformity originates medially (valgus-type CORA), the ankle joint tends to shift further into valgus after correction. Although the CORA tended to be located more distally in patients whose ankle alignment deviated further from neutral compared with those whose alignment deviated closer to neutral, this difference did not reach statistical significance. Finally, a moderate negative correlation was observed between the correction angle and ΔAJLO, indicating that larger correction angles were associated with a shift of the ankle joint line toward valgus. These findings highlight the importance of assessing distal tibial alignment when evaluating candidates for valgus-producing MOW-HTO in order to minimize potential postoperative ankle joint complications.

Furthermore, as expected after a MOW-HTO, the HKAA, mMPTA, and mLDTA all shifted toward valgus, confirming the intended correction effect of the procedure. This valgus shift in mLDTA is in line with biomechanical principles; however, the literature on this topic is not entirely consistent. While some studies report a significant change in mLDTA after osteotomy[294], others have found no statistically significant difference[299]. Interestingly, the CORA could be identified in 66% of cases, while it was absent in 34%. To our knowledge, no previous studies have reported on the prevalence of the CORA in adult patients with varus malalignment. The absence of a CORA may be explained by either a straight tibia without evident malalignment, or by a primarily translational deformity characterized by an S-shaped tibial contour (Figure 2D), leading to non-intersecting mechanical axes[227].

Postoperative changes in ankle joint alignment following MOW-HTO seem to have important clinical implications. New-onset unexplained ankle symptoms have been reported in 14–20% of cases, with a mean onset of symptoms around 20 months after surgery[300,301]. Ankle joints that are less parallel to the ground postoperatively are associated with significantly more ankle pain compared to those with more neutral alignment at a mean follow-up of over two years[293]. Moreover, patients with preexisting ankle OA experience a significant worsening of pain after MOW-HTO[300–302], and ankle joint alignment deviated further from neutral has been associated to increased patient-reported pain and may contribute to the development or progression of ankle OA, resulting in functional impairment and reduced quality of life[293,297,303]. Although some studies found no association between postoperative ankle joint alignment and short-term clinical outcome scores at one year[304], the long-term data suggest that malalignment can have meaningful consequences. Taken together, these findings indicate that patients with a valgus alignment of the distal tibia may be particularly susceptible to postoperative ankle joint related complications, highlighting the need for careful consideration of whether these patients truly benefit from proximal tibial osteotomies.

At birth, the lower limbs show a varus alignment that gradually shifts to valgus, peaking around 3–5 years of age, and stabilizing by age seven to a physiological pattern similar to adults, typically with a slight varus HKAA and mMPTA[53,54]. In our cohort, the HKAA shows varus alignment, whereas the mLDTA appears neutral or valgus. While 64–75% of patients with knee OA[60–62] and 13–25% of individuals without knee OA[55–58] have a varus knee alignment, comparable data for mLDTA are scarce. Limited evidence suggests that men tend to have a more valgus mLDTA than women[305]. These findings raise questions about the underlying deformity patterns observed in patients undergoing corrective osteotomy. A MOW-HTO is typically performed to correct a varus deformity of the knee by creating a valgus-producing osteotomy in the proximal tibia. However, in our cohort, 15 patients demonstrated a valgus tibial alignment, as indicated by a medially located CORA. This implies that knee surgeons frequently perform a valgus-producing osteotomy on a tibia that is already in valgus when considering the CORA location. Among these, 12 patients showed a postoperative deviation of ankle alignment further from neutral following MOW-HTO. Future studies should investigate whether modified surgical strategies, such as a double-level osteotomy involving both proximal and distal tibial corrections, could prevent postoperative deterioration of ankle joint alignment and potentially improve clinical outcomes. A distal tibial osteotomy alone primarily alters alignment within the distal tibia and therefore has no direct effect on the HKAA or on the mechanical load distribution across the knee joint. Combining proximal and distal corrections may, however, allow for a more balanced restoration of both knee and ankle alignment.

In recent years, several studies have reported significant alterations in coronal ankle joint alignment following MOW-HTO[293,294,306]. Lower preoperative mLDTA values have been associated with a more valgus ankle joint orientation[292–294,306], and the degree of coronal correction has been correlated with the magnitude of AJLO change[293,301]. However, no studies have yet examined the influence of CORA location on postoperative ankle joint alignment. Building on this, the present study combines a biomechanical rationale with clinical validation, not only theorizing the effect of mLDTA, CORA location, and correction magnitude on ankle joint alignment but also confirming these relationships using radiological patient data. This approach provides new insights into preoperative radiological parameters that are associated with postoperative ankle joint orientation and may guide more individualized surgical planning. The sample size was substantial, and all patients underwent standardized postoperative whole-leg radiographs at four months, ensuring consistent assessment of coronal alignment.

Despite the strengths, several limitations should be considered. First, for ankle joint alignment, only AJLO was assessed in this study, whereas other parameters, such as talar tilt, were not included. Second, clinical outcome data were limited, restricting the ability to directly correlate radiographic changes with patient-reported outcomes, especially the long-term clinical effect on the ankle joint. Third, the relatively short follow-up period may have influenced AJLO measurements, as recent evidence suggests that AJLO can continue to change for up to 12 months postoperatively[307]. Fourth, all radiographic measurements, including mLDTA, CORA, and AJLO, were performed by a single observer and subsequently checked by a second observer, providing internal verification, although measurements were not performed independently. Nevertheless, the measurement of mLDTA and CORA in patients with knee varus malalignment undergoing MOW-HTO provides valuable insight into which individuals may be at risk of postoperative deterioration in ankle joint alignment. These findings raise the possibility that patients with a valgus mLDTA could benefit from modified surgical strategies, such as additional distal tibial corrections, to prevent postoperative malalignment; however, this hypothesis requires further investigation in future studies.

5. Conclusion

In conclusion, this study aimed to determine the tibiotalar alignment in tibiae considered suitable for a valgus-producing MOW-HTO and to investigate the relationship between the mLDTA, CORA location, and the degree of mMPTA correction with postoperative ankle joint alignment. The findings indicate that the CORA was most frequently positioned medially within the distal tibia, suggesting an overall valgus configuration of the tibia. This shape is mostly the consequence of a valgus mLDTA and is associated with postoperative deviation of ankle joint alignment further from neutral, resulting in an even more valgus shape. Moreover, larger mMPTA correction angles correlated with greater postoperative changes in ankle joint alignment. These findings emphasize the importance of a comprehensive preoperative evaluation of tibial morphology to better anticipate postoperative talar changes.

09

Chapter 9

Four Decades of High Tibial Osteotomy: Trends in Technique, Fixation, and Concomitant Procedures

Eva A. Bax, Jan Eric Rohdenburg, Rana A. Ahmad, Nienke van Egmond, Michael J. Stuart, Aaron J. Krych, Mario Hevesi, Daniel B.F. Saris

Manuscript in preparation

Abstract

Background: High tibial osteotomy (HTO) is a treatment for knee osteoarthritis and facilitates concomitant joint-preserving procedures. Building on this role, the present study aimed to analyze longitudinal trends in HTO procedures, fixation strategies, and their use alongside concomitant treatments over the past decades, using comprehensive patient-level data from a large United States academic medical center.
Methods: Operative records were examined to identify HTO cases, yielding 840 procedures performed between 1988 and 2025. Collected data included patient age and gender, osteotomy technique (open vs. closed wedge), correction type (varus vs. valgus), fixation method (staples vs. plates), preoperative diagnosis, and any concomitant procedures.
Results: HTO volumes were highest between 1990 and 1997, followed by a decline and a renewed increase from 2012 onward. Valgus-producing osteotomies accounted for 94% of cases, while varus- and slope-correcting osteotomies were rare (2% and 1%, respectively). Closed-wedge techniques predominated before 2000 (56%), shifting gradually to open-wedge osteotomies thereafter (44%). Similarly, fixation evolved from staples, primarily used before 2000, to plates, which became the predominant method after 2000 (50% vs. 49%). Overall, 18% of HTOs were performed to facilitate concomitant procedures, with an increasing focus in the past decade.
Conclusions: Over four decades, HTO practice has evolved from closed- to open-wedge techniques and from staple to plate fixation, with a marked increase in procedures performed to enable concomitant joint-preserving interventions. These trends underscore HTO's enduring role in managing knee osteoarthritis and optimizing outcomes of combined surgical treatments.

1. Introduction

Osteotomy, derived from the Greek words *osteo* (bone) and *tomy* (cut), is a surgical technique with a history spanning over 2,000 years, traditionally used for the correction of limb deformities[100,101,308]. High tibial osteotomies (HTO) are widely performed for two purposes. The first is to achieve realignment, thereby transferring the weight-bearing load from a damaged area of the joint surface to a healthier, undamaged area[96]. The second is to facilitate concomitant joint-preserving procedures, such as (osteo)chondral interventions and meniscal treatments[94,309–311].

The concept of deformity correction dates back to Hippocrates (460–370 BC), who utilized the Hippocratic Scamnum, a traction device for bone realignment[312–314]. In the sixteenth century, osteoclasia, an early form of osteotomy, involved deliberately fracturing a deformed bone and stabilizing it in a corrected position to allow for proper healing[312–314]. In 1835, John Rhea Barton performed the first documented surgical knee osteotomy, a supracondylar wedge femoral procedure for an ankylosed knee[315,316], at a time when anesthesia was not yet available[317,318]. By the 1850s, Langenbeck—applying surgical techniques adapted from his experiences in the Schleswig–Holstein War—performed several osteotomies, which at the time carried a high risk of infection due to the absence of aseptic methods[319,320]. This problem was later addressed in 1879, when William Adams introduced subcutaneous osteotomy with antiseptic principles, significantly reducing infections[319]. A major milestone occurred in 1880 with Macewen's publication of the first dedicated osteotomy book, reporting 1,800 successful cases[315]. The spread of these techniques, supported by improved instruments and aseptic precautions, contributed to the growing popularity of osteotomy for deformity correction[321].

In the twentieth century, osteotomy was introduced as a treatment for knee osteoarthritis (KOA). In 1948, Brittain was the first to perform distal femoral osteotomy for adults with lateral compartment KOA[322]. Around the same time, Wardle reported his series of HTOs as a treatment for medial compartment KOA[323]. His results showed complete pain relief in all patients, with very few significant complications[323]. By 1964, the value of HTO in delaying joint degeneration was well established[324]. In 1985, Coventry refined the procedure by securing lateral closing-wedge HTOs with one or two staples, allowing early weight bearing[325]. He concluded that patients with early, symptomatic unicompartmental KOA remain ideal candidates for osteotomy—a principle that largely holds true today[325].

Following Coventry's refinement of staple fixation for lateral closing-wedge HTOs[325], osteotomy fixation continued to evolve. In 1971, AO T-plates were first reported for stabilizing osteotomies, providing greater mechanical support than staples alone[308]. By 2000, dedicated plates for medial opening-wedge HTOs were introduced[326–328], enabling more widespread use of opening-wedge procedures. This development reduced the need for tibial closed-wedge osteotomies, which require a fibular osteotomy and are associated with higher rates of neurovascular complications[329–331]. Modern anatomically contoured locking plates now offer both improved safety and stable angular fixation[100].

Building on the historical evolution of osteotomy techniques and fixation methods, this study aims to analyze the longitudinal trends in HTO procedures, fixation strategies, and their use alongside concomitant procedures over the past decades, using comprehensive patient-level data from a large academic medical center to assess how surgical practice has developed in response to technological and procedural advancements.

2. Methods

A comprehensive search of operative records was conducted to identify cases of HTO, using the terms “high tibial osteotomy,” “upper tibial osteotomy,” and “proximal tibial osteotomy,” including 14 variants. This search yielded 840 HTO procedures performed between 1988 and 2025 in one academic hospital in the United States.

For each procedure, data were collected on the date of osteotomy, patient age, and gender. Surgical details included the osteotomy technique (open- versus closed-wedge), type of osteotomy (varus- or valgus-producing), method of fixation (staples versus plates), and preoperative diagnosis. Furthermore, combined treatments were collected and categorized into diagnostic arthroscopy, chondroplasty/debridement, meniscus repair, meniscal transplantation, ligament reconstruction, cartilage treatment, osteochondral treatment, or combined procedures group. HTO procedures performed to facilitate or support another intervention, such as (osteo)chondral treatment, were classified as concomitant treatments.

3. Results

3.1 High Tibial Osteotomies Volume and Patient Demographics

The first recorded procedure in our cohort was performed by Dr. Bernard Morrey on July 26, 1988: a lateral closed-wedge high tibial osteotomy stabilized with staple fixation, with a radiograph 20-year post-osteotomy shown in Figure 1. Analysis of the annual number of procedures demonstrated that the highest numbers of HTOs occurred between 1990 and 1997 (Figure 2A). Thereafter, a decline was observed, followed by a renewed increase in procedure numbers beginning around 2012, continuing through the most recent years of observation.

Figure 1 - Radiograph, 20 years postoperatively, of the first recorded lateral closed-wedge high tibial osteotomy.

Over the four decades, the mean age at which patients underwent HTO gradually decreased, reflecting a trend toward earlier surgical intervention (Figure 2B). From 2014 onward, a slight increase in mean age was observed, although it remained lower than in earlier decades. Regarding gender, nearly every year more men than women underwent HTO, with men accounting for 70% of all patients across the entire study period.

3.2 Surgical Approaches in High Tibial Osteotomy

Valgus- producing osteotomies were performed in the majority of patients (94%) (Figure 3A). Varus- producing osteotomies were rare, accounting for only 18 patients (2%) over the entire study period (Figure 3B). Tibial slope–correcting osteotomies were performed in 1% of cases, with most of these procedures carried out in the past decade (Figure 3B). The first tibial slope–correcting osteotomy was performed on June 11, 1992, for a preoperative diagnosis of posterolateral instability. The procedure involved an anteromedial opening-wedge osteotomy of the proximal tibia.

Re-do osteotomies, performed due to nonunion, malunion, or post-osteotomy malalignment, accounted for 2% of cases (Figure 3B). Given the low numbers, varus-producing osteotomies, slope-reducing osteotomies, and re-do osteotomies are presented in Figure 3B according to four time periods.

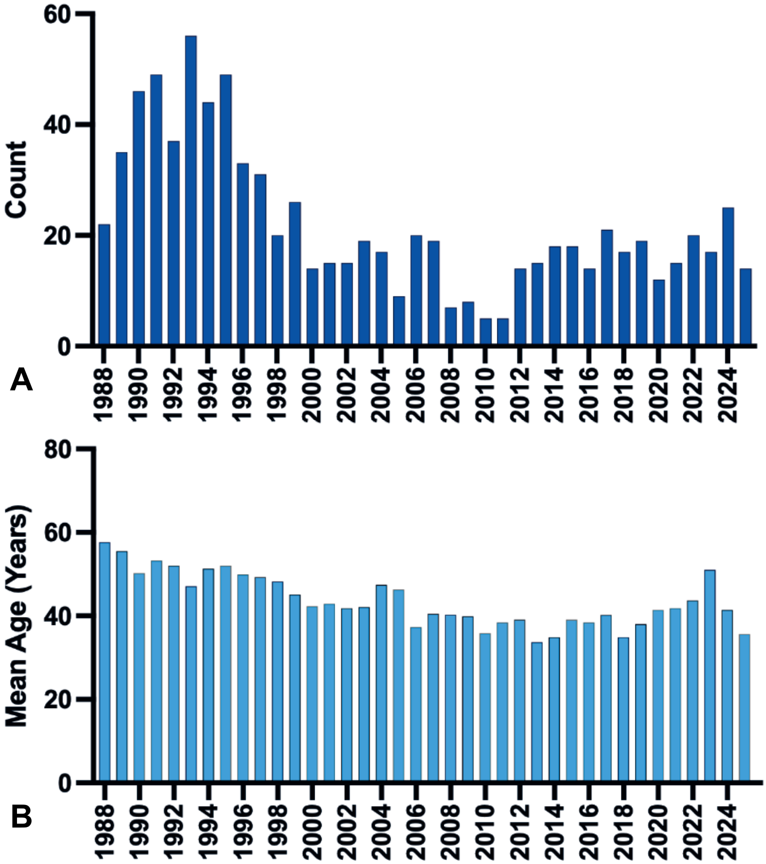

Figure 2 – Annual number of high tibial osteotomies performed between 1988 and 2025 (A) and mean patient age at the time of surgery over the same period (B).

3.3 Fixation Methods in High Tibial Osteotomy

The majority of HTOs were performed using a closed-wedge technique (56%), while open-wedge osteotomies accounted for 44% of cases. Figure 4A illustrates a clear trend, with closed-wedge osteotomies predominating before 2000 and a shift toward open-wedge osteotomies thereafter. A similar pattern was observed for fixation methods (Figure 4B), with staples predominantly used before 2000 and plates becoming the primary fixation method after 2000. Overall, plates were used in 50% of the patients, staples in 49%, and alternative fixation techniques in 1% of cases, including five procedures with bone graft only, two with Kirschner wires, and one with external fixation.

Among patients who underwent open-wedge osteotomy before 2000 (N = 26%), 65% were fixed with a plate, 12% with a bone graft, and 8% each with staples, pins, or Kirschner wires.

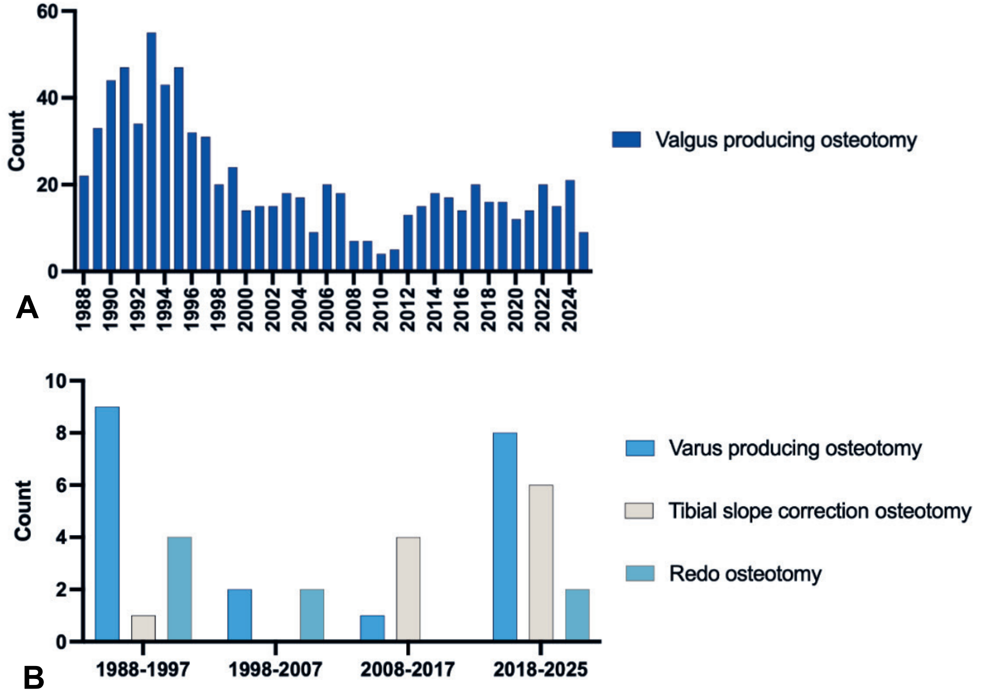

Figure 3 - Distribution of high tibial osteotomies between 1988 and 2025. Valgus-producing osteotomies are shown for the entire period (A), while varus-producing, tibial slope–correcting, and re-do osteotomies are subdivided into four distinct time periods (B).

3.4 Concomitant treatments

Overall, 50% of HTOs were performed in combination with another procedure (Table 1), whereas 50% were performed as isolated HTOs. Focusing on HTOs specifically performed to facilitate or support another intervention, 147 patients (18%) underwent HTO to enable a concomitant procedure. This trend was most pronounced in recent years, with HTOs increasingly being performed almost equally with and without concomitant procedures (Figure 5A). The use of HTO to support another concomitant intervention has predominantly been observed in the last decade (Figure 5B), highlighting a recent shift toward combining osteotomy with additional procedures.

Examining the distribution of concomitant treatments, a notable increase was observed in osteochondral procedures, including osteochondral allografts. Meniscus transplantations as a concomitant intervention were first performed from 2008 onward. Ligament reconstructions showed their peak incidence between 1998 and 2007.

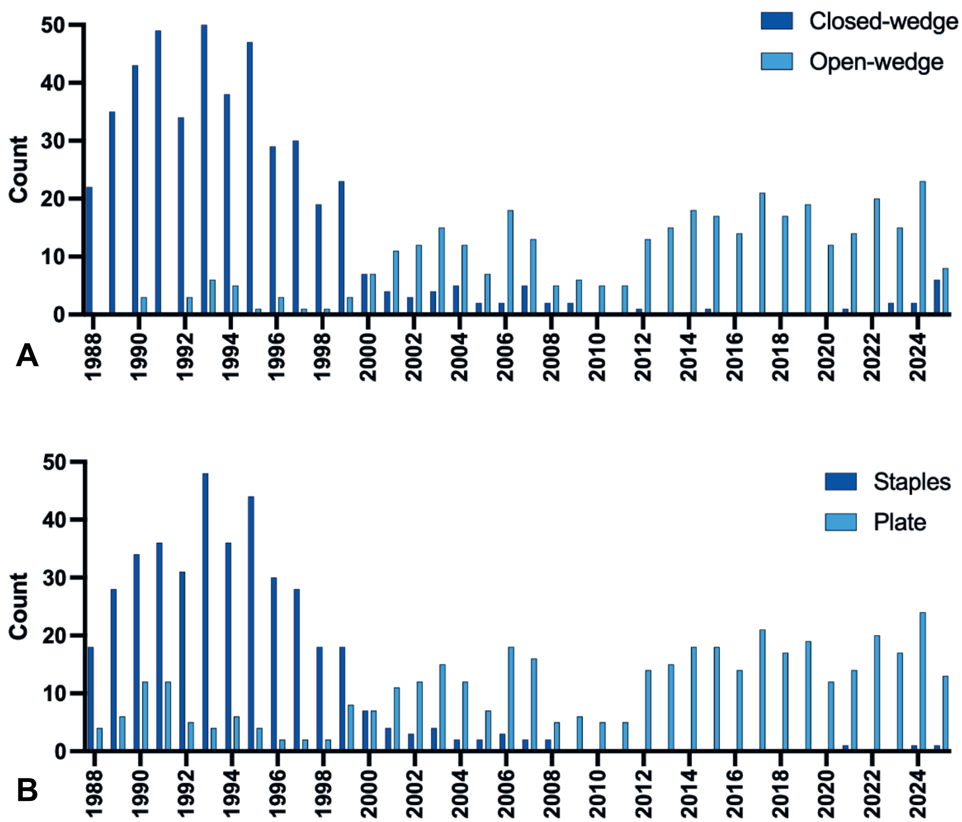

Figure 4 - Trends in high tibial osteotomy techniques and fixation methods. A) Distribution of closed-wedge versus open-wedge osteotomies, showing a predominance of closed-wedge procedures before 2000 and a shift toward open-wedge osteotomies thereafter. B) Distribution of fixation methods, illustrating predominant use of staples before 2000 and plates after 2000.

Table 1 - Frequency of procedures performed in combination with high tibial osteotomy (HTO).

Procedures performed in combination with HTO	Number (%)
Diagnostic arthroscopy	73 (17%)
Chondroplasty/debridement	181 (43%)
Meniscus repair	16 (4%)
Meniscus transplantation	11 (3%)
Ligament	52 (12%)
Cartilage treatment	22 (5%)
Osteochondral treatment	56 (13%)
Combined treatment	12 (3%)

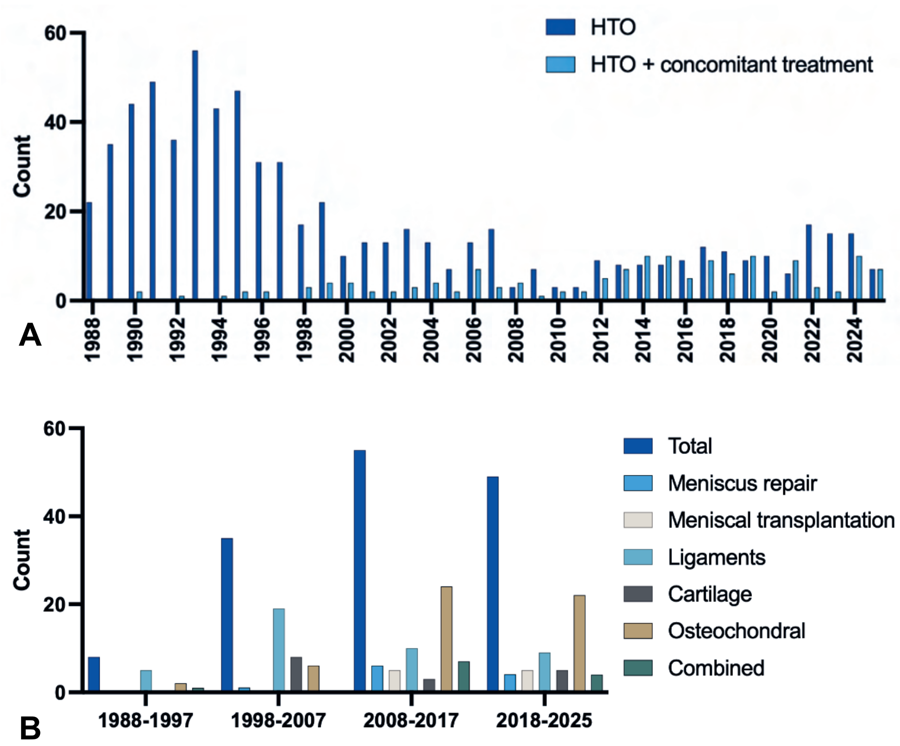

Figure 5 - Distribution of high tibial osteotomy (HTO) procedures. A) Proportion of patients undergoing isolated HTO versus HTO combined with concomitant treatment. B) Breakdown of the specific concomitant treatments performed alongside HTO, subdivided into four distinct time periods.

4. Discussion

This study provides a comprehensive longitudinal analysis of HTO procedures over the past four decades, highlighting important shifts in surgical practice as well as the growing number of HTOs performed with concomitant treatments. Using detailed patient-level data, we observed that the number of HTOs peaked between 1990 and 1997, subsequently declined—likely explained by the expanding adoption of knee arthroplasty—and showed a renewed increase from 2012 onward. Most procedures were valgus-producing osteotomies, with a clear transition from closed-wedge to open-wedge techniques and from staple to plate fixation after the year 2000. Notably, 18% of all HTOs were accompanied by concomitant procedures, and their frequency has shown a marked increase in recent years. To our knowledge, this is the first study to capture these long-term developments in HTO practice within a unique dataset spanning four decades, offering an in-depth perspective on evolving surgical strategies in real-world clinical practice.

Building on these trends, we observed a shift from closed-wedge to open-wedge techniques coincided with the introduction of dedicated fixation plates in the early 2000s [326–328], which facilitated the broader adoption of medial opening-wedge HTOs. In contrast to lateral closed-wedge osteotomies, which require a fibular osteotomy and are associated with higher rates of neurovascular complications[329–331], open-wedge techniques effectively overcome these limitations. Furthermore, open-wedge HTO offers improved predictability of the desired valgus correction compared with closed-wedge procedures and the locking plates enables earlier weight-bearing [332,333], further contributing to its increasing popularity in recent years.

In our cohort, valgus-producing osteotomies were performed more frequently than varus-producing procedures. This pattern likely reflects the predominance of medial compartment pathology, including a higher prevalence of medial osteoarthritis[160,161], chondral defects[334,335], and meniscal injuries[336], compared with the lateral compartment. Another contributing factor is the alignment of the lower limb, which is generally more varus than valgus[55,56,58,60–62,337], and even in a neutrally aligned knee, approximately 60% of the load is transmitted through the medial compartment compared with 40% laterally[338–340]. Furthermore, most tibial slope–correcting osteotomies have been performed in the past decade, although the first procedure in our database was recorded in 1992. Notably, posterior tibial slope–altering osteotomies were initially described by H. Dejour at the Lyon Knee Conference in 1991[341,342].

Given the rising prevalence of KOA[4–7], including among younger patients[34], driven by aging populations[4], increasing obesity[4], and a higher incidence of knee injuries[26,27], the need for joint-preserving treatments has become increasingly important. This is particularly relevant for younger patients, as those undergoing total knee arthroplasty face a higher risk of revision surgery[91,343]. HTO offers a valuable solution for this group, delaying the need for total knee arthroplasty and preserving long-term knee function. Studies have demonstrated excellent implant survival[97,113–117], improved patient-reported outcomes[103,104,106], and high return-to-sport rates[108–110] following HTO. Furthermore, a randomized controlled trial showed that HTO can slow structural joint damage and improve clinical outcomes compared with a control group[344]. Beyond standalone procedures, HTO enhances the effectiveness of concomitant treatments, optimizing sagittal alignment in anterior cruciate ligament reconstruction[345–347] and extending the longevity of cartilage repairs[309,348,349]. Collectively, these advantages highlight osteotomy as a powerful and versatile tool in the increasing important field of knee preservation.

Despite the strength of our study—being, to our knowledge, the first to capture these long-term developments in HTO practice within a unique dataset spanning four decades, offering an in-depth perspective on evolving surgical strategies in real-world clinical practice—there are several limitations to consider. First, our data are derived from a single hospital in the United States, which may limit the generalizability of our findings to other populations or countries. The annual number of HTOs performed in the U.S. is lower than that reported in many European countries[350–353], highlighting the need for further research that combines data across multiple continents to obtain a more comprehensive view of global HTO practice. Second, although this study describes trends in surgical techniques and procedural volume, it does not provide complete information on long-term functional outcomes, implant survival, or revision rates across the entire cohort. While this was not the primary aim of the current analysis, such outcomes remain important for future investigations. Finally, our study focuses exclusively on tibial osteotomies. Future research could expand this scope to include femoral osteotomies and double-level procedures to more fully characterize trends in knee osteotomy practice.

5. Conclusion

This study aimed to analyze the longitudinal trends in HTO procedures, fixation strategies, and their use alongside concomitant procedures over four decades, using unique detailed patient-level data from a large academic medical center. Our results demonstrate a clear transition from closed-wedge to open-wedge techniques, a shift from staple to plate fixation, and a notable increase in the use of HTO in combination with concomitant procedures in the last decade. Osteotomies continue to play a pivotal role in managing KOA and optimizing the outcomes of concomitant treatments.

10

Chapter 10

A Randomized Controlled Trial of AttraX® Putty vs. conventional open-wedge osteotomy without gap filler in open-wedge osteotomies – study protocol

Eva A. Bax, Nienke van Egmond, Moyo C. Kruyt, Roel J.H. Custers

Study protocol

1. Introduction

Open-wedge osteotomy provides clear clinical benefits but remains underutilized compared to unicompartmental knee arthroplasty[97,113,114,118–120,266], likely due to concerns about postoperative pain, complications, and rehabilitation[121]. Early postoperative pain following osteotomy is often severe and may be enhanced by bleeding and bone marrow leakage in the osteotomy gap[354,355]. Managing this blood leakage has been shown to reduce hematoma formation, limb swelling, and early postoperative pain[356–359]. Common gap-filling strategies include autologous iliac crest bone grafts, allografts, and synthetic ceramics. Autologous iliac crest bone graft remains the gold standard[360] due to its immune compatibility and cost-effectiveness, despite drawbacks such as donor site[360,361]. Allografts eliminate donor site morbidity but carry risks of disease transmission, higher costs, and limited availability[362,363]. Synthetic ceramics are widely used due to their biocompatibility, availability, lack of immunogenicity, though they typically lack osteoinductive properties[364,365].

AttraX® Putty (NuVasive Inc., San Diego, CA) is a synthetic ceramic (>90% β-TCP/<10% HA) with demonstrated osteoconductive and osteoinductive properties[364,366]. While it has shown promising results as a standalone graft substitute in spinal fusion, demonstrating non-inferiority to autograft, its use in osteotomies remains unstudied[365,367]. This randomized controlled trial (RCT) aims to determine the efficacy of AttraX® Putty as a gap filler in open-wedge osteotomies to reduce postoperative pain. Secondary objectives include assessment of local blood loss from the osteotomy gap, bone healing, and functional rehabilitation over time. Safety will be evaluated by the incidence and severity of treatment-related (serious) adverse events (S)AEs).

2. Study Design and Participant Eligibility

2.1 Study design

This single-blinded, prospective randomized controlled trial will be conducted at the Department of Orthopedic Surgery, UMC Utrecht, the Netherlands. Patients will be randomized 1:1 via variable block randomization stratified by osteotomy type (femoral, tibial, or double-level) using Castor EDC. The intervention group receives AttraX® Putty as gap filler; the control group receives no gap filling. Patients will be blinded to allocation, while surgeons and researchers are not, due to their roles in treatment and assessments. Randomization envelopes will be opened intraoperatively after osteotomy fixation.

2.2 Subjects

Adult patients (≥18 years), of both sexes, who are eligible for open-wedge osteotomy—whether femoral, tibial, or double-level — with a gap size < 10 mm will be included. Inclusion requires informed consent and compliance with imaging and 1-year follow-up. Exclusion criteria include concurrent cartilage procedures, pregnancy or planned pregnancy (because of a CT planned at 6 months), and inability to communicate in Dutch or English. Participants may withdraw from the study at any time without consequences; data collected up to withdrawal will be included in the analysis. Withdrawn or lost-to-follow-up patients after surgery will not be replaced, while those withdrawing before surgery will be. All withdrawn patients will continue to receive standard care.

2.3 Sample size calculation

This study was powered using G*Power (Version 3.1)[255] to detect a minimally clinically important difference of 2 points on the NRS for pain, with an assumed standard deviation of 2 points[368,369]. Using a two-tailed t-test with an alpha of 0.05 and a power of 80%, the required sample size was calculated to be 17 patients per group. To account for an estimated 10% loss to follow-up, the total sample size was increased to 19 patients per group, resulting in a total of 38 patients to be enrolled in the study.

3. Intervention

All participants will undergo a standardized open-wedge osteotomy. In the intervention group, AttraX® Putty will be applied to the osteotomy gap. The putty will be manually molded, with malleability achieved through pressure and warming. The applied volume will range from 3 to 11 mL, depending on wedge size and bone width.

4. Investigational product

AttraX® Putty (NuVasive Inc., San Diego, CA) is composed of macro and microporous biphasic calcium phosphate granules (β-TCP >90% / HA <10%), combined with an advanced dissolvable polymer carrier (alkylene oxide copolymer), which dissolves within 48 hours. The AttraX® Putty is CE-registered as a bone void filler for surgically created non-load-bearing defects. Unlike most synthetic grafts, AttraX® Putty is both osteoconductive and osteoinductive, as demonstrated in preclinical studies[364,366]. These studies also confirmed its biocompatibility, non-toxicity, and superior bone formation[370,371]. Clinical studies in spinal fusion have demonstrated that AttraX® Putty is safe and effective, with outcomes non-inferior to those of a standalone autologous bone graft[365,367].

5. Outcome measures and statistical analysis

The primary outcome, knee pain, will be measured using the Numeric Rating Scale (NRS; 0 = no pain, 10 = intolerable pain), assessed digitally preoperatively and daily in the evening for the first two postoperative weeks. Differences between treatment groups over time will be analyzed with linear mixed models, considering treatment and time as fixed factors.

Among the secondary objectives, leg circumference will be self-measured by the patients preoperatively and weekly during the first postoperative month. Specifically, thigh circumference will be measured at the upper patellar pole for distal femoral osteotomies, and calf circumference will be measured 10 cm below the lower patellar pole for proximal tibial osteotomies. Changes over time will be evaluated with mixed models incorporating treatment and time. Local blood loss will be assessed by comparing pre- and postoperative hemoglobin levels, with changes between groups analyzed using independent t-tests.

Bone healing will be evaluated on weight-bearing radiographs at 1, 3, 6, and 12 months postoperatively using the Uniform Bone Union (UBU) classification, with scores compared between groups through mixed models. The UBU classification is described in detail in Chapter 12. Consolidation on computed tomography scans performed at 6 months will be compared using independent t-tests, and correlations between radiographic and CT-based union scores will also be assessed.

Patient rehabilitation will be assessed with the Knee Injury and Osteoarthritis Outcome Score (KOOS), recorded preoperatively and at multiple postoperative time points (2 weeks, 1, 3, 6, and 12 months). Changes from baseline will be analyzed with mixed models including treatment and time.

All (serious) adverse events ((S)AEs) will be recorded and summarized descriptively in tabular form, including comparisons of frequency and severity between groups.

A detailed overview of the participant timeline is provided in Table 1. Procedures marked with an asterisk (*) are not part of routine clinical care but are performed specifically for the purposes of the study.

Table 1 – Participant timeline

<table>
<tr><td colspan="2">Preoperative
PROMs</td></tr>
<tr><td colspan="2">Surgery/1 day postoperative
Hemoglobin measurement
Leg circumference*
Visit physical therapist</td></tr>
<tr><td>First two weeks postoperative
Daily NRS assessment*</td><td rowspan="2">First month postoperative
Weekly leg circumference home measurement*</td></tr>
<tr><td>Two weeks postoperative
KOOS questionnaire*</td></tr>
<tr><td colspan="2">1 month postoperative
Outpatient clinic
Knee radiograph
PROMs</td></tr>
<tr><td colspan="2">3 months postoperative
PROMs</td></tr>
<tr><td colspan="2">4 months postoperative
Outpatient clinic
Knee radiograph
Whole leg radiograph</td></tr>
<tr><td colspan="2">6 months postoperative*
Outpatient clinic
Knee radiograph
CT-scan
PROMs</td></tr>
<tr><td colspan="2">1 year postoperative
Outpatient clinic
Knee radiograph
PROMs</td></tr>
<tr><td colspan="2">In case of osteosynthesis material removal
Biopsy*</td></tr>
</table>

*These procedures are not part of routine clinical care but are performed specifically for the purposes of the study.
PROMs, Patient-Reported Outcome Measures; NRS, Numeric Rating Scale; KOOS, Knee injury and Osteoarthritis Outcome Score; CT-scan, Computed Tomography scan.

6. Conclusion and implications

This randomized controlled trial will provide evidence on the efficacy of AttraX® Putty as a gap filler in open-wedge osteotomies for patients with unicompartmental knee osteoarthritis combined with lower limb malalignment. Including a control group without gap filling allows for direct comparison, enabling better insight into the true effect of the intervention on early postoperative pain. Secondary outcomes will assess blood loss, bone healing, and rehabilitation, while safety monitoring will evaluate potential risks. Findings from this study have the potential to improve patient outcomes following realignment osteotomies.

11

Chapter 11

Radiographic assessment of bone union in Proximal Tibia and Distal Femur Osteotomies: A systematic review

Eva A. Bax, Netanja I. Harlianto, Roel J.H. Custers, Nienke van Egmond, Wouter Foppen, Moyo C. Kruyt

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Abstract

Background: Osteotomies around the knee are a well-established treatment option for early and moderate unicompartmental osteoarthritis combined with a lower extremity malalignment. Moreover, osteotomies are often combined with cartilage treatment. Current image-based bone union assessments lack an accepted definition despite widespread use in research and clinical settings. This systematic review aims to identify definitions and classification systems for bone union on radiographs after a proximal tibia or distal femur osteotomy.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, we systematically searched MEDLINE and EMBASE database, applying specific inclusion and exclusion criteria. Two independent reviewers screened abstracts and full texts. The modified Cochrane risk of bias tool and Risk of Bias in Non-randomized studies of interventions tool were used. Data extraction included study characteristics, imaging modality, bone union definition, classification systems, assessment of gap fillers, use of modifiers, and osteotomy type.

Results: Out of the 1180 screened titles and abstracts, 105 studies were included, with the majority (69 studies (65.7%)) employing a retrospective design. 55 studies (52.4%) defined bone union based on one or more criteria, while 50 studies (47.6%) used a classification system. There were thirteen different criteria for bone union, and nine different classification systems. Interestingly, none of the classification systems incorporated negative criteria, such as hardware failure. Notably, 137 (49.1%) of studies described bone union as either a primary or secondary outcome, but do not describe a system for assessing bone union.

Conclusion: This systematic review highlights the lack of consensus in the literature in defining bone union after a proximal tibia or distal femur osteotomy, revealing many criteria and different classifications. None of the classification systems were applicable to osteotomies with and without gap filler. This systematic review shows the need for a straightforward, reproducible, and accurate methods to assess bone union after a proximal tibia or distal femur osteotomy.

1. Introduction

Knee osteoarthritis (OA) is the most prevalent joint disease, causing chronic pain, stiffness, and disability[207,238]. Osteotomies around the knee are a well-established treatment for early and moderate unicompartmental OA with lower extremity malalignment, as it reduces the mechanical force on the affected compartment[372,373]. Osteotomies are often combined with cartilage treatment[94]. The most commonly described osteotomy techniques are the closed wedge and the opening wedge osteotomy[374]. Many surgeons prefer to fill the open-wedge osteotomy with autograft, allograft or ceramic materials to enhance early mechanical stability, reduce local blood loss, and improved bone union[375]. Traditionally, the gap is filled with autologous iliac crest, however, this is associated with complications, including pain, infection, and hematoma at the donor site[376]. To eliminate these complications, allograft and ceramics can be used which may contribute to accelerated bone union and remodelling[377]. The choice to use a bone graft is largely based on its ability to facilitate healing of the osteotomy gap.

Image based bone union assessment is a commonly used outcome measure in osteotomy studies. According to the Concise Medical Dictionary, union is defined as "the successful result of healing of a fracture, in which the previously separated bone ends have become firmly united by newly formed bone"[378]. Despite this clear definition, authors have used multiple other definitions for evaluation bone union after an osteotomy, but there are no comprehensive studies to guide us[375,379–382]. The lack of consensus on image-based bone union assessment impedes meaningful comparisons of outcomes across osteotomy studies, including those focused on osteotomy gap treatments, thereby diminishing the clinical and scientific value of these studies[383].

Furthermore, bone union after an osteotomy is crucial for guiding patient care decisions, including the timing of hardware removal and modifying rehabilitation protocols[384,385]. Premature or delayed hardware removal can lead to complications or unnecessary discomfort[384]. Moreover, a clear definition of osseous union is crucial for facilitating decision-making regarding the necessity of surgical intervention in cases of nonunion[385]. Without such a definition, clinical decision-making remains challenging and uncertain.

Therefore, the primary objective of this systematic review is to identify the various available methods in assessing bone union on radiographs after open and closed wedge proximal tibia and distal femur osteotomies. Various definitions of union, delayed union, and nonunion will be addressed based on criteria and classification systems. In addition, we explore methods used to describe the development of bone union over time.

2. Materials and methods

2.1 Search Strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[386]. A structured literature search was performed in MEDLINE and EMBASE from inception till December 2023. The search was performed to identify articles related to bone union on radiographs after femoral or tibial osteotomies. The search terms used as single or combined terms were tibia osteotomy, femur osteotomy, healing, union, nonunion, gap, consolidation, and pseudoarthrosis (see Appendix A for the search string). Only studies published in English language were taken into consideration.

Table 1 - Inclusion and Exclusion Criteria.

Inclusion criteria	Exclusion criteria
Adult patients treated by distal femur or proximal tibia osteotomy for knee related problems	Osteotomy for limb lengthening
	Other imaging modalities than radiographs
Human studies	Finite element studies
Studies with outcome: bone union	Cadaveric studies
Imaging modality: radiographs	Reviews and meta-analysis
	Conference abstracts
	Case studies

2.2 Article Identification and Selection

All published articles from the search were considered for inclusion in this systematic review. Two independent reviewers (EB, NH) conducted screening or title and abstracts using Rayyan. Duplicates were systematically removed and studies unrelated to bone union on radiographs after femoral or tibial osteotomies were excluded. Full text assessment was performed on all articles meeting the eligibility criteria described in Table 1. Only articles that described a definition of bone union, delayed union or nonunion, or those describing a classification system to determine bone union were included. Disagreements were resolved through discussion, and in case of persistent disagreement, a third review author (WF) was consulted.

2.3 Quality assessment

Two independent reviewers (EB, NH) assessed the risk of bias for the included studies. The included randomized controlled trials (RCT) were assessed using the modified Cochrane Risk of Bias Tool[387]. Each domain was scored with high, low, unclear risk of bias, which together resulted in the overall risk of bias. Non-randomized studies were evaluated using The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) assessment tool[388]. Each domain was scored here with critical, serious, moderate, low, no information, which together resulted in the overall risk of bias. Disagreements were resolved through discussion, and in case of persistent disagreement, a third review author (WF) was consulted.

2.4 Data extraction

All data were extracted from the full text articles into an Excel spreadsheet (Microsoft, Redmond, WA, USA). The included articles were analyzed for 1) study characteristics including study design, year of publication, number of participants, age, gender, Body Mass Index (BMI), country, 2) imaging modality, 3) bone union criteria, 4) classification system (if used), 5) use of modifiers, 6) assessment of gap fillers, 7) type of osteotomy (closed vs. open), and 8) degree of correction. All data were independent collected by two reviewers (EB, NH). Disagreements were resolved through consensus.

2.5 Statistical analysis

The bone union assessment was divided into 'descriptive' criteria, in case of a description of union, and 'classification', if the criteria were structured in a grading or scoring system. Frequency of imaging modalities, bone union criteria, classification systems, modifiers, gap fillers, and type of osteotomy were determined. The (weighted) mean was determined for age, BMI, and degree of correction.

3. Results

3.1 Search Strategy

A total of 1584 studies were identified. After removing duplicates, 1,180 studies remained. After screening abstract and titles, 279 studies were selected. The primary reasons for exclusion were non-human studies (N = 405 (34.4%)) or a lack of information regarding bone union (N = 209 (17.7%)) (Figure 1). After reading full-text articles, a total of 105 studies were included according to the inclusion- and exclusion criteria. The primary reason for full-text exclusion was that bone union was not described. A high percentage (N = 137 (49.1%)) of studies described bone union as either a primary or secondary outcome but did not describe a system for assessing bone union. The selection process, following the PRISMA guidelines, is illustrated in Figure 1.

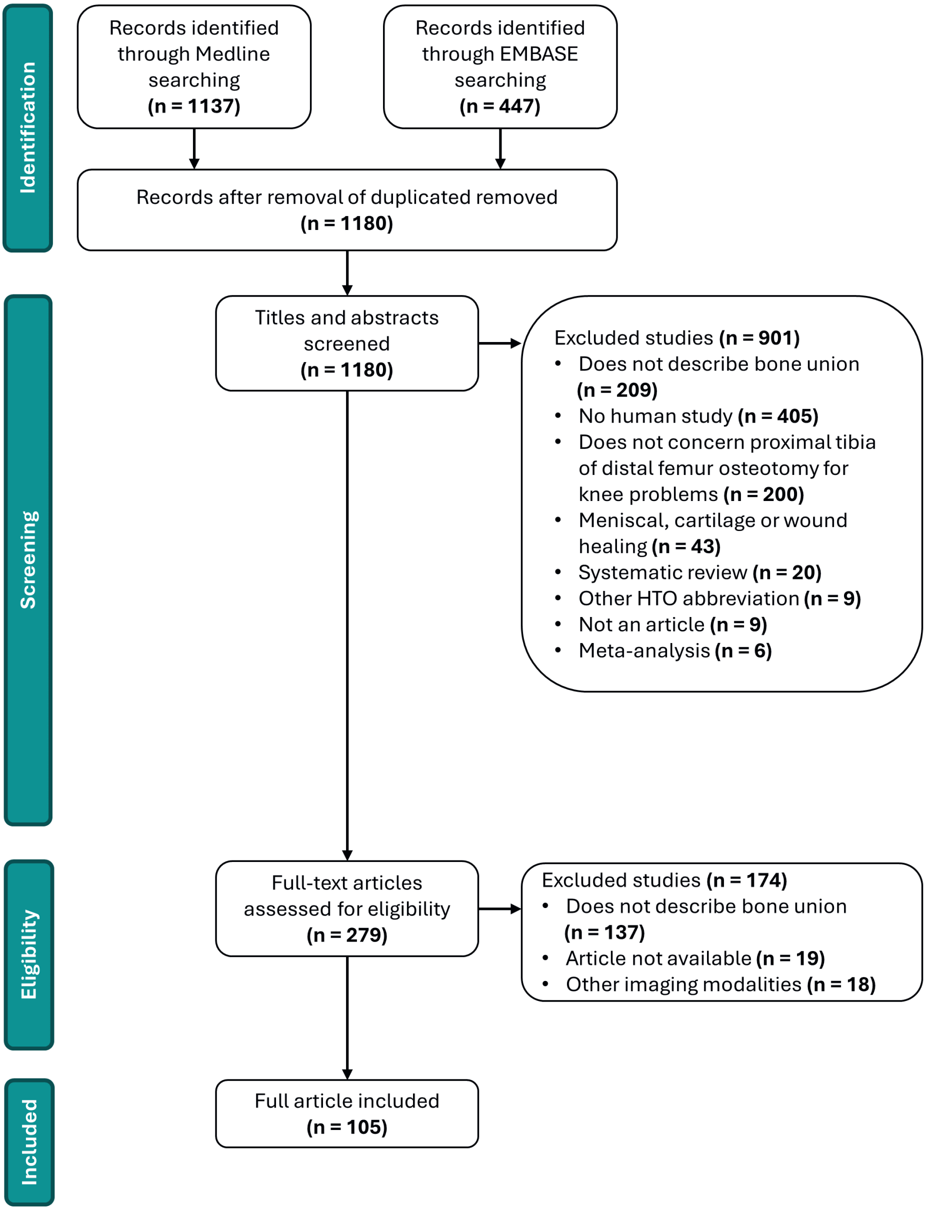

Figure 1 - Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of article selection

3.2 Quality assessment

The overall risk of bias in non-randomized studies was low in only two studies[23,24]. The overall risk of bias was moderate for 58 studies (60.4%) and serious for 23 studies (24.0%) (See Appendix B). The most notable risk of bias included partial bilateral intervention, enrolment in groups was choice of surgeon or patient, use of different gap fillers in one intervention group, and the lack of blinding of radiologist and/or patient. Partial bilateral intervention refers to some patients having an osteotomy of both knees and some patients of one knee. This methodology may introduce selection bias as dissatisfied patients might avoid surgery on the untreated contralateral knee, affecting studies on patient satisfaction. For thirteen studies, there was no information for one domain of the assessment tool, making the overall risk of bias no information.

The overall risk of bias in randomized controlled trials was low in four studies, high in four studies, and unclear in one study (See Appendix B). The most notable risk of bias included the lack of blinding of the patient and radiologist and insufficient reporting of incomplete data.

3.3 Data extraction

3.3.1 Study characteristics

The first published study dated from 1971[25]. Since the 2000s, scientific interest in knee osteotomies has increased, mostly in the last decade. Included studies had either a retrospective (N = 69 (65.7%)), prospective (N = 16 (15.2%)), unclear (N = 11 (10.5%)) or RCT (N = 9 (8.6%)) design. Most studies were published in South Korea (N = 23 (21.9%)) followed by Japan (N = 15 (14.3%)) and Germany (N = 13 (12.4%)). The number of knees included in the studies varied between 7 and 350, with a median of 58 knees (interquartile range 61 knees). In 62 studies (59%) a gap filler was used for the open-wedge osteotomy. The majority of studies focused on open-wedge tibial osteotomy, constituting (N = 87 (82.9%)). Additionally, six studies (5.7%) addressed both open-wedge and closed-wedge osteotomies. The data extraction of the included studies can be found in Appendix C.

3.3.2 Imaging modality

All included studies used conventional radiographs. Conventional radiographs were most often combined with computed tomography (CT) scans (N = 16 (15.2%))[354,389–393]. Only one study (1.0%) combined conventional radiographs with Dual Energy Xray absorptiometry (DEXA)[394]. In addition, there was one study (1.0%) that also used histology[395].

3.3.3 Criteria of bone union

In 55 studies (52.4%) bone union was based on descriptive criteria, mainly positive ones like bone bridging, callus formation, disappearance of osteotomy line, and clinical signs like no pain during weight bearing (Figure 2). Negative criteria, such as sclerosis at the osteotomy boundaries[390,396–401], resorption within the osteotomy[402,403], collapse [402,403], radiolucent areas within the osteotomy[404–406], hardware failure[400], and radiolucency around the implant[402] were used to define the lack of bone union. One or more of these negative signs were described in 12 studies (21.8%).

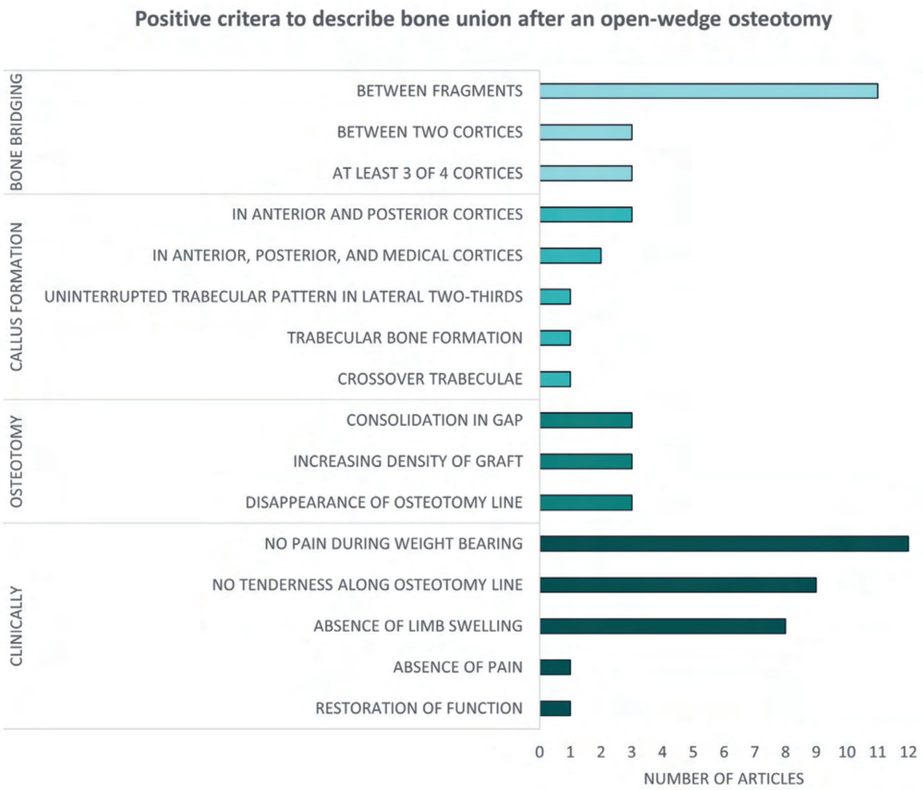

Figure 2 – Number of articles per union criterion.

The time interval for delayed union after open-wedge osteotomy varied, with delayed union most commonly defined as the absence of union at six months after surgery (Figure 3). Moreover, most studies (N = 12 (80%)) also defined nonunion as the absence of union at 6 months after surgery. The remaining 20% (N = 3) defined it as the absence of union at 1 year.

Six studies (5.7%) included both closed-wedge and open-wedge osteotomies, but used identical time intervals for bone union, delayed union, and nonunion without distinguishing between the groups. For these studies, delayed union was described as the absence of union at 4 months (N = 1 (16.7%)), 6 months (N = 2 (33.3%)), or 8 months (N = 1 (16.7%)). The remaining studies (N = 2 (33.3%)) did not describe a time interval for delayed union. Nonunion was described as the absence of union at 6 months (N = 1 (16.7%)) or 1 year (N = 1(16.7%)). The remaining studies (N = 4 (66.6%)) did not describe a time interval for nonunion.

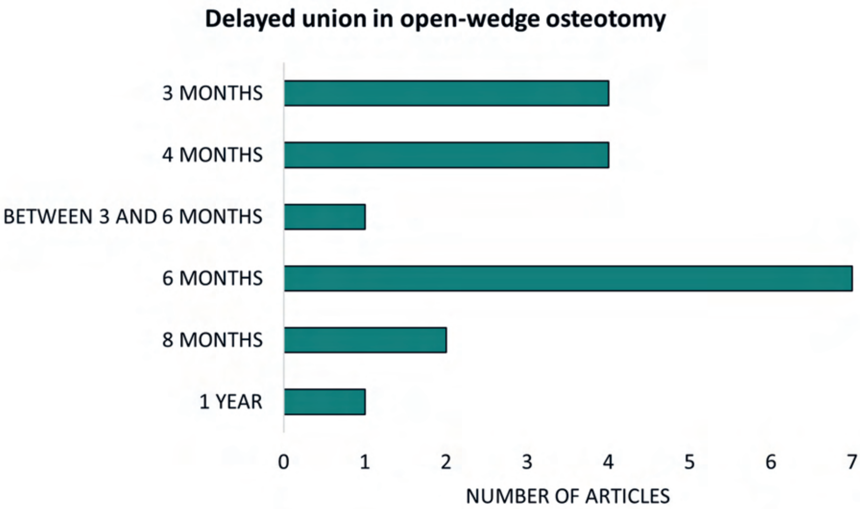

Figure 3 – Time interval for delayed union in open-wedge osteotomies.

3.3.4 Classification system for bone union

The bone union assessment was divided as a classification if the criteria were structured in a grading or scoring system. In fifty studies (47.6%) bone union was assessed using classification, where a distinction must be made between gap filler and no gap filler. Among these studies, 26 (52.0%) utilized a gap filler, while twenty (40.0%) did not. In the remaining four studies (8.0%), a combination of both gap fillers and no gap fillers was used. Within the gap filler group, the Schröter[407] method was predominant (N = 7 (27.0%)), whereas in the group without gap filler, the most commonly applied classification was the van Hemert[375] (Table 2) at a rate of (N = 8 (40.0%) (Figure 4). The Schröter method describes the percentage of the osteotomy that is filled with newly formed bone by dividing the distance of the osteotomy from medial to lateral by the part of the osteotomy gap that is not visible anymore (i.e. healed)[407]. None of the classification systems incorporated negative criteria or modifiers.

Table 2 - Hemert Classification System for Assessing Bone Union

	Phase name	Explanation
0	Direct postoperative	Hematoma
1	Vascular phase	Osteopenic bone, rounded osteotomy sites, clear distinction between tricalcium phosphate and bone
2	Calcification phase	Whitening of sites and blurred distinction between tricalcium phosphate and bone
3	Osteoblastic phase	Distinction between tricalcium phosphate and bone slightly visible, though healed osteotomy
4	Consolidation phase	Full reformation, though osteotomy recognizable, no tricalcium phosphate
5	Full reformation	No sign of osteotomy

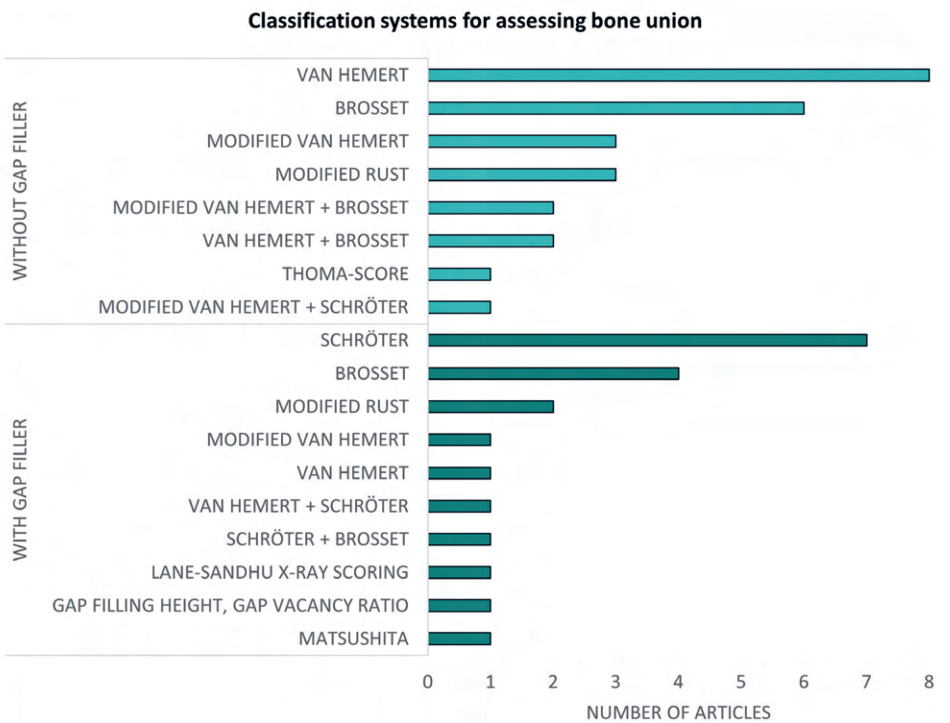

Figure 4 – The different classification systems for assessing bone union on radiographs, categorized into those applicable to cases without void fillers and those with void filler.

In four studies (8.0%), a combination of both gap fillers and no gap fillers was used. Among these, two studies employed the Brosset classification[408,409], while another study integrated the Brosset classification with the modified van Hemert[410]. Additionally, one study utilized Hemert's modified classification for the gap filler group and the Brosset classification for the group without gap fillers[411]. Different classification systems were used here because each classification system was developed for gap filler or without a gap filler and therefore no classification system was available for a randomized controlled trial between gap filler and no gap filler.

4. Discussion

This systematic review identified many methods in assessing bone union on radiographs after a proximal tibia or distal femur osteotomy. The most important finding is that there is an enormous variation in both definitions and classification systems for the same purpose of defining union. There were thirteen different criteria, and nine different classification systems, interestingly none of the classification systems incorporates negative criteria, such as hardware failure. Consequently, there is no consensus in the literature in defining bone union after knee osteotomies despite the widespread use in research and clinical settings, therefore, comparing between osteotomy studies is currently almost impossible.

Bone union criteria evaluated in these studies were primarily radiographic and clinical in nature. The most common of the criteria were the presence of bone bridging between fragments and lack of pain during weightbearing. Only a few studies focused on negative radiological criteria of union, such as sclerosis at the osteotomy boundaries, resorption within the osteotomy, collapse, radiolucent areas within the osteotomy, hardware failure, and radiolucency around the implant. Moreover, six different time intervals were defined for delayed union, not distinguishing between gap filler and without gap filler, and open-wedge versus closed-wedge. This is surprising, since the use of gap fillers may result in accelerated bone union and there is a perception that union occurs more rapidly with a closed-wedge compared to an open-wedge[408,409,411,412]. Furthermore, a high percentage of the studies (49.1%) described bone union as either a primary or secondary outcome but then do not describe a definition for union. This is surprising, since there is not any consensus on union, delayed union, and nonunion.

The literature encompasses various classification systems applicable to knee osteotomies, with or without gap fillers. None of the classification systems incorporate negative radiological criteria or modifiers, which are recognized as clear signs of nonunion in spinal fusion surgery[413]. Moreover, each system has been designed for either an osteotomy with gap filler or without gap filler. However, our findings reveal that commonly employed classification systems, including (modified) van Hemert[354,375,379,414], Brosset[382], and Schröter[407] classifications, are used for both an osteotomy with gap filler and without gap filler. Specifically, the (modified) van Hemert score[354,375,379,414] was initially developed for osteotomies involving gap fillers, whereas the Brosset[382] and Schröter[407] classifications were originally intended for osteotomies

Chapter 11

without. Intriguingly, Figure 4 illustrates that these classification systems are used for both. The study by Nha *et al.*[411] used the modified van Hemert score and the Brosset classification to compare bone union between synthetic graft and without bone graft, yielding two different outcomes that complicate the comparison of bone union between synthetic graft and without bone graft. This emphasizes the importance of a classification system specifically developed for open-wedge osteotomies with and without a gap filler.

The strengths of this systematic review are that it is the first study offering a comprehensive overview of the absence of consensus in evaluation bone union after osteotomy. In addition, it reveals a noteworthy observation that a high percentage of studies do not describe a definition of bone union. Despite the strengths of the systematic review, this review has several limitations. First, only articles written in English were included, posing a risk of language bias. Second, animal studies were excluded, resulting in the absence of validation studies. These studies are valuable in assessing the correlation between radiographic bone union and functional bone union based on histology and/or manual palpation. Only one study included biopsies in the hydroxyapatite group to determine the ratio of bone tissue and remnant hydroxyapatite[395]. Thirdly, various articles included in our systematic review exhibited a moderate to high risk of bias. We incorporated all studies in our analysis, focusing solely on the description of the radiological assessment of bone union without extracting additional results, like patient-reported outcomes. Finally, this systematic review did not assess the relation with the size of the osteotomy gap, as the definitions of bone union, delayed union, and nonunion are generally independent of the size of the osteotomy gap.

5. Conclusion

Our systematic review highlights the lack of consensus in defining bone union following a proximal tibia or distal femur osteotomy. Thirteen different criteria and nine classification systems were identified for assessing bone union, none of which are universally applicable to osteotomies with and without gap fillers. Moreover, existing classification systems lack negative criteria for the absence of bone union. This systematic review confirms the need for a straightforward, reproducible, and accurate methods to assess bone union after a proximal tibia or distal femur osteotomy.

Appendix

For the Appendix, I would like to refer to the publication in JBJS Open Access.

12

Chapter 12

Uniform and Reliable Assessment of Bone Union on Radiographs in Osteotomies around the Knee: A Novel Classification System

Eva A. Bax, Nienke van Egmond, Roel J.H. Custers, Koen L. Vincken, Moyo C. Kruyt, Wouter Foppen

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Abstract

Background: To evaluate the inter- and intra-rater reliability of the Unified Bone Union (UBU) classification for assessing time-dependent bone healing on radiographs in osteotomies around the knee, including negative union signs. Secondary aims included assessing union progression over time, applicability across osteotomy types, and correlation between radiographic and CT-based UBU scores.

Methods: The UBU classification assesses bone healing on anteroposterior radiographs in three anatomical zones, graded from phase 0 (no callus) to phase 3 (bridging callus), including radiological negative union signs. Radiographs (n = 110) from 38 medial opening-wedge high tibial osteotomy patients were retrospectively reviewed twice by three independent raters. Inter- and intra-rater reliability were assessed using quadratic-weighted kappa (κ). Percent agreement was calculated for classification modifiers. Time-dependent changes in union were analyzed. Reliability was also tested across osteotomy types. Correlation between 6-month radiographic and CT-based UBU scores was determined using Spearman's rho.

Results: Interrater reliability was substantial (κ 0.74–0.79), while intra-rater reliability showed almost perfect agreement (κ 0.78–0.98). Modifier agreement was good (inter-rater: 91–98%; intra-rater: 89–95%). The UBU score increased over time. The UBU showed substantial interrater reliability (κ = 0.75) across various osteotomy types. A strong correlation was found between radiographic and CT-based UBU scores ($r = 0.82$, $p < 0.01$).

Conclusion: The UBU classification provides a reliable and standardized method for evaluating bone union after osteotomies around the knee. It incorporates negative union signs and demonstrates strong inter- and intra-rater agreement, as well as strong correlation with CT imaging. Further research should validate its diagnostic accuracy and clinical utility.

1. Introduction

Lower limb malalignment (varus or valgus) contributes to the progression of unicompartmental knee osteoarthritis (KOA)[16,182,415], and an osteotomy can reduce the mechanical load on the affected compartment[97,266,267]. The most common techniques are closing-and opening-wedge osteotomies[374], with opening-wedge osteotomies leaving an open gap in the bone, and fillers sometimes used in in these cases to enhance stability and bone healing[375,416]. Postoperative knee radiographs are routinely performed to evaluate bone union, which the *Concise Medical Dictionary* defines as “the successful result of healing of a fracture, in which the previously separated bone ends have become firmly united by newly formed bone”[378]. However, no consensus exists on how to define bone union after an osteotomy, as highlighted in our recent systematic review[417]. On the contrary, we identified thirteen different criteria and nine different classification systems to assess union of a proximal tibia or distal femur osteotomy. These criteria focus on bone bridging (between fragments or cortices), callus formation, osteotomy gap (disappearance of the osteotomy line), and clinical signs of union, such as absence of pain during weight-bearing[417].

Beyond this inconsistency, most classification systems do not account for the progression of healing from the hinge side to the other side. Moreover, existing classification systems can currently be applied only to either opening-wedge or closing wedge osteotomies, with or without gap fillers, which impedes comparison across different osteotomy techniques[417]. Another notable shortcoming is the absence of negative signs of union—such as sclerosis at the osteotomy boundaries or hardware failure—despite their clinical relevance and well-established recognition as clear signs of nonunion[413]. For these reasons, we developed the Uniform Bone Union (UBU) classification in this study to address these shortcomings.

Negative signs of union, as a radiological modifier, such as hinge fractures[392,396,407], loss of correction[383], and hardware failure[383,400] (e.g. failure of screws or fixation plate) are strongly related to delayed or non-union. Other negative signs include sclerosis at the osteotomy boundaries[390,396–401], resorption of bone within the osteotomy[402,403], collapse[400,402,403], radiolucent areas within the osteotomy[404,405,407], and radiolucency around the implant[402].

This study develops and evaluates a uniform classification method that addresses the above shortcomings: the UBU classification. The primary objective was to assess its inter-and intrarater reliability in evaluating knee radiographs of patients who underwent a medial opening-wedge high tibial osteotomy (MOWHTO). Secondary objectives included analysis of time-dependent changes in UBU scores to evaluate the progression of bone union, evaluation of its applicability across different osteotomy types (opening- and closing-wedge, femur, and tibia, with and without gap fillers), and comparison with computed tomography (CT) scans.

2. Materials and Methods

2.1 The Uniform Bone Union classification

The UBU classification was developed in collaboration with treating physicians, a radiologist, and a technical physician-scientist, and is based on existing classification systems[417]. It was adapted to provide a uniform approach applicable to all osteotomy types, including opening-and closing wedge procedures of both the femur and tibia, with or without gap fillers.

The UBU classification is shown in Table 1 and assigns a score to anteroposterior radiographs based on the bone formation in three equally distributed different zones along the osteotomy: hinge side, middle, and gap side (Figure 1A). These zones allow standardized assessment of bone healing across the entire osteotomy. It ranges from phase 0 (a clearly visible osteotomy line without callus formation) to phase 3 (bridging callus or bone formation). The UBU classification is described in detail in Table 1. This assessment was always made by comparing the radiograph to be scored with the radiograph obtained on the first postoperative day. The total score ranges from 0 (three times phase 0) to 9 (three times phase 3).

Table 1 – The Uniform Bone Union classification system for assessing bone union on anteroposterior radiographs in any of the three anatomical zones from the hinge side to the gap side.

Phase	Explanation
0	The osteotomy line is as clearly visible as immediately post-surgery; no signs of callus formation.
1	Blurring of one of the two osteotomy surfaces; And/or limited callus formation (< 50%).
2	Blurring of both osteotomy surfaces; And/or moderate callus formation (≥ 50%).
3	Bridging callus or bone.
	Radiological modifiers
	Sclerosis of the osteotomy
	Lucency line around a screw
	Failure of hardware, including plate and screw breakage
	Loss of correction
	Hinge fracture not present immediately postoperatively

Additionally, radiological negative signs, which are strongly associated with delayed or non-union[383,390,392,396–405,407], were included as modifiers and were derived from existing literature (Table 1). In the UBU classification, modifiers were considered as relevant confounders, as they are strongly associated with delayed or non-union and may explain deviations or atypical trends in the UBU score over time. The included modifiers are sclerosis of the osteotomy[390,396–401], lucency line around a screw[402,404,405,407], failure of hardware (including plate and screw breakage)[383,400], loss of correction[383], and hinge fracture[392,396,407] not present immediately postoperatively.

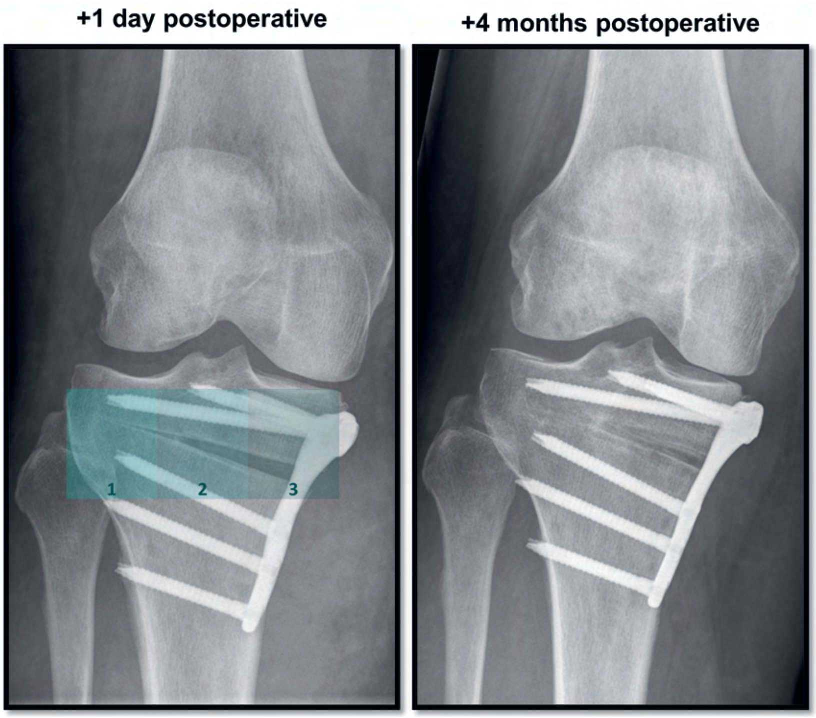

Figure 1 - Postoperative radiographs following a medial open-wedge high tibial osteotomy. The +1 day postoperative radiograph displays the three different zones. When comparing the +4 months radiograph to the postoperative radiograph, zone 1 and zone 2 are classified as phase 3, while zone 3 as phase 2.

2.2 Study design and study population

Data was retrieved from the knee registry at the University Medical Center Utrecht, the Netherlands. Adult patients aged 18 and above, who underwent a MOWHTO, between February 2017 and March 2023 were included. Additionally, patients were included if consecutive anteroposterior knee radiographs were available at approximately one day, four weeks, and four months postoperatively. Data on age, degrees of correction, sex, and use of autologous iliac crest were collected from the patient chart. Autologous iliac crest was used in patients when the correction height exceeded 10 mm. In total, 110 follow-up radiographs from 38 patients were available for the assessment of the reproducibility of the UBU classification system, with additional follow-up radiographs being used when available. This study does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act. Informed consent was obtained from all participants for their participation in the knee registry (registered on ClinicalTrials.gov, NCT04364334).

2.3 Primary Objective: Testing Reproducibility

The Guidelines for Reporting Reliability and Agreement Studies (GRRAS) were followed in this study[418]. A total of 110 radiographs were reviewed by three independent raters (radiologist (WF), orthopaedic surgeon (NvE) and a researcher (EB)), who were blinded to the clinical outcome and time of assessment. Ratings were conducted independently. The raters had experience of 11 years, 10 years, and 3 years in clinical practice. A standardized protocol for radiographic evaluation was followed to assess bone union and other relevant parameters using the VQuest platform (https://vquest.nl). Prior to the study, all raters participated in a training session of the UBU classification system. During this session, ten radiographs that were not included in this study were reviewed together. Intrarater reliability was evaluated by having the three independent raters reassess all radiographs after a minimum of 1 month to avoid recall bias.

2.4 Secondary Objective

2.4.1 Time effects of union

To evaluate the progression of bone union, radiographs were assessed over time (by three observers) using the UBU score. Postoperative radiographs taken at four weeks and four months were evaluated, along with any available further follow-up radiographs, from patients who had undergone a MOWHTO, as part of the knee registry. The effect of the presence of one of the modifiers on the bone union process was also examined by categorizing radiographs into "modifier present" and "no modifier" groups, to compare whether patients with a modifier showed delayed bone union compared to those without a modifier.

2.4.2 Comparison of radiographs and CT-scans

Thirteen patients from a randomized controlled trial (RCT) investigating the effect of a bone filler (registered on ClinicalTrials.gov, NCT05992038) were included for the comparison of the UBU score on radiographs with CT findings. These patients representing a distinct study population from that described above. They were randomized to the control group (opening-wedge osteotomy without gap filler) or the intervention group (opening-wedge osteotomy with AttraX® Putty (NuVasive Inc, San Diego, CA)). Patients participating in this study all had a correction height of less than

10 mm. Postoperative radiographs were taken at four weeks, four months, six months, and, for some, at one year. At six months, a CT scan (slice thickness 1 mm) was performed. The six months knee radiographs were compared with six-month CT scans using the same bone union assessment method, with a single UBU score assigned to all slices in the coronal reconstruction (Figure 2), with sagittal and transverse planes evaluated if needed. Two independent raters (a radiologist with 10 years and a researcher with 3 years of clinical experience) each scored the radiographs and CT scans once using VQuest (https://vquest.nl). Thirteen CT scans and 48 radiographs were available from thirteen patients for this analysis.

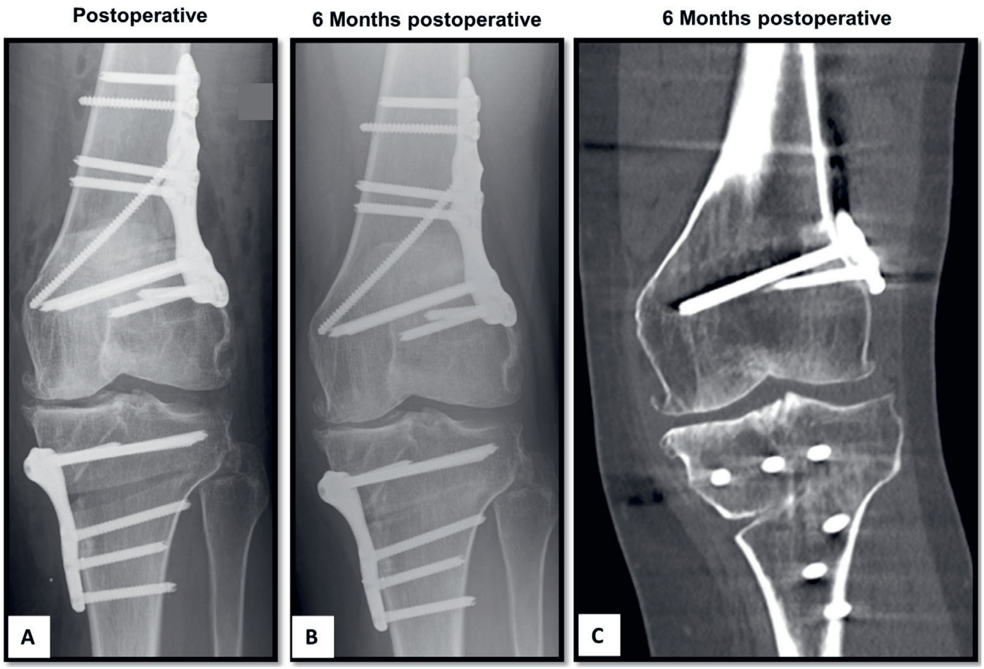

Figure 2 - Postoperative and 6-month follow-up imaging of a patient who underwent double-level osteotomy (medial open-wedge proximal tibial osteotomy and lateral closed-wedge distal femoral osteotomy). A) Postoperative radiograph. B) Radiograph at 6 months. EBU scores for the hinge side, middle, and gap side of the distal femur were classified as phase 3 for all zones. For the proximal tibia, the hinge side was classified as phase 3, while the middle and gap sides were classified as phase 2. C) CT scan at 6 months. The distal femur hinge side, middle, and gap side were classified as phase 3. For the proximal tibia, the hinge and middle sides were classified as phase 3, and the gap side as phase 2.

2.4.3 Evaluation across different types of osteotomies

To evaluate the interobserver reliability across different types of osteotomies (opening-wedge vs. closing wedge, femur vs. tibia, with vs. without filler), radiographs from the RCT were independently evaluated once by two raters (a radiologist with 10 years and a researcher with 3 years of clinical experience). A total of 48 radiographs were available for this part of the study. Among the patients, seven underwent a medial opening-wedge high tibial osteotomy, one had a lateral opening osteotomy of the distal femur, and five had a double-level osteotomy (lateral closing osteotomy of the distal femur and medial opening osteotomy of the proximal tibia). For patients with a double-level osteotomy, both the proximal tibia and distal femur were scored separately. For the analysis, patients were grouped by osteotomy type (opening-wedge vs. closing-wedge), anatomical location (femur vs. tibia), and use of gap filler (with vs. without).

2.5 Statistical analyses

All statistical calculations were performed using IBM SPPS Statistics (Version 25). Reliability was assessed per GRRAS guidelines using squared weighted kappa for ordinal grades, with corresponding P-values and 95% confidence intervals (CI)[418–420]. Kappa values were interpreted according to Landis and Koch: i.e., 0–0.20 slight agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement; 0.81–1 almost perfect agreement[421]. Percent absolute agreement was calculated for modifiers. The required sample size of 93 radiographs was calculated to determine a minimum acceptable kappa of 0.6 with $\alpha = 0.05$ with a power of 80%[422,423]. Spearman's rho (ρ) evaluated the correlation between bone union assessment on radiographs and the corresponding assessment on CT scans. The average score for radiographs and CT scans of the two raters was used. Furthermore, Spearman's rho (ρ) evaluated correlations between UBU scores and correction angle, as lager corrections are correlated with a delayed union[424,425]. Spearman's rho values between 0.00 and 0.19 were considered very weak, 0.20–0.39 weak, 0.40–0.59 moderate, 0.60–0.79 strong, and 0.80–1.00 very strong[253]. A Wilcoxon signed-rank test compared the UBU score at 4 months and 4 weeks postoperatively, while a Mann-Whitney U test assessed whether patients with a modifier had a lower UBU score than those without. P-values ≤ 0.05 were considered statistically significant.

3. Results

For the evaluation of inter- and intra-rater reliability, 38 patients were included, with an average age of 42.3 ± 11.7 years and a male predominance of 81.1%. The mean correction angle in this group was 7.6 ± 2.7°. In 32.4% of these cases (N = 12), the osteotomy was filled with autologous iliac crest. For the secondary outcomes, an additional thirteen patients from an RCT, with a mean age of 47.8 ± 7.0 years and 69% female, were included. The mean correction angles were 5.5 ± 1.7° for opening-wedge and 5.0 ± 0.7° for closing-wedge osteotomies. In 61% of opening-wedge procedures, the gap was filled with AttraX® Putty.

3.1 Primary objective: Reproducibility of the Uniform Bone Union classification system

A total of 110 radiographs of MOWTHO in 38 patients were assessed twice by three independent observers. Intra-observer reliability of the UBU classification system was substantial to almost perfect, with the squared weighted kappa values ranging from 0.78 to 0.98 (Table 2). Reader 1 demonstrated a kappa of 0.98 (95% CI: 0.97–0.99), while reader 2 showed a kappa of 0.81 (95% CI: 0.76–0.86). Reader 3 exhibited a kappa of 0.78 (95% CI: 0.72–0.83).

The inter-observer reliability was substantial, with the squared weighted kappa values ranging from 0.74 to 0.79 (Table 2). The squared weighted kappa for reader 1 and reader 2 was 0.78 (95% CI: 0.73–0.83), indicating substantial agreement. Between reader 1 and reader 3, the kappa was 0.79 (95% CI: 0.73–0.84), also reflecting substantial agreement. The agreement between reader 2 and reader 3 yielded a kappa of 0.74 (95% CI: 0.69–0.80).

Table 2 - Intra- and interobserver reliability for the three observers, reported as squared weighted kappa with corresponding confidence intervals.

Reader(s)	Type	Kappa	Confidence Interval	P-value
Reader 1	Intra-observer	0.98	0.97;0.99	< 0.001
Reader 2	Intra-observer	0.81	0.76;0.86	< 0.001
Reader 3	Intra-observer	0.78	0.72;0.83	< 0.001
Reader 1 vs. Reader 2	Inter-observer	0.78	0.73;0.83	< 0.001
Reader 1 vs. Reader 3	Inter-observer	0.79	0.73;0.84	< 0.001
Reader 2 vs. Reader 3	Inter-observer	0.74	0.69;0.80	< 0.001

Radiological modifiers of nonunion were observed in ten out of 38 patients. In three patient, multiple modifiers were scored. In total, sclerosis of the osteotomy was scored nine times, loss of correction was observed three times, and hinge fracture was scored five times. The agreement for modifiers ranged from 88% to 98% for interobserver agreement and from 84% to 96% for intraobserver agreement. Specifically, reader 1 exhibited an absolute intra-observer agreement of 98%, while reader 2 showed an agreement of 96%, and reader 3 demonstrated an agreement of 88%. For interobserver agreement, reader 1 and reader 2 achieved an absolute agreement of 96%, reader 1 and reader 3 showed an absolute agreement of 84%, and reader 2 and reader 3 reached an absolute agreement of 86%.

3.2 Secondary objectives

3.2.1 Time effects of union

At one month (mean 1.0 ± 0.4 month), the mean UBU score was 4.3 ± 2.3. A significant negative correlation between the UBU score and degree of correction was observed (ρ = -0.46, $P < 0.01$), indicating larger corrections were associated with lower UBU scores irrespective of graft application. By four months (mean 4.1 ± 0.9 months), the mean UBU score increased to 6.5 ± 2.0, with still a significant negative correlation with correction angle (ρ = -0.5, $P < 0.01$). The UBU score at 4 months was significantly higher than the UBU score at 4 weeks ($P < 0.01$). At six (mean 6.6 ± 0.5 months) and twelve months (mean 12.2 ± 0.4 months), scores showed further increase, with the mean UBU score of 7.4 ± 1.3 and 8.7 ± 0.4, respectively. Figure 3 illustrates a trend of increasing UBU scores over time, with a distinction made between large (≥ 7°) and small corrections (< 7°), based on the mean correction angle of 7.6° in this group. Smaller corrections exhibit higher UBU scores compared to larger corrections, but both approach a score of 9 points at the 1-year follow-up.

At one month postoperatively, no significant differences ($P = 0.63$) in UBU scores were observed between patients with and without a modifier. By 4 months, the total UBU score increased to 6.9 ± 2.0 in patients without a modifier, compared to 5.2 ± 1.6 in those with ($P < 0.05$). Patients with a modifier had a significantly higher correction angle of 9.2 ± 2.2 compared to 6.5 ± 2.7 in those without a modifier ($P < 0.05$).

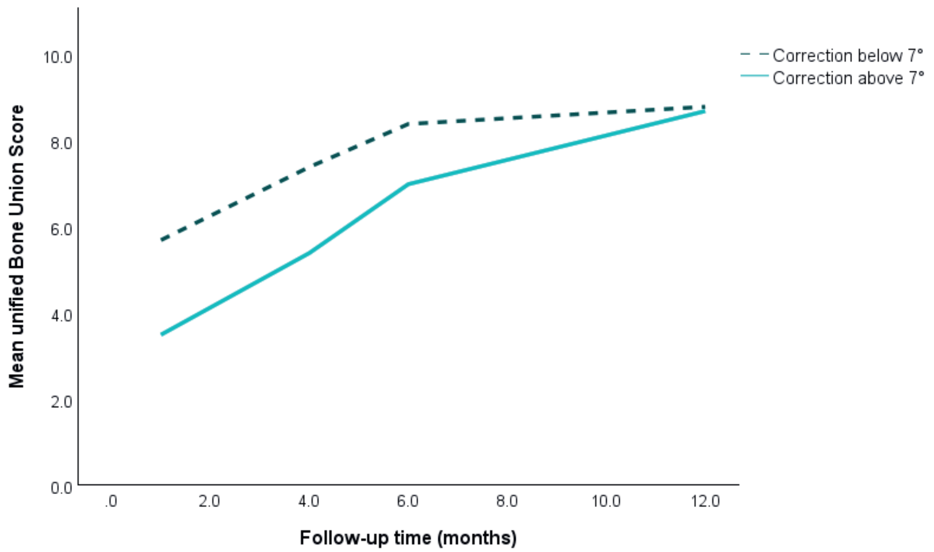

Figure 3 - The mean Enhanced Bone Union score over time for all patients, stratified by corrections less than 7° and corrections greater than 7°. The mean score represents the average of the assessments provided by the three raters.

3.2.2 Comparison of radiographs and CT-scans

The mean UBU score for the six-month radiograph of any type of osteotomy was 7.5 ± 1.5. For the six-month CT scan, the mean UBU score was 8.2 ± 0.9. The correlation between the UBU score on the radiograph and the CT scan was 0.82 (95% CI: 0.71–0.90, P < 0.01), indicating very strong agreement.

3.2.3 Evaluation across different types of osteotomies

The inter-observer reliability of the UBU classification system in patients undergoing tibia (N = 48 radiographs) and femur osteotomies (N = 24 radiographs), including both closing and opening-wedge procedures, was found to be substantial, with a quadratic weighted kappa of 0.75 (95% CI: 0.70–0.79, P < 0.01). Specifically, for closing-wedge osteotomy, the kappa value was 0.73 (95% CI: 0.63–0.83, P < 0.01), while for opening-wedge osteotomy, it was 0.74 (95% CI: 0.69–0.79, P < 0.01). Closing - wedge osteotomies exhibit higher UBU scores compared to opening-wedge osteotomies (Figure 4). The mean UBU scores for closing wedge osteotomies at 1 month, 4 months, 6 months, and 1 year were 4.9 ± 2.5, 8.0 ± 1.5, 8.3 ± 1.6, and 8.8 ± 0.4, respectively. The mean UBU scores for opening-wedge osteotomies at 1 month, 4 months, 6 months, and 1 year were 4.3 ± 2.6, 6.4 ± 2.6, 7.3 ± 1.4, and 8.4 ± 1.1, respectively. When considering osteotomy with gap filler, the kappa value was 0.75 (95% CI: 0.68–0.83, P < 0.01), compared to 0.72 (95% CI: 0.64–0.80, P < 0.01) for those without gap filler. See Figure 4.

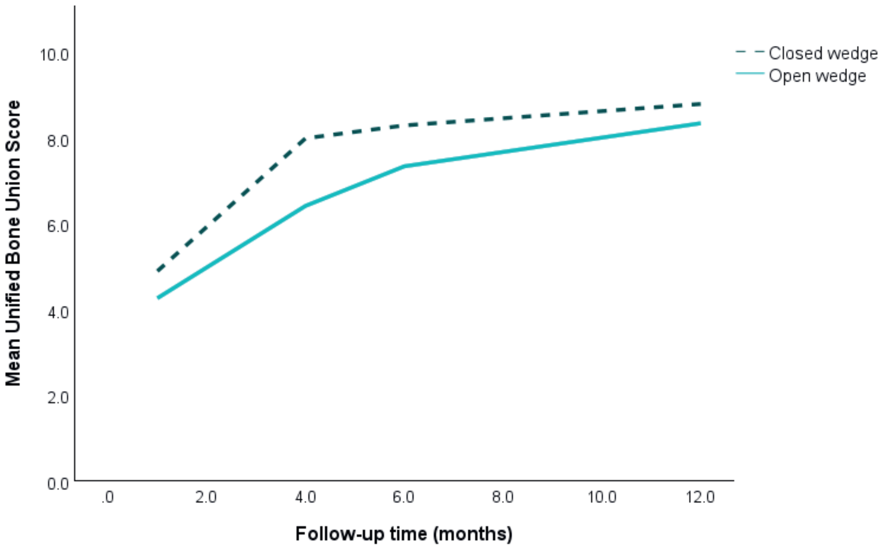

Figure 4 - The mean Enhanced Bone Union score over time for all patients, stratified by closed- and open-wedge osteotomies. The mean score represents the average of the assessments provided by the three raters.

4. Discussion

This study introduced the UBU classification to assess bone union on radiographs after osteotomy and evaluated its reliability. Unlike existing systems, UBU applies to osteotomies with and without gap fillers, closing- and opening-wedge osteotomies, and accounts for negative union signs associated with delayed or nonunion. The intra- and inter-observer reliability was substantial to almost perfect, underscoring that the UBU classification demonstrates robust reproducibility regardless of observer experience. Good agreement was also observed for the presence or absence of radiological modifiers. In addition, we observed a strong correlation between the UBU score on radiographs and CT scans.

Expanding the UBU classification to include different osteotomy types, such as opening- and closing-wedge procedures, as well as femoral and tibial osteotomies, showed consistently substantial inter-observer reliability. The classification also maintained its reliability when distinguishing between techniques with and without gap fillers. These findings reinforce its applicability across various surgical approaches. This consistency highlights the UBU classification as a reliable tool for assessing bone union in both clinical practice and research. Moreover, the UBU classification offers a standardized approach that accommodates both opening- and closing-wedge osteotomies, with or without gap fillers. This makes it particularly suitable for studies where treatment arms differ in the use of fillers, eliminating the need for separate systems and avoiding non-comparable outcomes. Furthermore, the current lack of a universally applied classification system hinders meaningful cross-study comparisons between treatments. By providing a comprehensive and reproducible framework, the UBU classification has the potential to enhance standardization and improve the comparability of osteotomy research, thereby contributing to the optimization of osteotomy procedures and patient outcomes. In clinical practice, the UBU classification can be utilized to guide decisions regarding the removal of osteosynthesis material, with the expectation that osteosynthesis material may be removed at a phase 3 score in two out of three zones (hinge, middle, and gap side) of the osteotomy.

In addition to its reproducibility and broad applicability, the UBU classification also demonstrated a general trend of increasing scores over time, indicating progressive bone union. At four months postoperatively, the total UBU score was significantly higher than at four weeks. We observed a trend toward lower UBU scores at four months postoperatively in patients with at least one modifier on their radiographs compared to those without modifiers. Furthermore, larger correction angles correlated significantly with lower UBU scores, aligning with previous findings[424,425]. These results further underscore the value of the UBU classification in assessing bone healing over time, reinforcing its potential as a standardized tool for monitoring bone union in both clinical and research settings.

Beyond its reproducibility and broad applicability, the UBU classification also proved effective in assessing bone union over time. Radiographs are commonly used for assessing bone union over time, but CT is considered the gold standard for imaging bone and has been shown to be superior in evaluating bone union[426–428]. To explore the diagnostic accuracy of the UBU classification, a preliminary analysis was conducted, revealing a strong, significant, correlation between UBU scores on radiographs and those on CT scans. This finding further supports the validity of the classification system and suggests that UBU may be reliably applied across different imaging modalities. Such applicability is particularly relevant in clinical practice, where radiographs remain the primary imaging tool despite their limitations. Nonetheless, it is important to acknowledge that this preliminary analysis was based on a small cohort of thirteen patients. Furthermore, we recognize that CT imaging is not the gold standard, which is manual assessment after removal of the hardware. As this test is not an option as a standardized outcome measure in clinical research, the CT-scan remains the best non-invasive reference modality currently available, providing the closest approximation to reality. Future research with larger sample sizes is required to further evaluate the UBU classification's accuracy compared to CT, and to solidify its role in clinical decision-making.

Several limitations should be acknowledged. First, we included patients who underwent MOWHTO to test the reproducibility of the UBU score while maintaining a homogeneous study population. For the secondary outcome, both closing- and opening-wedge osteotomies of the femur and tibia were included to assess the broader applicability of the UBU score. However, this was evaluated using fifty radiographs. Second, radiographs and CT-scans were assessed on different computer screens with varying resolutions, which may have influenced image interpretation. However, this reflects real-world clinical practice, where radiologists typically use high-resolution diagnostic monitors while treating physicians often review images on lower-resolution screens. Additionally, the UBU classification is purely a radiographic system for evaluating bone union and does not incorporate clinical factors such as pain during weight-bearing[396,429,430], which may also be relevant in assessing healing. Third, we realize that some scores can be biased due to the interaction between parameters. For example, larger gaps involved bone graft and CT scans were only made for small gap sizes in our research. Fourth, the analysis comparing patients with and without modifiers was based on small groups (10 patients with modifiers versus 28 without). This limited sample size should be taken into account when interpreting the results.

Fifth, by using the average UBU score across raters to compare with CT scans, the direct relationship between individual user scores and CT-based validation may be diminished. This approach provides a surrogate measure, which could limit the assessment of correlation at the level of individual raters. Lastly, beyond assessing reproducibility, we performed a preliminary evaluation of the diagnostic accuracy of the UBU classification in a small cohort of thirteen patients. For this preliminary evaluation of diagnostic accuracy, we used CT imaging as the best available non-invasive reference standard, as described in the previous paragraph.

5. Conclusion

The UBU classification system provides a standardized and reproducible method for assessing progression of bone union after an osteotomy, demonstrating substantial to almost perfect inter- and intra-observer reliability. Unlike existing systems, UBU applies to osteotomies with and without gap fillers, closing- and opening-wedge osteotomies, and accounts for negative union signs. This study further provides valuable insights into bone healing over time, demonstrating a general trend of increasing UBU scores in time which allows early assessment as a proxy for success. Additionally, the preliminary evaluation of diagnostic accuracy suggests very strong correlation between UBU scores on radiographs and those on CT scans. Future research should focus on further validating the diagnostic accuracy of the UBU classification, particularly through CT-based assessments and potential intraoperative validation, to enhance its clinical applicability and establish its broader utility in bone healing monitoring.

13

Chapter 13

Hinge Position Dominance Over Osteotomy Inclination in Medial Open-Wedge High Tibial Osteotomy: A Key Factor in Posterior Tibial Slope Changes

Eva A. Bax, H. Chien Nguyen, Nienke van Egmond, Cornelis H. Slump, Moyo C. Kruyt, Roel J.H. Custers, Edsko E.G. Hekman

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Abstract

Objective: A medial open-wedge high tibial osteotomy (MOWHTO) may increase the posterior tibial slope (PTS). The purpose of this study was to determine the effect of the osteotomy inclination angle (in the sagittal plane) in combination with different hinge positions (in the transverse plane) on the change in PTS due to a MOWHTO.

Methods: We developed a mathematical approach to determine the effect of the osteotomy inclination angle combined with different hinge positions. The change in PTS was determined for different osteotomy inclination angles, hinge positions, and intended wedge angles. Anterior-inclined, parallel, and posterior-inclined osteotomy inclination angles were simulated. Hinge positions varied between 5° anterolateral and -45° posterolateral. The wedge angles were 5°, 10°, and 15°. Moreover, two in-silico osteotomies were performed to verify the results of the mathematical model.

Results: The PTS was maintained when the osteotomy cut was performed parallel to the tibial plateau with a lateral hinge position. The PTS changed when the osteotomy was not aligned in the sagittal plane, ranging between 0.0° to 0.6°. Different hinge positions, however, had a large effect on post-operative PTS change, ranging between 0.1° to 10.7°.

Conclusions: Our mathematical approach showed that the hinge position has a strong effect on the PTS. The sagittal osteotomy inclination angle had little effect on the PTS. An inclination angle parallel to the medial tibial plateau combined with a lateral hinge position does not change the PTS.

1. Introduction

Medial open-wedge high tibial osteotomy (MOWHTO) is an established treatment for relatively young and active patients with an early stage of unicompartmental medial osteoarthritis and varus deformity of the knee[431–433]. MOWHTO redistributes the mechanical load from the medial to the lateral compartment in the coronal plane and, therefore, reduces the articular cartilage pressure in the medial compartment. This results in a reduction of pain and improvement of knee joint function[431]. However, in addition to coronal alignment, unintended changes may also occur in the sagittal plane due to a MOWHTO[434,435].

Several studies indicate an increase of posterior tibial slope (PTS) due to a MOWHTO, which increases the tensile load on the anterior cruciate ligament (ACL) and affects knee stability[431,436,437]. Sometimes, the osteotomy is performed with the intention to decrease the PTS as a treatment for ACL instability, for example when one or more previous ACL reconstruction(s) failed or when there is a pre-existent high PTS in combination with an ACL rupture. In general, this increase in the tensile load on the ACL is not intended. Moreover, a change in the PTS results in a different distribution of the mechanical load on the articular surface. For example, an increased PTS results in anterior translation of the tibial plateau, resulting in decompression of the posterior femoral condyles[438]. Factors that could cause a PTS change during a MOWHTO are the sagittal osteotomy inclination angle and the hinge position.

Recently, several studies have investigated that to maintain the PTS, the sagittal osteotomy inclination angle should be parallel to the medial tibial plateau, and the hinge should be located laterally[431,434,435,439–441]. Moreover, a posterolateral hinge position increases the PTS[435,439,442]. However, several of these studies have also shown that performing the perfect osteotomy according to these requirements is difficult in practice[435,441]. Whereas the effect of the osteotomy inclination angle and the effect of the hinge position on the PTS have been studied separately, we found no study which examines the combined effect[431,435,439–442]. This is unfortunate, since studying the effect of one parameter while not taking into account the other can lead to non-conclusive outcomes. Moon *et al.*[440] concluded that changes in PTS are probably greater if the hinge position is considered in addition to only the osteotomy inclination angle. This confirms the need for virtual model studies, especially since a MOWTHO is rarely performed perfectly.

In this study we investigated the effect of the osteotomy inclination angle in combination with different hinge positions on the change in PTS in a MOWHTO using a mathematical model. We hypothesized that a posterior-inclined osteotomy and posterolateral hinge positions would increase the PTS. Moreover, we expected the PTS to decrease with an anterior-inclined osteotomy and anterolateral hinge positions. Finally, for illustration purposes, the results were presented in an in-silico model.

2. Methods

We performed in-silico MOWHTOs for a range of osteotomy inclination angles, hinge positions, and wedge angles. The osteotomy inclination angle (φ) was defined as the angle between the medial tibial plateau line and the osteotomy line[431]. The osteotomy line was defined as the projection of the osteotomy plane in the sagittal plane. A posterior-inclined osteotomy was defined as being positive, and an anterior-inclined osteotomy as negative (Figure 1). Different osteotomy inclination angles were simulated: posterior-inclined osteotomy of 10°, parallel osteotomy, anterior-inclined osteotomy of -10°, and anterior-inclined osteotomy of -20°. Furthermore, we defined the hinge position (ω) as the angle between the sagittal plane and the end of the osteotomy cut. We defined the hinge position as negative when the cut was made in a posterolateral position relative to a lateral hinge, and as positive when the cut was made anterolaterally relative to a lateral hinge (Figure 1). A lateral hinge position refers to a hinge position parallel to the osteotomy line in the sagittal plane when the osteotomy was performed from the medial to the lateral side of the tibia. In our simulations, we varied these hinge positions from -10° posterolateral to 5° anterolateral, with increments of 5°. Posterolateral hinges of -30° and -45° were added for illustration as extreme values. Moreover, the wedge angles (θ) were defined parallel to the direction of the saw blade (Figure 1) and varied between 5°, 10°, and 15°. Table 1 summarizes the osteotomy inclination angles, hinge positions, and wedge angles.

Table 1– Overview of the different osteotomy inclination angles (φ), hinge positions (ω), and wedge angles (θ).

Osteotomy inclination angle (φ)	**Hinge positions (ω)**	**Wedge angles (θ)**
Posterior-inclined osteotomy of 10°	Anterolateral hinge of 5°	5°
Parallel osteotomy	Lateral hinge of 0°	10°
Anterior-inclined osteotomy of -10°	Posterolateral hinge of -5°	15°
Anterior-inclined osteotomy of -20°	Posterolateral hinge of -10°	
	Posterolateral hinge of -30°	
	Posterolateral hinge of -45°	

To describe the in-silico osteotomy, we included a right-handed coordinate system which is defined as shown in Figure 2. In accordance with the axes of a computed tomography imaging device, the positive Z-axis was directed cranially (in the direction of the anatomical axis of the tibia), the positive X-axis laterally, and the positive Y-axis anteriorly. The transverse plane was defined perpendicular to the anatomical axis of the tibia. The sagittal plane was defined as perpendicular to the transverse plane and between the medial tuberosity and the attachment point of the posterior cruciate ligament. The coronal plane was perpendicular to the transversal and sagittal plane. This coordinate system is fixed with respect to the tibia. Since we are interested in rotations and changes of angles, the position of this coordinate system can be arbitrarily chosen.

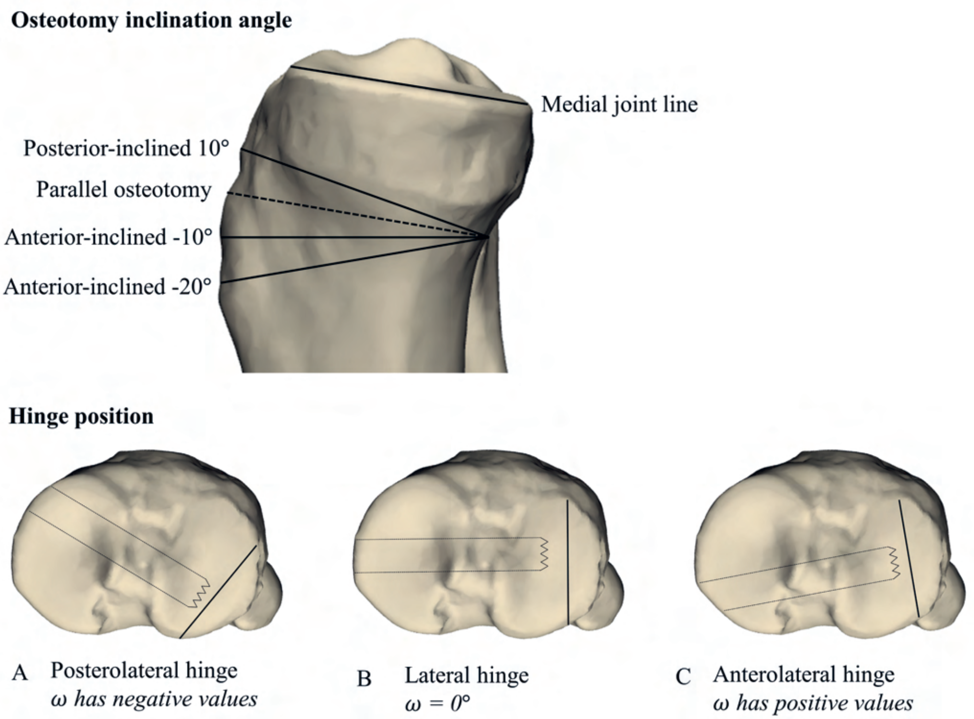


Figure 1 - Osteotomy inclination angle: Medial view of the 3-dimensional model of a right knee with associated osteotomy inclination angles. The osteotomy inclination angle was defined as the angle between the medial tibial plateau line and the osteotomy line (dashed line). Posterior-inclined osteotomies were defined as positive. Anterior-inclined osteotomies as negative. Hinge position: Transverse view of the 3-dimensional model of a right knee with associated hinge positions (ω). The dashed line represents the oscillating saw blade, and the black solid line represents the hinge line. Figure A shows posterolateral hinge position. Figure B and C show lateral and anterolateral hinge positions, respectively. A lateral hinge position refers to a hinge position parallel to the osteotomy line in the sagittal plane.

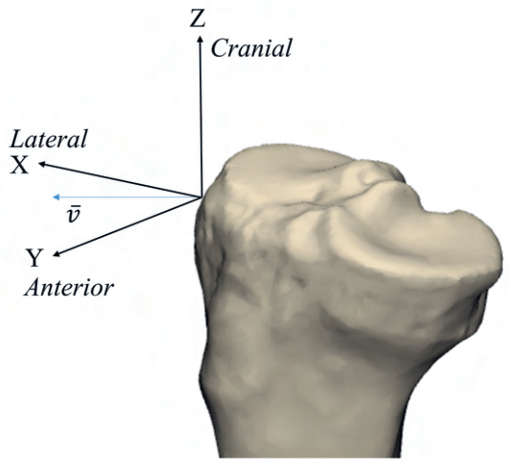


Figure 2 - Definition of the axis for a 3-dimensional model of a right knee. $\bar{v}$ represent the posterior tibial slope in the sagittal plane.

In practice, the MOWHTO consists of one rotation of the tibial plateau around the hinge axis, but for mathematical modelling, it is convenient to envision the in-silico MOWHTO as a series of five consecutive rotations around one of the fixed axes of the coordinate system. These rotations describe the process of an osteotomy. By using the rotations, in-silico osteotomies were performed, and the changes in PTS were measured. The rotation matrices are described in detail in the additional file 1.

A tibia with PTS of 10° was used for modelling the effects of osteotomy inclination angles and hinge positions. The PTS was defined using the anatomical axis of the tibia. We performed three series of calculations:

- Lateral hinge, variation of osteotomy inclination angle between -20° and 10°
- Parallel osteotomy, variation of hinge position between -45° and 5°
- Combination of varying osteotomy wedge angles and varying hinge positions

In each case, the in-silico osteotomies were performed, and the changes in PTS were measured.

For illustration purposes, an existing computed tomography (CT) scan (slice thickness 2mm; 120kV; 60 mAs; Siemens Medical Solutions, Erlangen, Germany) of the lower limb of one patient was anonymized and imported into Mimics 23.0 (Materialise, Leuven, Belgium), to create a three-dimensional (3D) bone model of the right tibia and fibula. The segmented 3D model was transferred to 3-Matic (Materialise, Leuven, Belgium) to perform an in-silico MOWHTO. The PTS was defined as the angle between the line along the medial tibial plateau and the line perpendicular to the anatomical axis of the tibia (Figure 3)[443]. The PTS measurements were performed in the sagittal plane, which was defined as being perpendicular to the transverse plane and runs through Akagi's line[280]. The transverse plane was oriented perpendicular to the mechanical axis of the tibia. Two in-silico osteotomies were performed. One osteotomy with an inclination angle parallel to the medial tibial plateau and lateral hinge position. The other with an anterior-inclined osteotomy of -10° and a posterolateral hinge position of 45°. An anterior-inclined osteotomy of 10° was performed, as it varies in the literature between 5° and 15°[435,441]. Both osteotomies were performed with a wedge angle of 10°. The difference between pre-and postoperative PTS was determined.

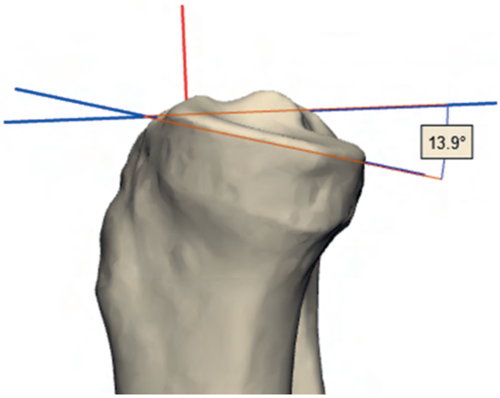
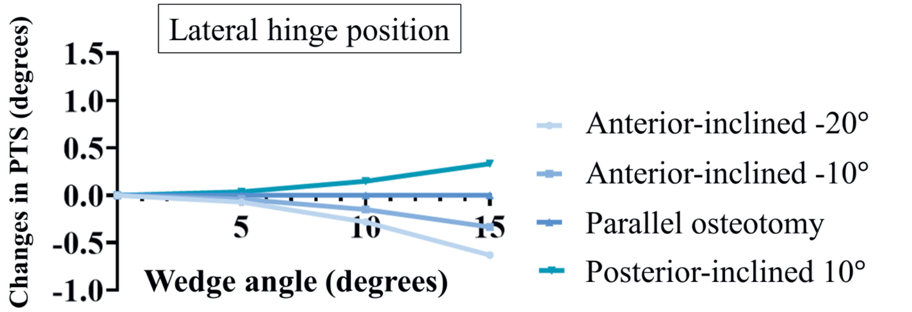


Figure 3 - Medial view of the measurement of the posterior tibial slope. In the sagittal plane, the posterior tibial slope was defined as the angle between the line along the medial tibial plateau and the line perpendicular to the anatomical axis of the tibia. The anatomical axis is represented by the red line. The measured posterior tibial slope in this figure is 13.9°.

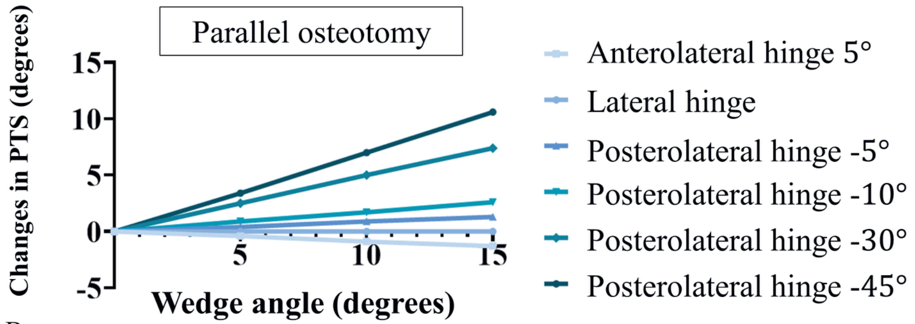
3. Results

A minimal change in PTS was found due to MOWHTO with a lateral hinge position (ω=0) but with different osteotomy inclination angles, see Figure 4A. The PTS increased with a posterior-inclined osteotomy and decreased with an anterior-inclined osteotomy. There was no change in PTS with a parallel osteotomy.

The changes in PTS resulting from different hinge positions, with a perfectly parallel osteotomy (ϕ=0), are illustrated in Figure 4B. An anterolateral hinge position resulted in a decreased PTS whereas a posterolateral hinge position resulted in an increase in PTS. A parallel osteotomy combined with a lateral hinge position resulted in no PTS changes. An osteotomy parallel to the medial tibial plateau and a posterolateral hinge position of -45°, resulted in a PTS change of 3.5°, for a wedge of 5°. For a wedge angle of 10° and 15°, the change in PTS is 7.0° and 10.6°, respectively. Table 2 and Figure 5 represent the difference in PTS for combinations of different hinge positions and osteotomy inclination angles. A positive value indicates an increase in PTS and a negative value a decrease in PTS.



A.



B.

Figure 4 - Changes in posterior tibial slope for different wedge angles. A) shows changes in posterior tibial slope for a lateral hinge position for different osteotomy inclination angles and wedge angles. B) shows changes in posterior tibial slope based on parallel osteotomy for different hinge positions and wedge angles. Note that the Y-axis in Figure B is 10x larger than in Figure A.

3.1 In silico test

The pre-surgical PTS of the 3D model of the included tibia was 13.9°. After performing a 10° MOWHTO with an osteotomy inclination angle parallel to the medial tibial plateau and a lateral hinge position, the PTS remained 13.9° (Figure 6A and B). After performing a MOWHTO of 10° with an anterior-inclined osteotomy of -10° and a posterolateral hinge position of -45°, the PTS was 20.9° (Figure 6C and D), an increase of 7.0°. This was fully consistent with our mathematical approach, which indicated a similar increase in PTS of 7.0° for this inclination angle, hinge position and wedge angle.

Table 2 – The difference in posterior tibial slope for different hinge positions (ω) and osteotomy inclination angles (φ). The different osteotomy inclination angles are anterior-inclined osteotomy of -20°, anterior-inclined osteotomy of -10°, parallel osteotomy, and posterior-inclined osteotomy of 10°. Negative hinge values correspond to a posterolateral hinge, positive values to an anterolateral hinge. A positive posterior tibial slope difference indicates an increase in slope; a negative value indicates a decrease in slope.

	ω=5°	ω=0°	ω=-5°	ω=-10°	ω=-30°	ω=-45°
Wedge angle θ = 5°						
Anterior inclined osteotomy of -20°	-0.5°	-0.1°	0.4°	0.8°	2.4°	3.5°
Anterior inclined osteotomy of -10°	-0.5°	0.0°	0.4°	0.8°	2.5°	3.5°
Parallel osteotomy	-0.4°	0.0°	0.4°	0.9°	2.5°	3.5°
Posterior inclined osteotomy of 10°	-0.4°	0.0°	0.5°	1.0°	2.5°	3.6°
Wedge angle θ = 10°						
Anterior inclined osteotomy of -20°	-1.2°	-0.3°	0.6°	1.5°	4.8°	6.9°
Anterior inclined osteotomy of -10°	-1.0°	-0.2°	0.7°	1.6°	4.9°	7.0°
Parallel osteotomy	-0.9°	0.0°	0.9°	1.7°	5.0°	7.0°
Posterior inclined osteotomy of 10°	-0.7°	0.2°	1.0°	1.9°	5.1°	7.1°
Wedge angle θ = 15°						
Anterior inclined osteotomy of -20°	-1.9°	-0.6°	0.7°	2.0°	7.0°	10.3°
Anterior inclined osteotomy of -10°	-1.6°	-0.3°	1.0°	2.3°	7.2°	10.4°
Parallel osteotomy	-1.3°	0.0°	1.3°	2.6°	7.4°	10.6°
Posterior inclined osteotomy of 10°	-1.0°	0.3°	1.6°	2.9°	7.7°	10.7°

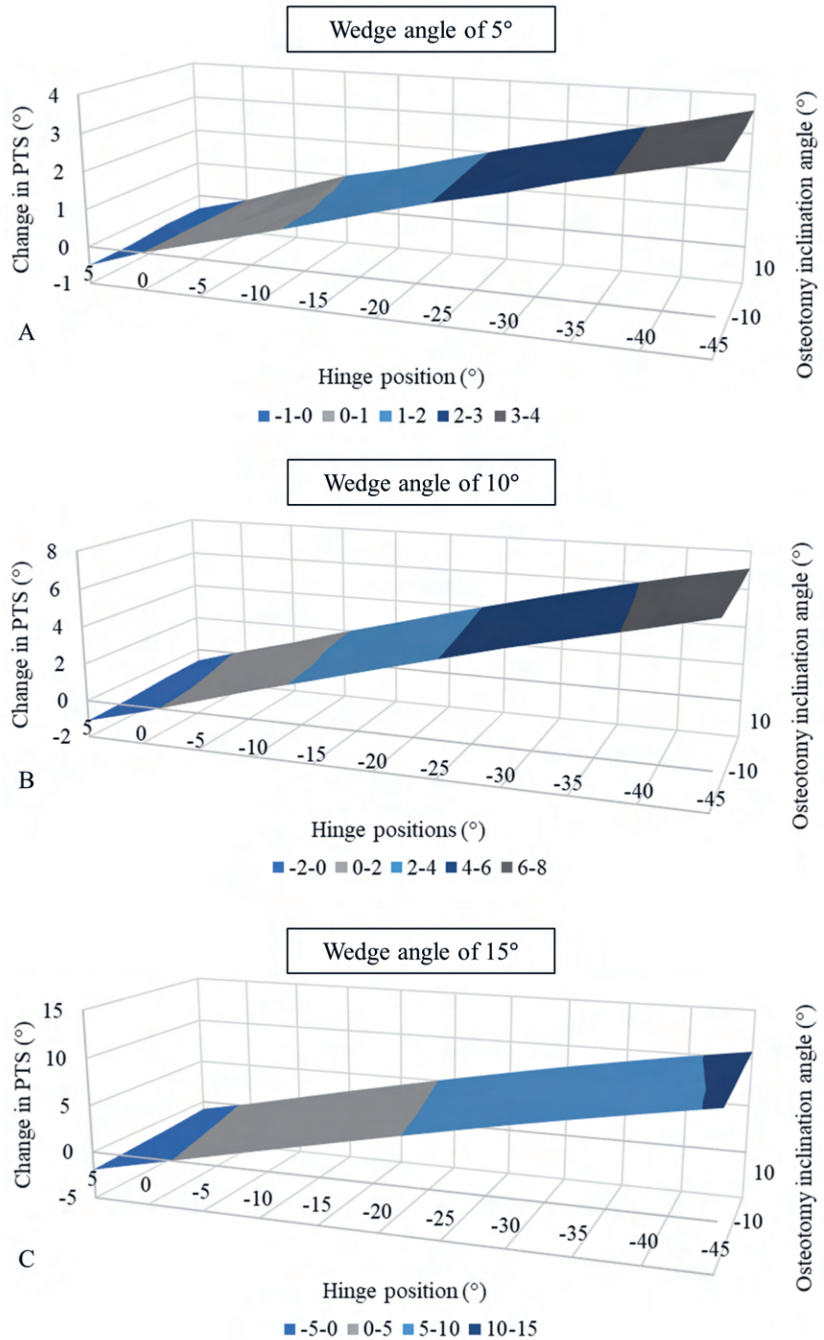


Figure 5 - Combined effect of osteotomy inclination angle and hinge position on changes in posterior tibial slope for different wedge angles.

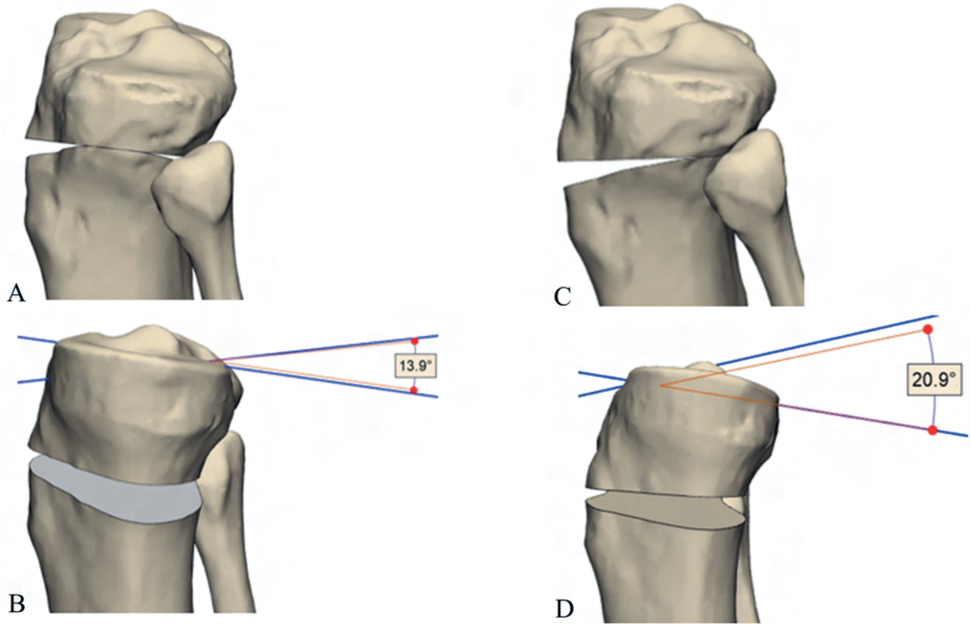


Figure 6 - Results of the virtual osteotomy. A) shows a 3-dimensional lateral view of an osteotomy inclination angle parallel to the medial tibial plateau and a lateral hinge position. B) shows a 3-dimensional medial view of the measurement of the posterior tibial slope using the proximal tibial anatomic axis method. The measured posterior tibial slope was 13.9°. C) shows a 3-dimensional lateral view of the anterior-inclined osteotomy of −10° and a posterolateral hinge position of −45°. D) shows a 3-dimensional medial view of the measurement of the posterior tibial slope using the proximal tibial anatomic axis method. The measured posterior tibial slope was 20.9°.

4. Discussion

In this study, we determined the effect of the osteotomy inclination angle combined with different hinge positions on the change in PTS in a MOWHTO using a mathematical approach. The most important finding of this combined effect demonstrated that the hinge position had a strong effect on the PTS, in contrast to the osteotomy inclination angle. As a result of different osteotomy inclination angles, the PTS changed by a maximum of 0.6° in a lateral hinge condition, which may not be clinically relevant. The different hinge positions resulted in PTS changes up to 10.7°. Therefore, the hinge position had a stronger effect on PTS changes compared to the inclination angle.

The position of the hinge appeared to be an important parameter to determine changes in the PTS. Frings et al.[444] investigate the impact of variable hinge positioning and osteotomy gap height on alignment in both the sagittal and coronal planes, using twenty uniplanar MOWHTOs in solid-foam proximal tibia models. They concluded that changes in PTS can be minimized by positioning the hinge in a straight lateral alignment. Other studies presented the same results[434,435,439,442,444]. However, performing a lateral hinge can be difficult[434,435]. First, a study suggested that the Kirschner wire, used to guide the osteotomy, should be placed from the medial to the lateral cortex of the proximal tibia rather than from the anteromedial to the posterolateral side[439]. Second, a lateral hinge position can be achieved by inspecting the osteotomy using the gap ratio[435,439]. The gap ratio is the ratio of anterior gap to posterior gap in a true lateral view in the MOWHTO[435]. The gap ratio increases with a posterolateral hinge.

Furthermore, our results indicated that the effect of the osteotomy inclination angle on the PTS was marginal. The PTS increased due to a posterior-inclined osteotomy, while remaining the same in case of a parallel osteotomy and decreased due to the anterior-inclined osteotomy. This was also reported by other studies [431,440,441]. Chung *et al.*[431,440] concluded that a parallel osteotomy inclination angle was required to overcome changes in PTS. Moon *et al.*[440] reported in a virtual simulation of a square column model that an osteotomy inclination angle parallel to the medial joint line caused no change in PTS. Moreover, the PTS increased in the posterior-inclined osteotomy and decreased in the anterior-inclined osteotomy. This was consistent with the results found in our study for a laterally oriented hinge. Also, Lee *et al.*[441] concluded that the osteotomy should be performed parallel to the medial joint line to avoid PTS changes, but on the same time they showed that performing a parallel osteotomy was difficult in practice. On the contrary, our results showed that due to different inclination angles, the PTS changed by a maximum of 0.6° in a lateral hinge condition, which does not appear to be clinically relevant[445].

Several studies have investigated the change in PTS due to a MOWHTO. Nha *et al.*[446] reported an increase in PTS of 2.0° and Giffin *et al.*[447] concluded an increase of 4.4° due to a MOWHTO. Our mathematical approach showed that a hinge position, which varies between 5° anterolateral and -10° posterolateral yielded a PTS change comparable to the literature. The effect of the osteotomy inclination angle on changes in PTS is negligible. Therefore, orthopedic surgeons should make every effort to perform a lateral hinge position to avoid unintended PTS changes.

This study had several limitations. First, this study is a mathematical, theoretical model. The influence of other factors, such as soft tissue, the absence of the proximal tibiofibular joint, surgical techniques, and the trapezoid concept of the tibia were not considered in our mathematical model. This may limit the translation of mathematical model to the clinical setting. However, it is important to mention that the strength of a mathematical model is that only one simulation is needed, and it is applicable to all situations without being influenced by external variables. Additionally, we only presented the results for an average PTS of 10°. Second, this mathematical model does not consider the effect of the investigated parameters on tibial rotation. Third, in our study, we performed a horizontal oblique osteotomy targeting the tip of the fibular head. However, to preserve the tibial tubercle and the patellar height, often a biplanar osteotomy will be performed intraoperatively[448]. We expect this does not affect the results of this study, as the horizontal oblique osteotomy remains the same in a biplanar osteotomy. Fourth, in our research, we considered the imposed wedge angle while not accounting for the resulting correction in the coronal plane. We realize that the wedge angle is usually not equal to the correction angle, except when the hinge is perfectly perpendicular to the coronal plane. An unintended, non-lateral hinge position combined with a sagittal osteotomy inclination angle, will cause undercorrection or overcorrection [435,439,442,449]. Our study did not investigate this, as our primary focus was on examining the impact of the osteotomy inclination angle and hinge position on PTS changes, rather than the resulting correction. This will be interesting to investigate in future research, as explored by Frings *et al.*[444] by solid-foam proximal tibia models Finally, there is a shared commitment in the literature to minimizing PTS changes after MOWTHO. To our knowledge, no previous studies have addressed the definition of clinically relevant PTS changes, making this a crucial area for future research.

Despite these limitations, our mathematical approach has the advantage to study the combined effect of the osteotomy inclination angle and hinge position. Studying the effect of one parameter without taking the others into account can lead to non-conclusive outcomes. Moreover, this method enabled us to vary several parameters separately or combined, across any range we wanted to consider, and without taking measurement errors into account.

5. Conclusion

Our mathematical approach showed that the hinge position has a much stronger effect on changing the PTS than the osteotomy inclination angle. An osteotomy parallel to the medial tibial plateau with a lateral hinge position results in no change in PTS. We hope that this study will create awareness among orthopedic surgeons about the importance of a lateral hinge positing to reduce PTS changes during a MOWHTO.

Additional file – Method of mathematical approach

Suppose we represent the original PTS by a vector $\overline{\boldsymbol{v}}$ in the sagittal (YZ) plane, in the direction of the tibial plateau. After opening the wedge, the new PTS is then represented by the vector $\overline{\boldsymbol{v}}'$. The rotation process can then be mathematically written as consecutive multiplication of this vector by a set of five so-called ‘rotation matrices. Each of these matrices describes one of the rotations, which must be performed to describe the in-silico osteotomy. Using these rotation matrices the effect of the osteotomy inclination angle in combination with different hinge positions on the change is PTS can be determined. First, a rotation around the negative X-axis with angle $-\varphi$ was performed to locate the saw cut in the XY plane. The hinge position was rotated around the negative Z-axis with angle $-\omega$ to position it in the direction of the Y-axis. The osteotomy wedge was opened along the Y-axis with angle θ, whereafter rotated back around the Z-axis and the X-axis with angles ω and φ, respectively. The total rotation matrix is provided in Equation 1. The rotation matrix is provided in Equation 2.

$$\mathrm{Rot_{total}}(\theta,\varphi,\omega) = \mathrm{Rot_x}(\varphi)\cdot\mathrm{Rot_z}(\omega)\cdot\mathrm{Rot_y}(\theta)\cdot\mathrm{Rot_z}(-\omega)\cdot\mathrm{Rot_x}(-\varphi) \tag{1}$$

With:

$$\mathrm{Rot_x}(\varphi) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos(\varphi) & -\sin(\varphi) \\ 0 & \sin(\varphi) & \cos(\varphi) \end{pmatrix}$$

$$\mathrm{Rot_y}(\theta) = \begin{pmatrix} \cos(\theta) & 0 & \sin(\theta) \\ 0 & 1 & 0 \\ -\sin(\theta) & 0 & \cos(\theta) \end{pmatrix}$$

$$\mathrm{Rot_z}(\omega) = \begin{pmatrix} \cos(\omega) & -\sin(\omega) & 0 \\ \sin(\omega) & \cos(\omega) & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

$$\mathrm{Rot_{total}}(\theta,\varphi,\omega) = \begin{pmatrix} R_{1,1} & R_{1,2} & R_{1,3} \\ R_{2,1} & R_{2,2} & R_{2,3} \\ R_{3,1} & R_{2,3} & R_{3,3} \end{pmatrix} \tag{2}$$

With:

$$R_{1,1} = \sin(\omega)^2 + \cos(\omega)^2\cos(\theta)$$

$$R_{1,2} = -\cos(\varphi)\,(\cos(\omega)\sin(\omega) - \cos(\omega)\cos(\theta)\sin(\omega)) - \cos(\omega)\sin(\varphi)\sin(\theta)$$

$$R_{1,3} = \cos(\omega)\cos(\varphi)\sin(\theta) - \sin(\varphi)(\cos(\omega)\sin(\omega) - \cos(\omega)\cos(\theta)\sin(\omega))$$

$$R_{2,1} = \cos(\omega)(\sin(\varphi)\sin(\theta) + \cos(\varphi)\cos(\theta)\sin(\omega)) - \cos(\omega)\cos(\varphi)\sin(\omega)$$

$$R_{2,2} = \cos(\varphi)(\cos(\omega)^2\cos(\varphi) + \sin(\omega)(\sin(\varphi)\sin(\theta) + \cos(\varphi)\cos(\theta)\sin(\omega))) + \sin(\varphi)(\cos(\theta)\sin(\varphi) - \cos(\varphi)\sin(\omega)\sin(\theta))$$

$$R_{2,3} = \sin(\varphi)\left(\cos(\omega)^2\cos(\varphi) + \sin(\omega)(\sin(\varphi)\sin(\theta) + \cos(\varphi)\cos(\theta)\sin(\omega))\right) - \cos(\varphi)(\cos(\theta)\sin(\varphi) - \cos(\varphi)\sin(\omega)\sin(\theta))$$

$$R_{3,1} = -\cos(\omega)(\cos(\varphi)\sin(\theta) - \cos(\theta)\sin(\omega)\sin(\varphi)) - \cos(\omega)\sin(\omega)\sin(\varphi)$$

$$R_{3,2} = \cos(\varphi)\left(\cos(\omega)^2\sin(\varphi) - \sin(\omega)(\cos(\varphi)\sin(\theta) - \cos(\theta)\sin(\omega)\sin(\varphi))\right) - \sin(\varphi)(\cos(\varphi)\cos(\theta) + \sin(\omega)\sin(\varphi)\sin(\theta))$$

$$R_{3,3} = \cos(\varphi)(\cos(\varphi)\cos(\theta) + \sin(\omega)\sin(\varphi)\sin(\theta)) + \sin(\varphi)(\cos(\omega)^2\sin(\varphi) - \sin(\omega)(\cos(\varphi)\sin(\theta) - \cos(\theta)\sin(\omega)\sin(\varphi)))$$

In each case, the rotated vector $\bar{\boldsymbol{v}}'$ can be calculated according to Equation 3. Finally, the resulting new PTS was calculated in the sagittal plane according to Equation 4, in which $\bar{v}'_Y$ and $\bar{v}'_Z$ are respectively the Y- and Z-component of vector $\bar{\boldsymbol{v}}'$.

$$\bar{v}' = \mathrm{Rot}_{\mathrm{total}}(\theta, \varphi, \omega) \cdot \bar{v} \qquad (3)$$

$$\mathrm{PTS}_{\mathrm{rotated}} = \tan^{-1}(\bar{v}'_Y / \bar{v}'_Z) \qquad (4)$$

Chapter 13

Part IV

Impact of Osteotomies on Knee Arthroplasty Outcomes

14

Chapter 14

Outcomes After Conversion of High Tibial Osteotomy to Total Knee Arthroplasty: Nearly 14-Year Follow-Up in a United States Population

Eva A. Bax, Rana A. Ahmad, Marieke A. Kietselaer, Sean C. Clark, Roel J.H. Custers, Michael J. Taunton, Rafael J. Sierra, Mario Hevesi, Daniel B.F. Saris

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Abstract

Background: High tibial osteotomy (HTO) is a joint-preserving treatment for younger patients who have unicompartmental knee osteoarthritis. Although effective, concerns persist that prior HTO may compromise subsequent total knee arthroplasty (TKA). This study aimed to assess the revision-free survival of TKA following ipsilateral HTO and identify factors associated with failure of both procedures in a U.S. population.

Methods: Patients who underwent TKA after prior ipsilateral HTO between 2000 and 2023 at a single academic institution were prospectively followed (n = 134), with a mean follow-up of 13.5 years (range, zero to 24.0) postoperative TKA and median ages at HTO and TKA of 52 and 63 years, respectively. Preoperative TKA radiographs were assessed using the Kellgren and Lawrence system. Kaplan–Meier analysis was performed to assess HTO and TKA survival. The mean HTO survival was 11.7 years (range, zero to 31.0), with a 10-year TKA conversion rate of 35.8%. Cox regressions identified factors associated with osteotomy survival.

Results: Older age (hazard ratio [HR]: 1.06; $P < 0.001$), higher body mass index (HR: 1.03; $P = 0.033$), and lower Charlson Comorbidity Index (CCI) (HR: 0.79; $P < 0.001$) were significantly associated with earlier conversion. Following TKA, 6.0% underwent revision surgery. Revisions were more common in younger patients ($P = 0.01$) and those who had lower CCI ($P = 0.002$). The infection rate for postoperative TKA was 2.2%.

Conclusion: In this U.S. cohort, TKA following prior ipsilateral HTO demonstrated a revision rate of 6.0%, with younger patients who have lower CCI scores more likely to require revision. The mean survival of HTO was approximately 12 years, with age, body mass index, and comorbidity index significantly influencing longevity. These findings support HTO as a durable joint-preserving treatment in younger patients, helping to guide clinical decision-making and may contribute to increased consideration of HTO as a treatment option in suitable people.

1. Introduction

The global incidence and prevalence of knee osteoarthritis (KOA) is rising, primarily due to increasing obesity rates and longer life expectancy[4–7]. In addition to this overall trend, KOA is being diagnosed more frequently in younger patients[450]. For people with symptomatic KOA who experience insufficient symptom relief with conservative treatments, knee arthroplasty remains a well-established treatment option[87]. However, in younger patients, the risk of revision surgery is notably higher, partly attributable to their higher functional demands and longer projected lifespan[91,92]. In this population, joint-preserving procedures—particularly realignment osteotomies—offer an established alternative for the treatment of unicompartmental KOA[94–96]. This procedure has demonstrated favorable long-term survival and clinical outcomes[97,113–115].

Despite these benefits, some surgeons remain hesitant to perform osteotomies, as it has been suggested that a prior osteotomy may compromise future total knee arthroplasty (TKA) outcomes. Reported concerns include underlying angular deformity, patella baja, the potential need for hardware removal, and an elevated risk of infection[451–454]. These factors may increase the technical complexity of the procedure and affect long-term outcomes following TKA. Several meta-analyses have investigated these concerns, but results remain mixed[454,455]. There was one analysis that reported higher revision rates in patients who underwent TKA following a previous osteotomy, while another found no statistically significant difference. Both, however, identified higher infection rates in patients who had a history of high tibial osteotomy (HTO)[454,455]. Overall, the evidence is inconsistent, with most available data derived from studies conducted in Europe. Evidence from the United States (U.S.) population remains limited, highlighting the need for further research in this population.

Given the limited and regionally skewed evidence to date, there remains a need for population-based studies from the United States to better understand the long-term outcomes of TKA following prior osteotomy. To address this gap, the present study aimed to evaluate the survival of TKA, defined by revision-free survival, in patients who had a history of ipsilateral HTO within a U.S. population, with a mean follow-up of nearly 14 years. As a secondary objective, we assessed the survivorship of the HTO itself and investigated risk factors associated with osteotomy and TKA failure.

2. Methods

2.1 Study design

A retrospective review was conducted of all patients who underwent TKA between July 25, 2000, and May 11, 2023, at a single academic medical center. Institutional review board (Mayo Clinic IRB #15-000601) approval was obtained prior to data collection. Inclusion criteria encompassed patients who had previously undergone an HTO of the same knee prior to their TKA. Patients who had distal femoral osteotomies or combined procedures involving both distal femoral and proximal tibial osteotomies were excluded. Following TKA, patients were prospectively monitored through the Mayo Clinic Total Joint Registry (TJR) to evaluate implant survival, as well as the incidence of revision surgeries and complications, such as postoperative infections. The TJR systematically collects patient demographics, surgical data, and postoperative complications in a prospective manner for every person receiving joint arthroplasty at the institution.

2.2 Patients

A total of 134 patients met the inclusion criteria, having undergone an HTO followed by TKA. These patients were followed for a mean duration of 25.7 years (range, 7.0 to 36.0) after their HTO. The HTO surgeries were performed between 1988 and 2017, all at the Mayo Clinic. Subsequent TKA procedures were carried out at the same institution between 2000 and 2023. Lateral closing wedge osteotomy was the predominant technique utilized, with medial opening wedge osteotomies comprising the minority of the cohort. Patient characteristics are summarized in Table 1.

Table 1 - Patient Demographics and HTO Characteristics.

Variable	Value
Age (median (IQR))	
At HTO, years	52.0 (13)
At TKA, years	63.5 (14)
Sex (median (IQR))	
Women	38 (28.4%)
Men	96 (71.6%)
Body Mass Index, kg/m^2 (median (IQR))	30.3 (7.9)
Charlson Comorbidity Index (median (IQR))	3.0 (3.0)
Laterality (Number (%))	
Left	70 (52.2%)
Right	64 (47.8%)
Osteotomy performed (Number (%))	
Medial opening wedge	30 (22.4%)
Lateral closing wedge	104 (77.6%)

IQR; Interquartile Range

2.3 Measured Outcomes

Revision surgery was defined as the replacement of the tibial, femoral, or patellar components and/or exchange of the polyethylene insert. Isolated polyethylene inserts exchanges performed due to infection were not classified as revision surgery. Detailed intraoperative TKA data—including use of femoral and tibial stems, implant constraint levels, and insert size—were systematically collected. The Charlson Comorbidity Index (CCI) was recorded for all patients, adjusted for disease severity and age. Prior to TKA, the severity of KOA was assessed on weight-bearing radiographs using the Kellgren and Lawrence (KL) grading system, independently scored by two observers. Discrepancies were resolved through consensus discussion. In addition, the Joint Line Obliquity (JLO) angle was measured on preoperative TKA radiographs and was defined as the angle between the tibial plateau joint line and a line parallel to the ground (Figure 1). Also, range of motion (ROM) was recorded prior to TKA in the TJR and was defined as flexion minus extension.

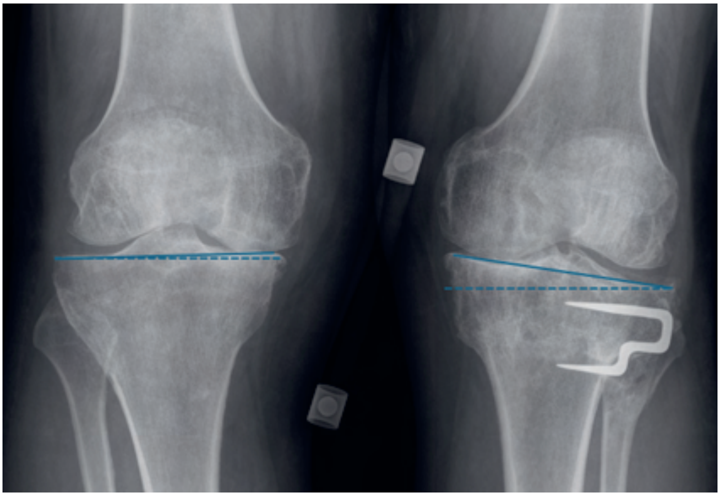

Figure 1 - Measurement of joint line obliquity (JLO) in a patient who previously underwent a high tibial osteotomy of the left knee. The JLO is defined as the angle between the tibial plateau joint line and a line parallel to the ground (dotted line).

2.4 Data Analyses

Patient demographics and surgical characteristics were summarized using means and SDs for normally distributed variables and medians with interquartile ranges for non-normally distributed variables. Categorical variables were reported as absolute numbers and corresponding percentages. Kaplan–Meier survival analysis was performed to evaluate both osteotomy and TKA survival. The end date of follow-up was June 2025, unless an earlier event had occurred, defined as death, revision surgery, or reoperation. Cox proportional hazards regression models were used to identify factors associated with osteotomy survival, including age at the time of osteotomy, body mass index (BMI), and CCI. Differences in continuous variables—including age, BMI, CCI, and JLO—between patients who did and did not undergo revision surgery were assessed using Mann–Whitney U-tests. Interobserver reliability for KL grading was evaluated using the percentage of agreement between observers. All statistical analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria). P-values of < 0.05 were considered statistically significant.

3. Results

3.1 Survival osteotomies and TKA

All patients underwent conversion to TKA, which occurred at a mean of 11.7 years (range, zero to 31.0) following HTO. Cumulative conversion rates were 6.7% at five years and 35.8% at 10 years postoperative HTO (Figure 2A). In a regression model examining correlating factors with the subsequent conversion to TKA, older age was significantly associated with a hazard ratio (HR) of 1.06 (95% confidence interval [CI]: 1.04 to 1.09; P < 0.001). The BMI was associated with an HR of 1.03 (95% CI: 1.00 to 1.06; P = 0.03), and CCI with an HR of 0.79 (95% CI: 0.72 to 0.87; P < 0.001).

The mean follow-up duration after TKA was 13.5 years (range, zero to 24.0) (Figure 2B). In total, eight knees (6.0%) underwent revision surgery, with a mean time to revision of 7.6 years (range, zero to 22.0). Indications for revision included hyperextension laxity in one case, infection in one case, pain of unknown origin in two cases, and tibial component loosening in four cases. There was one revision for tibial component loosening, which involved stemmed tibial and femoral components. Postoperative infection occurred in three knees (2.2%), all of which were managed with irrigation and debridement and component retention (Table 2). Patients who underwent revision surgery were significantly younger than those who did not (median age 52 versus 64 years; U = 239.0; P = 0.01). There was no statistically significant difference in BMI and JLO between the revision and no-revision groups (median BMI 26.3 versus 29.9; U = 477.0; P = 0.8) (median JLO 5.5 versus 6.0; U = 363.5; P = 0.62). The CCI was significantly lower among patients who underwent revision surgery (median 1.0) than those who did not (median 3.0) (U = 206.0; P < 0.01). Of the patients who underwent revision surgery for tibial component loosening, one had both a stemmed tibial and a stemmed femoral component.

Reoperation for any cause was performed in seven HTO-TKAs: debridement in three cases, periprosthetic fractures in two cases, manipulation in two cases, and lysis of adhesions with manipulation in one case. Preoperative ROM was recorded in 81 patients (60.5%), with a median ROM of 110.0° (interquartile range, 20°).

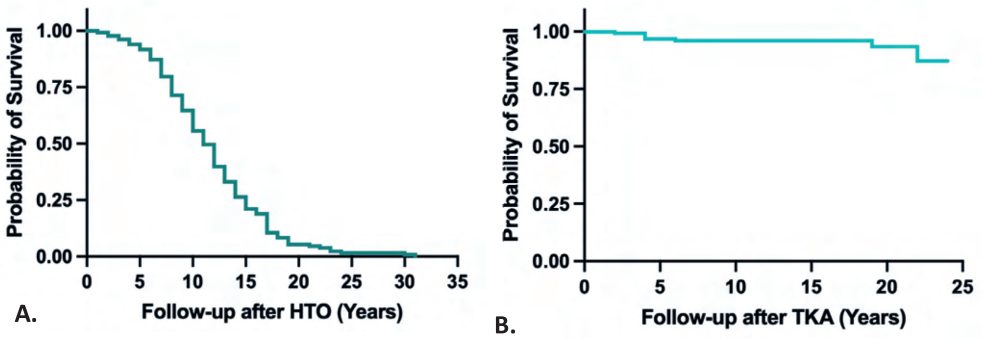

Figure 2– Kaplan-Meier curves illustrating cumulative incidence. Panel A shows the cumulative incidence of conversion from High Tibial Osteotomy (HTO) to Total Knee Arthroplasty (TKA) over time. Panel B displays the cumulative incidence of the TKA.

Table 2 - TKA survival, including number of revisions and reasons for revision.

Variable	
Follow-up time after TKA	13.5 years (range, 0.0 to 24.0 years)
Revision of TKA	
No	126 (94.0%)
Yes	8 (6.0%)
Reason revision TKA	
Tibial component loosening	4 (50.0%)
Pain of unknown origin	2 (25.0%)
Infection	1 (12.5%)
Hyperextension laxity	1 (12.5%)

TKA; Total Knee Arthroplasty

3.2 Intra-operative

A total of 20 surgeons performed osteotomies and subsequent TKAs, with 80 knees (59.7%) undergoing both procedures by the same surgeon. Tibial stems were used in 14.9% of TKAs, while femoral stems were utilized in 5.2% of cases. The most used tibial polyethylene insert design was a posterior-stabilized implant, accounting for 94.0% of TKAs. The median insert size was 12.5 (IQR, 3.3) mm. The implant details are summarized in Table 3.

3.3 Radiographs

Prior to TKA, 124 knee radiographs (92.5%) were available. The KL grading was independently assessed by two observers, with an agreement rate of 96.0%. Discrepancies in five radiographs were resolved through consensus discussion. The medial compartment was the most affected compartment in 121 cases (97.6%), while the lateral compartment was most affected in three cases (2.4%). Distribution of preoperative KL grades was 4 (3.2%) with Grade 2, 39 (31.5%) with Grade 3, and 81 (65.3%) with Grade 4. The mean JLO was 5.8 (range, 0.2 to 12.2), which indicated a tendency toward medial joint line obliquity.

Table 3 - Components Used at TKA placement.

Variable	**Value**
Stemmed tibial component	
Yes	20 (14.9%)
No	114 (85.1%)
Stemmed femoral component	
Yes	7 (5.2%)
No	127 (94.8%)
TKA tibial polyethylene insert design	
Cruciate retaining	5 (3.7%)
Posterior stabilized	126 (94.0%)
Varus/valgus constrained	3 (2.2%)
Polyethylene inserts, mm	12.5 (IQR 3.3)

TKA, Total Knee Arthroplasty; mm, millimeter

4. Discussion

The purpose of the present study was to determine the survival of TKAs, defined by revision-free survival, in patients who had a history of ipsilateral HTO within a U.S. population, with a mean follow-up of nearly 14 years. We observed a revision rate of 5.2% in this cohort, with an average follow-up duration of nearly 14 years postoperative TKA. Patients who required revision surgery were younger at the time of TKA, consistent with previous findings that younger age is a recognized risk factor for TKA failure[91]. Reported revision rates in the literature for patients who have undergone both an HTO and subsequent TKA range from 3 to 8%[351,456–458], with most studies reporting rates exceeding 5.0%. However, these studies have been predominantly conducted in European populations. A recent meta-analysis reported a revision rate of 7.7% for TKAs in patients who had a history of osteotomy, also primarily based on European data[457]. In contrast, our findings in a U.S. based cohort with substantially longer follow-up demonstrate comparable revision rates, which are even lower than those reported in many previous studies[456–458].

Furthermore, we observed a mean survival time of HTO of nearly 14 years, with 64.0% of patients not requiring conversion to TKA at 10-year follow-up. Cox regression analysis showed that the risk of conversion to TKA increased by 6.0% for each additional year of age at the time of HTO. Similarly, each unit increase in BMI was associated with a 3.0% higher risk of conversion. European studies report that approximately 75.0% of patients remain free of TKA at 10 years following HTO[351,459,460]. However, the mean BMI in our cohort was 4 units higher than in these European populations, which may explain the slightly higher cumulative conversion rates observed in our U.S. population. Nonetheless, despite this higher BMI, 64.0% of patients in our study did not require TKA even 10 years after HTO. Also, we found that each unit increase in the Charlson Comorbidity Index was associated with a 21.0% lower likelihood of TKA conversion. Potential explanations for this include that healthier patients may have higher postoperative expectations and therefore pursue TKA sooner, or alternatively, that patients who have greater comorbidity are less likely to undergo additional surgery due to elevated perioperative risk.

The knee radiographs demonstrate a mean JLO of approximately 6°, which is likely a consequence of the prior osteotomy, especially when correction is excessive or too close to the joint line[461,462]. Biomechanical studies show that a 4° change in JLO can induce significant medio-lateral femoro-tibial subluxation and alter compartmental contact pressures[461]. Finite element analyses have shown that a JLO of 5° or more increases shear stress in the medial tibial cartilage from approximately 1.6 MPa to between 3 and 7 MPa, depending on the degree of obliquity (5°, 7.5°, and 10°, respectively)[462]. In our study, postoperative osteotomy radiographs were limited; however, preoperative TKA radiographs demonstrated a mean JLO of nearly 6°, which is higher than typically reported in the literature. Patients who underwent revision surgery had higher preoperative TKA JLO values compared to those who did not require revision. While a direct relationship between JLO and osteotomy survival has not yet been established, this area warrants further investigation. Additionally, it remains unclear whether preoperative TKA JLO influences TKA survival, as current evidence on this association is mixed[463,464].

The use of HTOs in the U.S. is rare compared to arthroplasty procedures. Data from the PearlDiver database identified only 2,183 HTOs over a 12-year period[350], whereas, for example, in the Netherlands more than 1,000 HTOs are performed annually[118]. Dutch literature further reports that over a 16-year period, more than 10,000 patients who had undergone TKA following a prior ipsilateral osteotomy, implying that the total number of osteotomies performed was even higher, as not all patients require conversion[351]. Despite the limited use of HTO in the U.S., available literature reports a 10-year survivorship of 56.0%[465] and a mean survival time of 14 years[114], although the latter finding is based on a relatively small sample size. Revision studies are equally scarce; one U.S. study included only 40 patients and reported a 15-year revision rate of just 3.0%[466]. To our knowledge, the present study includes the largest U.S. cohort of patients who underwent TKA following HTO, with a substantially longer follow-up compared to most prior studies. These strengths enhance the relevance and generalizability of our findings to clinical practice in North American populations.

Despite the strengths of our study, several important limitations must be acknowledged. Our cohort included only patients who underwent both HTO and subsequent TKA, representing a potentially biased subgroup, as not all HTO patients ultimately require conversion. This design inherently biases the reported HTO-to-TKA survival time upward and limits the reliability of a true survivorship analysis of HTO, as such an analysis would require inclusion of the entire HTO population, not only those who eventually failed. Future research should focus on identifying factors associated with HTO survival in a U.S. population and patient satisfaction after HTO. Knee radiographs before and after HTO were limited, which prevented us from incorporating radiographic parameters into our osteotomy survival analysis. Previous studies have shown that, in addition to patient-related factors, both preoperative osteoarthritis severity and postoperative alignment are important predictors of HTO failure[96,115,459,460]. Unfortunately, these variables could not be accounted for in our current analysis. This limitation reflects the nature of our cohort, which consisted of patients receiving routine clinical care. Most HTOs were performed before 2000 because we aimed to include patients who have long-term follow-up after TKA. As a result, we did not have access to whole-leg radiographs, and alignment parameters could not be systematically measured for the majority of patients. Additionally, JLO was assessed on weight-bearing knee radiographs, which may be less accurate compared to measurements taken on whole-leg radiographs. Most procedures involved lateral, closing-wedge osteotomies with staple fixation, reflecting common practice during the studied period. Additionally, the majority of conversions to TKA were performed by the same surgeon, which may further limit the generalizability of our results. As medial opening-wedge techniques with modern fixation systems have become more widely adopted, their different biomechanical and clinical outcomes may limit the applicability of our results to contemporary HTO practice. These differences should be considered when interpreting our long-term findings, and further investigation is warranted. All procedures were performed in a tertiary referral center with high surgical expertise in complex primary TKA, potentially limiting generalizability to other practice settings. Outcomes observed in this high-volume, expert setting may not reflect results achievable in community or lower-volume hospitals, thus limiting external validity. Notably, TKA after HTO is a technically demanding procedure, and revision rates may be higher when performed by less experienced surgeons. Also, this study lacked a control group of patients undergoing TKA without prior HTO. Future research, particularly within U.S. populations, should include matched-controlled studies comparing patients who have and those who do not have a history of osteotomy, which would allow for more definitive conclusions regarding TKA survival, including revisions, reoperations, and patient-reported outcomes.

5. Conclusion

This study aimed to assess the revision-free survival of TKAs in patients who had a history of ipsilateral HTO within a U.S. population. We observed a 6.0% revision rate after TKA, with patients who underwent revision surgery being younger and healthier. The mean survival time of HTO was approximately 12 years, with age, BMI, and comorbidity index identified as statistically significant factors influencing survival. These findings offer valuable insights into HTO-to-TKA conversion outcomes in the U.S. population. Future matched controlled studies are warranted to guide clinical decision-making and may contribute to increased consideration of HTO as a viable joint-preserving option in appropriately selected people.

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Chapter 15

Comparable Outcomes and Implant Survivorship of Total Knee Arthroplasty following High Tibial Osteotomy and Primary Arthroplasty: A Matched Cohort Study

Eva A. Bax, Rana A. Ahmad, Sean C. Clark, Roel J.H. Custers, Michael J. Taunton, Rafael J. Sierra, Daniel B.F. Saris, Mario Hevesi

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Abstract

Background: Total knee arthroplasty (TKA) is the treatment of choice for end-stage knee osteoarthritis in many patients. In younger patients with predominantly medial compartment disease, high tibial osteotomy (HTO) is performed as a joint-preserving treatment. However, concerns remain regarding potentially compromised outcomes of TKA following prior HTO given axial deviation, osteotomy site, secondary surgery, prior hardware and instrumentation. Therefore, this study compared long-term implant survival, revision and infection rates, and patient-reported outcomes between patients undergoing TKA after HTO and matched TKA-only controls.

Methods: Postoperative complications and revision surgeries were prospectively recorded in patients who underwent TKA from 2000 to 2023 at a single academic center. Patients with prior ipsilateral HTO formed the study group and were propensity matched 1:2 to TKA-only patients without a prior osteotomy based on age, sex, and BMI. Knee Society Scores (KSS) were collected prospectively. Implant survivorship was analyzed using Kaplan–Meier survival curves and Cox proportional hazards models.

Results: The study included 134 HTO-TKA and 268 matched TKA-only patients, with mean follow-up of 10.5 ± 6.4 years (range: 0-24 years) after TKA. Both groups showed significant postoperative improvements in KSS ($p < 0.02$) with comparable clinical outcomes (HTO-TKA: 79.0 (6.0), TKA-only: 79.0 (11.8)). Revision arthroplasty rates were 5.2% for HTO-TKA and 4.5% for TKA-only ($p = 0.69$); mean time to revision was 8.1 ± 8.7 years vs. 4.4 ± 3.5 years, respectively ($p = 0.30$). Infection rates were 2.2% and 1.1%, respectively ($p = 0.74$).

Conclusions: Revision and infection rates were comparable between HTO-TKA and matched TKA-only patients, with no statistically significant differences. Our findings demonstrate comparable patient-reported outcomes in both groups. These findings indicate that a prior HTO does not adversely affect TKA implant longevity or clinical outcomes when compared with matched primary TKA patients within the U.S. population.

1. Introduction

Total knee arthroplasty (TKA) is a widely accepted surgical intervention for end-stage symptomatic knee osteoarthritis (KOA), aiming to relieve pain and restore joint function [87,467,468]. Although TKA generally offers favorable long-term outcomes, with reported survival rates of around 93% at 15 years[469,470] and 82% at 25 years[469], implant failure remains a significant concern. The global rise in TKA use has been accompanied by an increasing number of revision procedures[88–90], often due to aseptic loosening, periprosthetic joint infection, persistent pain, or instability[470–472]. Compared to primary TKA, revision surgeries are more invasive, costlier, and typically result in poorer functional outcomes satisfaction[87,91].

Given the higher revision risk in younger patients, joint-preserving treatments are increasingly emphasized[87,91,93]. Realignment osteotomies have demonstrated favorable long-term results in this group[97,113–115]. Nevertheless, concerns persist among some surgeons regarding their potential to complicate potential future TKA. Reported challenges include residual angular deformities, patella baja, the need for hardware removal, and a potentially elevated risk of infection—factors potentially increasing surgical complexity and affecting outcomes[451–454].

Despite these concerns, evidence on long-term TKA outcomes after prior osteotomy remain incompletely characterized across different populations. While several meta-analyses[454,455,473] and registry studies have reported comparable outcomes[122,458,474], many are predominantly based on European and Asian cohorts. In the United States (U.S.), long-term outcome data on TKA following high tibial osteotomy (HTO) are scarce[475–479], largely reflecting the relatively limited use of HTO compared with arthroplasty[350,480]. Although excellent long-term survivorship of TKA after HTO has been demonstrated in a U.S. study[475], the lack of a matched primary TKA control group limits meaningful comparative interpretation[481]. Collectively, these limitations underscore the need for well-designed comparative studies with long-term follow-up in a U.S. population.

Therefore, this study assessed long-term implant survival by comparing revision rates and patient-reported outcomes between individuals with prior HTO and matched TKA-only controls. We hypothesized that patients with a history of HTO would show similar clinical results and revision rates as those receiving TKA without prior history of osteotomy. These findings may help guide surgical decision-making in younger patients considering joint-preserving procedures.

2. Methods

2.1 Study design

This matched-controlled study included patients who underwent TKA between 2000 and 2023 at a single academic medical center. Those with a HTO on the same knee, both performed at the same center, were retrospectively identified. These patients formed the study group and were matched 1:2 using nearest-neighbor propensity score matching with controls who underwent primary TKA without prior HTO, based on age, sex, and body mass index (BMI), using R (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria). All patients were prospectively followed through the Mayo Clinic Total Joint Registry, which systematically collects demographic data, surgical details, postoperative complications, and patient-reported outcome measures. Outcomes of interest included implant survivorship, revision surgery, and postoperative infection. Institutional Review Board approval was obtained prior to data collection (Mayo Clinic IRB #15-000601).

2.2 Measured Outcomes

Revision procedures were defined as the replacement of any prosthetic component, including the femoral, tibial, or patellar elements, and/or exchange of the polyethylene insert. Isolated insert exchanges performed solely for infection management were excluded and classified under postoperative infections. Intraoperative data—such as use of femoral or tibial stems, insert design, and polyethylene thickness—were systematically recorded. Tibial and femoral stems were used at the surgeon's discretion based on bone quality, alignment, and implant stability. The Charlson Comorbidity Index, a validated measure that accounts for both the number and severity of comorbid conditions and is adjusted for age, was calculated for each patient. The Knee Society Score (KSS)[482] and range of motion (ROM), defined as flexion minus extension, were prospectively collected through the Total Joint Registry. Postoperative patellar height index was measured on lateral radiographs using the Insall-Salvati Index (ISI). Patella baja was defined using ISI < 0.8.

2.3 Statistical analysis

Descriptive statistics summarized patient and surgical characteristics. Continuous variables were expressed as means ± standard deviations or medians (IQR) as appropriate, categorical variables as frequencies and percentages. Between-group differences were assessed using the Mann–Whitney U test for continuous data and the Chi-square test for categorical data. Implant survival following TKA was analyzed with Kaplan–Meier curves, and Cox proportional hazards models estimated adjusted hazard ratios (HRs) for revision and infection, using the TKA-only group as reference. Time to revision was also compared using the Mann–Whitney U test. Analyses were performed in SPSS (version 29.0; IBM Corp., Armonk, NY, USA), with $p < 0.05$ considered significant.

3. Results

3.1 Patients

A total of 134 patients undergoing both HTO and subsequent TKA were matched to 268 TKA-only patients, forming the matched-controlled study cohort. Mean follow-up after TKA was 10.5 ± 6.4 years (range 0–24), with 0-year follow-up indicating revision within the first year. HTOs were performed between 1988 and 2017; all TKAs between 2000 and 2023 at the same institution. Lateral closing wedge osteotomy predominated (77.6%), with medial opening wedge in 22.4%. Baseline characteristics did not differ between groups (Table 1).

Table 1 - Baseline patient characteristics of the HTO-TKA and TKA-only groups. Values are presented median with interquartile range or number with percentage. P-values indicate comparisons between groups using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables.

Variable	HTO-TKA patients	TKA-only patients	P-value
Age (median (IQR))			
At TKA, years	63.5 (14)	64.0 (14)	0.68
Sex (median (IQR))			0.52
Female	38 (28.4%)	58 (25.4%)	
Male	96 (71.6%)	200 (74.6%)	
BMI, kg/m^2 (median (IQR))	30.3 (7.9)	30.5 (7.6)	0.37
Charlson Comorbidity Index (median (IQR))	3.0 (3.0)	3.0 (4.0)	0.27

IQR; Interquartile Range, TKA; Total Knee Arthroplasty; BMI, Body Mass Index; HTO, High Tibial Osteotomy

3.2 Intra-operative

A total of 29 surgeons performed the TKAs. In the HTO-TKA group, 59.7% had both procedures by the same surgeon, and 3.7% underwent osteotomy hardware removal prior to TKA. Tibial stems were used in 14.9% versus 13.8% of TKA-only cases ($p = 0.85$), and femoral stems in 5.2% versus 3.2% ($p = 0.48$). Posterior-stabilized inserts were most common in both groups. Polyethylene inserts were thicker in HTO-TKA than TKA-only (12.5 vs. 10.0 mm, $p < 0.001$). Implant details are in Table 2.

Table 2 - Overview of components used at the time of TKA in the HTO-TKA and TKA-only groups. Data includes the use of tibial and femoral stems, tibial polyethylene insert design, and polyethylene insert thickness.

Variable	HTO-TKA	TKA-only	P-value
Stemmed tibial component			0.85
Yes	20 (14.9%)	35 (13.8%)	
No	114 (85.1%)	218 (86.2%)	
Stemmed femoral component			0.48
Yes	7 (5.2%)	8 (3.2%)	
No	127 (94.8%)	245 (96.8%)	
TKA tibial polyethylene insert design			0.07
Cruciate retaining	5 (3.7%)	29 (10.8%)	
Posterior stabilized	126 (94.0%)	233 (86.9%)	
Varus/valgus constrained	3 (2.2%)	4 (1.5%)	
Hinged	0 (0.0%)	2 (0.7%)	
Polyethylene inserts, mm	12.5 (IQR 3.3)	10.0 (IQR 3.5)	< 0.001

TKA; Total Knee Arthroplasty; HTO, High Tibial Osteotomy

3.3 Survival Total Knee Arthroplasty

In the HTO-TKA group, eight knees (6.0%) underwent revision at a mean of 7.6 ± 8.2 years, with 96% unrevised at 15 years (Figure 1). Revisions were mainly due to tibial component loosening (n = 5), valgus malalignment with leg length discrepancy (n = 1), instability (n = 1), and infection (n = 1). Revised patients were younger and had lower CCI scores than non-revised patients (median age 52 vs. 64 years, p = 0.01; CCI 1.0 vs. 3.0, p < 0.01), with no BMI (26.3 vs. 29.9, p = 0.80) or sex (female: 12.5% vs. 29.4%, p = 0.31) differences.

All-cause reoperations occurred in 10 HTO-TKAs (7.5%), including three cases (2.2%) of postoperative periprosthetic joint infection managed with irrigation, debridement, and component retention at a mean of 1.5 ± 2.1 months postoperatively. Other reoperations included debridement (n=3), periprosthetic fracture fixation (n=2, both distal femoral fractures), manipulation under anesthesia (n=2), and lysis of adhesions combined with manipulation (n=1).

In the TKA-only group, 12 knees (4.5%) were revised at 4.4 ± 3.5 years; 94% remained unrevised at 15 years. Revisions included loosening (tibial n = 2, femoral n = 3, both n = 2), infection (n = 2), instability (n = 2), and osteolysis (n = 1). No significant differences were found between revised and non-revised patients in age (median 59 vs. 64 years, p = 0.37), BMI (35.2 vs. 30.5, p = 0.17), CCI (2.5 vs. 3.0, p = 0.12), and sex (female: 25.0% vs. 25.4%, p = 0.98).

All-cause reoperation occurred in 15 cases (5.6%), including three periprosthetic joint infection (1.1%) requiring insert exchange at a mean of 26.0 ± 28.5 months. Other reoperations included debridement (n = 2), periprosthetic fracture fixation (n = 1, distal femoral fracture), manipulation under anesthesia (n = 8), and quadriceps tendon repair (n = 1).

No significant differences were found between the HTO-TKA and TKA-only groups in revision rates (HR = 1.2, p = 0.69), infection rates (HR 0.7, p = 0.74), or time to revision (p = 0.30).

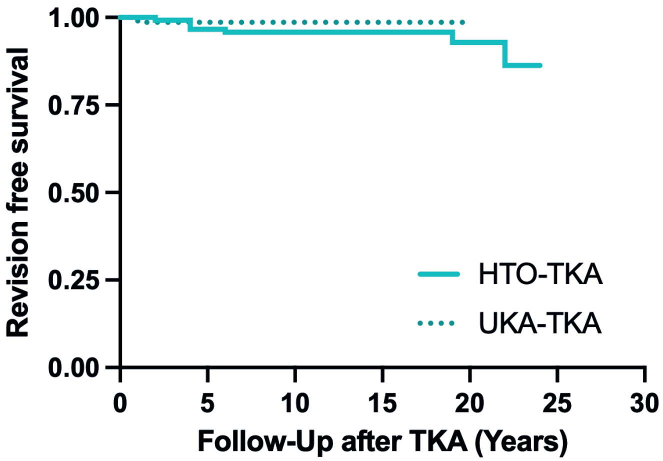

Figure 1 – Kaplan–Meier survival curves showing the cumulative incidence of TKA survivorship in both the HTO-TKA and primary TKA groups over the follow-up period.

3.4 Patient Reported Outcome Measures

Following TKA, both KSS Knee and Functional Scores improved significantly at 2-, 5-, and 10-year (Figure 2) (all p ≤ 0.02 for Knee; all p < 0.001 for Functional). Preoperatively, KSS Knee Scores did not differ between HTO-TKA and TKA-only groups (p = 0.61), whereas Functional Scores were higher in the HTO-TKA group (p < 0.01). Throughout follow-up, no significant group differences were observed for Knee Scores at 2 (p = 0.69), 5 (p = 0.32), or 10 years (p = 0.29), or in KSS Functional Scores at 2 (p = 0.28), 5 (p = 0.75), or 10 years (p = 0.49). See Table 3. Patient-reported outcome response rates ranged from 60.4% (HTO-TKA) and 44.8% (TKA-only) preoperatively, to 78.0% vs. 71.1% at 2 years, 68.0% vs. 58.2% at 5 years, and 50.5% vs. 45.6% at 10 years. Preoperative ROM data were available for 193 patients (48.0%), with a median of 110° (IQR 20°) and no difference between groups.

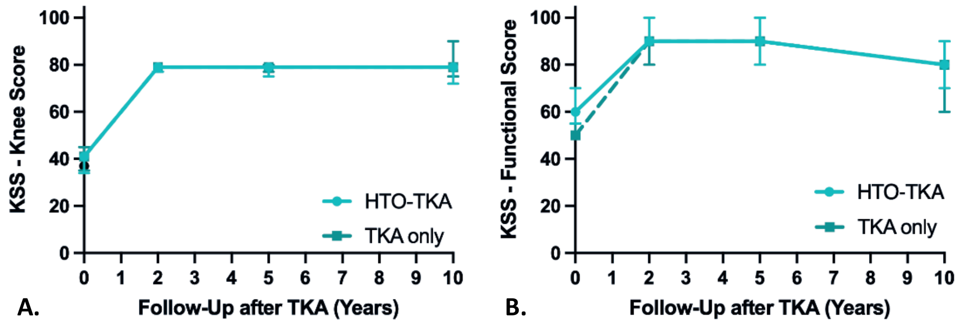

Figure 2 - Preoperative and postoperative KSS Knee and Function sub-scores are presented for both HTO-TKA and primary TKA groups, with time point zero (t = 0) representing the preoperative assessment.

3.5 Postoperative Patellar Height

Postoperative ISI differed significantly between groups, with higher values observed in the TKA-only group (1.13 ± 0.22) compared to the HTO-TKA group (1.04 ± 0.16; $p < 0.001$). However, the incidence of patella baja was low and did not differ between groups (5.3% vs 4.7%, $p = 0.99$).

4. Discussion

This study evaluated long-term implant survival by comparing revision rates and patient-reported outcomes between patients with prior HTO and matched TKA-only controls. Our results show comparable outcomes and no significant difference in revision rates between groups. Although previous meta-analyses and cohort studies have reported mixed findings[454,455,458,473], most matched-controlled studies—mainly from Europe and Asia with small samples and limited follow-up—also found no significant differences[483–486]. In the U.S., few matched cohort studies have examined this question and similarly reported comparable revision rates[114,466]. By including a larger U.S. cohort with extended follow-up, our study adds to existing evidence demonstrating no significant difference in revision rates between HTO-TKA and TKA-only patients.

Postoperative infection rates were 2.2% in the HTO-TKA group and 1.1% in the TKA-only group, with no significant difference observed. Although prior meta-analyses reported a higher infection risk after TKA following osteotomy[454,455], our HTO-TKA rates fall within the ranges described for primary TKA in the literature[487–489].

The HTO-TKA and TKA-only groups demonstrated similar use of tibial polyethylene insert designs and tibial and femoral stem components. The comparable use of tibial and femoral stems suggests that HTO-TKA procedures more closely resemble primary TKA rather than revision arthroplasty or other complex interventions. In both groups, the posterior-stabilized insert design was the most commonly used across all years. However, in 2022 and 2023, cruciate-retaining designs were employed nearly as frequently as posterior-stabilized designs. Polyethylene insert thickness was significantly higher in HTO-TKA, likely due to increased tibial resection from prior osteotomy, highlighting the importance of thorough preoperative planning. Nonetheless, the clinical relevance of this 2.5 mm median difference in insert thickness remains unclear.

With the rising burden of KOA[4–7], especially among younger patients[34], effective and durable treatment strategies are increasingly important. This need is emphasized by the growing number of younger individuals undergoing TKA[490], a procedure associated in this group with higher revision risk[91,343]. Revision arthroplasties are more complex, costlier, and associated to lower patient satisfaction compared to TKA-onlys[87,91], highlighting the value of joint-preserving options such as HTO. Prior studies have shown favorable implant survival[97,113–117], improved patient-reported outcomes[103,104,106], and high return-to-sport rates[108–110] after HTO. Nevertheless, some patients eventually require TKA[97,113–117], raising concerns about technical difficulty and outcomes after osteotomy. Our study found comparable revision rates between HTO-TKA and matched TKA-only controls, supporting HTO as a joint-preserving option for selected younger patients with unicompartmental KOA, including in the U.S.

Several limitations should be considered when interpreting these results. First, all procedures were performed at a tertiary referral center with high surgical expertise in complex TKA, which may limit generalizability. However, the involvement of multiple surgeons enhances the generalizability of our findings while potentially introducing variability in surgical technique and expertise that may have influenced outcomes. Second, most osteotomies involved lateral closing-wedge techniques with staple fixation, reflecting historical practice. As medial opening-wedge approaches and newer fixation methods have become more common, applicability to current practice may be limited. Third, radiographic parameters such as Kellgren–Lawrence grading were not included, as the focus was on TKA survival rather than preoperative severity. Future studies including radiographic and alignment data could clarify how baseline degeneration and malalignment affect outcomes. Fourth, patients included in this cohort underwent TKA between 2000 and 2023, during a period characterized by considerable advancements in implant design, surgical techniques, perioperative management, and infection prevention[491], which were not independently assessed in this analysis. Fifth, patient-reported outcome measures were not available for all patients at each follow-up time point, with response rates gradually declining over time, which may limit the completeness of long-term outcome data. Sixth, the relatively low number of revisions and infections reduced statistical power; although infections were less frequent in the TKA-only group, this difference was not significant. Seventh, the impact of robotic-assisted techniques and cementless fixation was not analyzed due to the infrequent identification of these characteristics in the registry. Finally, the 20-year follow-up limit may restrict very long-term assessment but is unlikely to affect overall conclusions. Additionally, given the expected lifespan of a TKA implant, the clinical relevance of very late revisions (>15–20 years) may be debated; nevertheless, these events were conservatively counted as revisions.

5. Conclusion

This matched cohort study compared long-term outcomes between patients undergoing TKA after HTO and matched TKA-only controls. Revision and infection rates were comparable, with no statistically significant differences. Our findings demonstrate comparable patient-reported outcomes in both groups. These findings indicate that a prior HTO does not adversely affect TKA implant longevity or clinical outcomes when compared with matched primary TKA patients within the U.S. population.

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Chapter 16

General Summary and Discussion

General summary

The increasing global burden of knee osteoarthritis (KOA)—particularly among younger and physically active individuals—highlights the pressing need for strategies that preserve, rather than replace, the native joint. While total knee arthroplasty (TKA) remains a successful end-stage treatment, it is less ideal for young and active patients whose expectations and activity levels demand long-term preservation of joint function. In this context, osteotomy has gained substantial attention because of its potential to achieve favorable clinical outcomes and long-term joint preservation in younger patients.

Recognizing the importance of optimizing joint-preserving strategies, this thesis focuses on four interrelated domains of KOA research that together span the continuum from disease characterization to surgical treatment. Collectively, this thesis contributes to more accurate diagnostics and more effective joint-preserving strategies for individuals with KOA—particularly relevant for the growing population of younger, active patients in the midst of their professional and social lives, who strive to maintain mobility and function while delaying or avoiding joint replacement. The following paragraphs summarize the main findings related to each of these research domains.

Part 1 - Imaging Knee Osteoarthritis

We first aimed to improve radiographic assessment of KOA by exploring how radiographic and magnetic resonance imaging (MRI) can more accurately evaluate joint structure and disease progression, while accounting for technical factors such as patient positioning. These efforts aimed to establish more reliable and clinically meaningful methods for monitoring KOA progression and assessing treatment effects.

Chapter 2 examined the effect of knee positioning during radiographic acquisition on the difference between radiographic minimal Joint Space Width (mJSW) and MRI-based cartilage thickness[170]. Despite standardized imaging using the Buckland-Wright protocol, the statistical shape model revealed that knee rotation and flexion described the two largest principal components of shape variation, resulting in apparent reductions in mJSW that did not reflect actual cartilage loss. This highlights the critical importance of accounting for positioning errors when interpreting mJSW measurements and drawing conclusions in longitudinal studies.

Building upon these findings, **Chapter 3** explored the relationships between radiographic JSW and MRI-derived measures of cartilage and meniscal morphology[492]. Specifically, we evaluated cross-sectional associations between whole-joint cartilage and meniscal characteristics and uni- versus bicompartmental JSW, as well as their correlations with Kellgren–Lawrence (KL) grading. MRI-based indicators of joint degeneration showed similar associations with uni- and bicompartmental JSW, while bicompartmental measures correlated more strongly with KL grades. These findings emphasize the importance of incorporating both compartments in KOA assessments, as reliance on unicompartmental measures alone may not fully capture whole joint cartilage and meniscal morphology.

Part 2 - Impact of Lower Limb Malalignment

The second aim of this thesis was to examine the impact of lower limb malalignment through both longitudinal and cross-sectional analyses. This part explored how sport activities influence alignment parameters and how malalignment affects joint health, thereby highlighting the complex interplay between physical activity, biomechanical alignment, and long-term musculoskeletal health.

Chapter 4 investigated the association between the alpha angle of the hip and lower limb alignment in a healthy population. We found that higher alpha angles were associated with more tibial varus, and that men exhibited both higher alpha angles and more tibial varus compared to women. Additionally, individuals who reported higher levels of sports participation during youth showed more tibial varus. These findings suggest that both cam morphology and varus alignment may develop through similar adaptive mechanisms of the growth plates in response to mechanical loading. Further research is needed to explore how mechanical load adjustments during growth might prevent the development of varus alignment and cam morphology, thereby reducing future osteoarthritis risk.

Chapter 5 focused on characterizing lower limb malalignment by distinguishing between bony and intra-articular alignment to improve predictions of KOA progression[493]. Over a two-year period, most bones showed a shift toward a more varus shape. In addition, patients with bone varus but normal intra-articular alignment developed progressive intra-articular varus—consistent with medial KOA progression. These findings suggest that bone geometry remains a dynamic process and emphasize the importance of leg malalignment in the progression of intra-articular joint changes during the early stages of KOA.

Chapter 6 applied the same distinction between bony and intra-articular alignment to investigate the cross-sectional relationship between knee cartilage quality (T2) and lower limb malalignment[494]. Using MRI-based T2 mapping, a technique sensitive to cartilage composition, the study found that malalignment—particularly intra-articular—was associated with compartment-specific lower cartilage quality. Future studies should explore the potential of T2 analysis as a screening tool to identify KOA progression in patients with lower limb malalignment, thereby guiding the optimal timing of corrective osteotomy.

Part 3 - Optimizing Osteotomy Care in Knee Osteoarthritis

The third aim of this thesis was to improve osteotomy care by refining preoperative planning, enhancing the assessment of bone healing, and optimizing surgical techniques. By evaluating new planning concepts, biomaterials, and standardized outcome measures, this work aims to advance the clinical care and improve outcomes for patients undergoing realignment surgery.

Chapter 7 expanded upon traditional preoperative planning for KOA patients, which typically corrects deformities at the metaphyseal level[495]. By analyzing patients with tibial malalignment, this study identified the center of rotation and angulation (CORA) and calculated the resulting secondary translational deformities in KOA patients. It revealed that the CORA was predominantly located in the diaphysis rather than the metaphysis, leading to secondary translational deformities in these patients.

Chapter 8 further investigated the combined influence of CORA location, distal tibial geometry, and correction magnitude on postoperative talar orientation relative to the ground in patients undergoing valgus-producing medial opening-wedge high tibial osteotomy (MOW-HTO). The tibia in these patients showed an overall valgus configuration, mainly due to a valgus-shaped distal tibia, which was associated with postoperative worsening of ankle alignment. These results suggest that patients with valgus distal tibial anatomy are more prone to ankle-related complications, underscoring the importance of evaluating the entire lower-limb geometry—beyond the knee—when planning realignment osteotomies.

Chapter 9 analyzed long-term trends in high tibial osteotomy (HTO) techniques, fixation methods, and the use of concomitant procedures over the past decades using comprehensive patient-level data. The study revealed a clear transition from closed-wedge to medial open-wedge techniques, a shift from staple to plate fixation, and a growing use of HTO in combination with concomitant procedures.

Chapter 10 presented the framework of a randomized controlled trial comparing AttraX® Putty placed in an open-wedge osteotomy with conventional open-wedge osteotomy without a gap filler. The study aimed to evaluate the efficacy of AttraX® Putty as a bone graft substitute in reducing postoperative pain, while secondary outcomes included assessments of bone healing and functional rehabilitation. This trial provided a structured approach to objectively assess the clinical value of synthetic biomaterials in enhancing recovery and optimizing outcomes after open-wedge osteotomy.

Building on the evaluation of bone healing, **Chapter 11** presented a systematic review that identified the various methods used to assess bone union on radiographs after open- and closed-wedge proximal tibial and distal femoral osteotomies[417]. The review revealed substantial variation and a lack of consensus in defining bone union, emphasizing the need for a simple, reproducible, and standardized approach to reliably evaluate bone healing following osteotomy.

In response to this, **Chapter 12** evaluated the inter- and intra-rater reliability of the newly developed Unified Bone Union (UBU) classification for assessing time-dependent bone healing on radiographs after osteotomies around the knee[496]. The study also examined the correlation between radiographic and Computed Tomography (CT)-based UBU scores. The results demonstrated that the UBU classification is a reliable, standardized tool that accurately reflects bone healing, showing strong inter- and intra-rater reliability and excellent correlation with CT imaging. Clinically, the UBU classification offers a practical method for consistent monitoring of bone healing in daily practice.

Finally, **Chapter 13** provided insights into the combined effect of osteotomy inclination and hinge position on changes in posterior tibial slope (PTS) following MOW-HTO[497]. This mathematical analysis demonstrated that hinge position strongly influences PTS, whereas the sagittal inclination angle has minimal impact. These findings emphasize that surgeons should pay particular attention to maintaining a lateral hinge position during MOW-HTO to prevent an excessive increase in PTS and the associated rise in tensile load on the anterior cruciate ligament.

Part 4 – Impact of Osteotomies on Knee Arthroplasty Outcomes

The final part of this thesis focused on assessing the impact of previous osteotomy on TKA, aiming to clarify how joint-preserving surgery influences the outcomes of subsequent procedures.

Chapter 14 evaluated the revision-free survival of TKA after prior ipsilateral HTO in a United States (U.S.) population[481]. The study found a 6.0% revision rate after a mean follow-up of 13.5 years, with younger age and lower comorbidity scores associated with higher revision risk. The mean HTO survival was about 12 years, influenced by age, Body Mass Index (BMI), and comorbidity index. These findings highlight the need for further matched studies comparing TKA after HTO with primary TKA to better understand potential differences in long-term survival.

Chapter 15 addressed this gap by conducting a matched controlled study comparing implant survival, revision, infection rates, and patient-reported outcomes between patients undergoing TKA after HTO and matched TKA-only controls[498]. The results demonstrated comparable revision and infection rates, as well as similar patient-reported outcomes between groups. These findings confirm that prior HTO does not compromise the success of subsequent TKA, supporting the role of HTO as an effective joint-preserving option for appropriately selected younger patients.

Discussion

Societal and Economic Burden of Knee Osteoarthritis

Through this thesis, the societal impact of knee osteoarthritis KOA has become increasingly evident. KOA is a chronic, progressive joint disease that causes pain, stiffness, deformity, and disability in many patients, leading to limitations in mobility, work participation, and daily functioning [238]. Beyond its physical consequences, KOA substantially affects mental health and overall quality of life, with patients often reporting increased rates of anxiety, depression, and lower life satisfaction compared with the general population[499].

The societal relevance of KOA becomes even more pronounced in light of global demographic trends. The problem of an aging population, particularly in Western countries, is no longer a surprise. The combination of global aging and declining birth rates is placing increasing pressure on the available workforce and underscores the growing importance of maintaining a healthy musculoskeletal system that keeps the elderly at work. Within this context, the orthopedic surgeon plays a key role[500] —both through conservative treatments and surgical interventions aimed at preserving joint function.

Consequently, the economic implications are considerable, as KOA not only limits individual participation but also contributes to rising healthcare utilization. Compared with controls, all-cause healthcare costs are significantly higher for patients with KOA — nearly double those of matched individuals without KOA[501,502]. With the rising incidence and prevalence of KOA[4], the associated healthcare and socioeconomic burden is projected to become an even greater challenge in the coming decades. In this context, joint-preserving treatments such as osteotomy may play an important role, as they appear to offer better cost-effectiveness compared with UKA or TKA[503].

Reconsidering Radiographic Assessment in KOA

Radiographic assessment remains the most widely used method for diagnosing and monitoring the severity of KOA[30,31]. The KL grading system is commonly applied in both clinical practice and research. However, its categorical nature limits sensitivity to subtle structural changes — the changes that clinical investigations are often most interested in detecting. Consequently, many studies have relied on unicompartmental mJSW as a surrogate for disease progression. Yet, as demonstrated in **Chapter 2** and **Chapter 3**, unicompartmental mJSW does not adequately reflect the radiographic progression of KOA. It remains unclear whether observed changes in mJSW represent true structural alterations, measurement variability, or positioning errors. Nevertheless, if conclusions are to be drawn from mJSW measurements, it is essential that both compartments are considered, as this provides a more comprehensive and representative assessment of whole-joint structural damage, as demonstrated in **Chapter 3**. Although this approach may seem intuitive, it is noteworthy that many KOA studies still assess only a single compartment, thereby potentially overlooking important structural alterations occurring elsewhere in the joint. Moreover, it is worth questioning whether continued reliance on mJSW measurements alone is justified, given the uncertainty about whether observed changes truly reflect disease progression or are merely the result of measurement variability or suboptimal positioning.

Why Do Only Some Knees Develop Osteoarthritis?

Knee osteotomy has proven to be effective for most patients with unicompartmental KOA, with survival rates exceeding ten years in many cases[97]. However, the combination of an increasing disease burden and already favorable osteotomy outcomes urges a reconsideration of how clinical care can best be improved. While optimizing osteotomy techniques may enhance surgical outcomes, it does not address the broader challenge - the rising societal burden of KOA[4]. A deeper understanding of the mechanisms driving KOA development and progression is therefore essential. Although the focus of this thesis is on mechanical alignment as a key driver of KOA progression, it is worth noting that other factors also contribute, including genetic susceptibility. For example, twin studies report higher progression rates in monozygotic than in dizygotic twins, indicating that KOA progression is partly heritable[504].

Humans naturally exhibit a slight overall varus alignment, often referred to as constitutional varus, with a considerable proportion of the population showing more than 3° of varus alignment[58], given that the normal range for the mechanical hip–knee–ankle angle (mHKAA) is 180° ± 3°. However, the fact that not all individuals with constitutional varus develop KOA raises important questions about why only some knees progress to KOA. Known contributors to the development of KOA include post-traumatic changes[27]; age-related factors such as degeneration of the meniscus, subchondral bone alterations, cartilage defects[505], and loss of muscle strength, leading to a reduction in biomechanical joint stability[505]; and obesity[21].

I would argue that three-dimensional (3D) joint geometry plays a more substantial role in the development of KOA than currently recognized. When studying the lower limb malalignment phenotype, attention is typically limited to varus and valgus alignment in the coronal plane. However, such a simplified two-dimensional perspective may overlook important geometric factors in the sagittal and axial planes—such as posterior tibial slope, femoral torsion, or tibial rotation—that could influence load distribution and cartilage stress. To address this, longitudinal studies assessing 3D bone geometry in patients with coronal plane malalignment are needed. Comparing patients who do and do not show KOA progression could help clarify the influence of sagittal and transverse geometric features. A more comprehensive 3D assessment of joint geometry could therefore reveal phenotypic patterns that help explain why only some individuals with malalignment (the mechanical overload phenotype) progress to KOA or whether progression instead reflects a combination of geometric factors with other risk factors. Such insights may ultimately support earlier identification and more personalized interventions.

The Role of Growth Plate Mechanics in Lower Limb Alignment

The question arises as to why individuals develop lower limb malalignment in the first place. Repetitive mechanical loading during growth appears to play a key role, as athletes, particularly those involved in high-impact sports, frequently develop varus alignment during growth[63,64,66,67]. It remains uncertain whether this represents a form of natural selection, in which individuals with varus alignment perform better in certain sports such as soccer, or whether an alternative underlying mechanism explains this phenomenon. As discussed in **Chapter 4**, the observed association between cam morphology and varus alignment suggests the latter. Both cam morphology and varus alignment appear to result from adaptive responses of the growth plate to mechanical loading[67,179,180]. According to the Hueter–Volkmann principle, increased compressive forces perpendicular to the physis inhibit longitudinal growth, whereas reduced loading accelerates it, leading to asymmetric physeal development[69–74]. Although empirical evidence for a direct causal link remains limited[77–86], case reports and experimental models provide intriguing support. For instance, a case study in a patient with cam-type femoroacetabular impingement demonstrated asymmetric closure of the capital femoral epiphyseal plate on MRI[506], while animal models showed that localized physeal injury or repetitive loading can induce asymmetric growth, resulting in both varus deformity and cam-type morphology[507,508].

I have the impression that asymmetric growth of the physes contributes to the development of lower limb malalignment. Such growth disturbances may be influenced by behavioral factors during childhood, such as the age at which a child starts walking, the amount of physical activity, or participation in high-impact sports. Understanding these relationships represents the first step; the next is to explore how malalignment might be prevented rather than merely treated. After all, prevention is, in my opinion, better than cure. This highlights the need for prospective research in pediatric populations to better understand growth patterns of the proximal and distal femoral and tibial physes, with particular attention to asymmetric closure of these growth plates. Such insights could form the foundation for preventive strategies, exploring whether mechanical load modification in at-risk individuals might reduce the development of malalignment. Notably, even small degrees of frontal-plane malalignment (1–3°) increase the odds of developing KOA, with angles exceeding 3° associated with substantially higher risks. Although malalignment >3° appears to confer the greatest risk, even milder deviations are not without consequence, suggesting that preventive efforts could theoretically benefit all children. Ultimately, prevention should, if you ask me, take a more prominent role in addressing the lifelong consequences of lower limb deformity.

Does the Ideal Osteotomy Candidate Exist?

At present, no compartment-specific preventive treatments for unicompartmental KOA exist, and clinical management remains primarily focused on symptom alleviation and joint preservation once degenerative changes have developed. Although general preventive strategies—most notably weight reduction—can lower overall KOA risk[509], they do not address established unicompartmental disease. Within this context, osteotomy remains an effective surgical strategy for carefully selected patients. Nevertheless, the question arises: does the ideal osteotomy candidate exist? In principle, the indication for a proximal tibial osteotomy can be summarized as the correction of a substantial extra-articular deformity responsible for intra-articular symptoms[510]. Traditionally, the optimal patient for realignment osteotomy has been described as a physically active individual aged 40–60 years with isolated unicompartmental KOA, a BMI below 30 kg/m^2, non-smoking status, varus deformity less than 15°, a bony deformity greater than 5°, full range of motion, intact ligamentous stability, and adequate pain tolerance[102]. Increasing evidence suggests that age, BMI, and smoking are no longer absolute contraindications[96]. Younger patients (< 50–55 years) generally achieve better outcomes, while obesity and smoking primarily increase surgical complication rates without clearly compromising functional results[96]. Moreover, mild degeneration in the unaffected or patellofemoral compartments does not appear to adversely affect outcomes[96].

Therefore, in clinical practice, we increasingly deviate from the traditional "ideal" osteotomy candidate, as TKA is not a suitable option for every patient[91,92]. Especially in younger individuals, TKA carries a higher revision risk[88–90], which is associated with significantly higher surgical costs and lower patient satisfaction compared to primary procedures[87,91]. Consequently, osteotomies are increasingly considered even in patients with more advanced KOA and malalignment (>15°), with several studies reporting significant pain relief and functional improvement at short-, mid-, and long-term follow-up for these patients[107]. These findings highlight that patient selection is not always straightforward and must be individualized in the spirit of personalized medicine, balancing patient characteristics, disease severity, and the available surgical alternatives. Decisions should ultimately be made together with the patient through shared decision-making. I believe that we are gradually moving away from the concept of the “ideal” osteotomy candidate, sometimes perhaps pushing the boundaries by performing realignment osteotomies that intentionally create a bony malalignment in an anatomically straight limb to address primarily intra-articular problems. Whereas an osteotomy is traditionally indicated for correcting extra-articular (bony) deformities responsible for intra-articular symptoms, it is now increasingly used to treat intra-articular deformities—such as abnormalities in the joint line convergence angle (JLCA)—thereby creating a deliberate malalignment in an otherwise straight bone to address an intra-articular problem. One could argue that in such cases an UKA might be more appropriate, yet this option remains less attractive for younger, more active patients, such as those in their thirties. This raises the question of how best to manage this challenging patient group.

The Strength of Osteotomy

The strength of osteotomy as a joint-preserving procedure has been demonstrated throughout this thesis. Patient-reported outcome measures consistently show significant improvements in pain, function, and quality of life following surgery[103–107], while many patients are able to return to their pre-symptom activity levels[104,107–110]. Long-term survival rates are encouraging, confirming the durability of these procedures over decades[97,113–117,290]. For valgus-producing HTO, reported survival rates prior to conversion to TKA range between 64% and 90% at 10 years, and 45% to 68% at 15 years[97]. In contrast, for patients with valgus malalignment and lateral compartment KOA, the 10-year survival rate of varus-producing distal femoral osteotomy has been reported as approximately 89%[266]. This difference in survival between tibial and femoral osteotomies may be attributed to several factors. Distal femoral osteotomies are less commonly performed and may often be carried out by more experienced surgeons[511]. In addition, differences in patient selection and characteristics - such as younger age, higher activity levels, and less advanced degenerative changes - can also contribute to higher reported survival rates.

Beyond its clinical durability, osteotomy may also induce biological benefits, as partial or even full regeneration of articular cartilage in the previously overloaded compartment has been observed[98,99]. Furthermore, HTOs appears to slow the progression of structural joint damage compared with conservative treatment[344], and is increasingly used to support other joint-preserving interventions such as cartilage repair procedures[94,309,310,512], as also demonstrated in **Chapter 9**. Collectively, these findings highlight the multifaceted role of osteotomy in contemporary knee-preserving care, combining mechanical correction, biological restoration, and clinical durability.

Timing of Osteotomy

The timing of osteotomy is a critical factor for optimizing outcomes in patients with KOA. Ideally, the procedure should be performed before end-stage KOA[512], as patients with advanced degeneration have a significantly reduced osteotomy survival[115]. Changes in the JLCA, a measure of cartilage and/or meniscus loss[159,245] and an indirect indicator of KOA, can already be observed within a two-year timespan, as shown in **Chapter 5**. This highlights the importance of timely intervention, with the optimal JLCA generally below 6°, and preferably below 4°, for osteotomy[220,513]. While this suggests that osteotomy should not be delayed, it also raises the question of whether surgery can be performed too early. In other words, should osteotomy be considered before any degenerative changes occur, as previously discussed in this thesis, similar to preventive strategies used in pediatric orthopedics, where realignment procedures are performed to prevent long-term joint damage? From a biomechanical perspective, early realignment normalizes load distribution across the knee, reducing prolonged asymmetric stress that can accelerate cartilage wear[22,514]. In my view, there is indeed potential value in considering osteotomy as a preventive intervention—if we can first identify which patients, based on alignment and other risk factors, are truly at risk of developing KOA and which are not. For those at risk, timely realignment may preserve joint health and delay or even prevent degenerative changes. Nevertheless, these potential benefits must be carefully weighed against the inherent surgical risks and the demands of postoperative rehabilitation. Importantly, there are currently no trials providing high-level evidence for the optimal timing of osteotomy, and clinical decisions remain largely based on observational data and expert consensus.

Toward Personalized and Dynamic Preoperative Planning in High Tibial Osteotomy?

Preoperative planning is essential for achieving accurate alignment correction in patients with KOA. In 1979, Fujisawa *et al.*[515] identified the optimal weight-bearing axis at approximately 62.5% of the tibial plateau width from the medial edge. This so-called *Fujisawa point* has since served as a reference for planning of osteotomies[515]. However, subsequent studies have reported target correction points ranging between 58% and 62.5%, indicating a lack of consensus regarding the ideal alignment[516]. In current clinical practice, the degree of correction often still depends largely on the surgeon's experience rather than on patient-specific parameters. This raises the question of whether correction planning should become more personalized, potentially accounting for factors such as age, activity level, severity of OA[512], and soft tissue characteristics. Furthermore, osteotomies are still sometimes planned solely on the mHKAA, even though this angle reflects both bony alignment (mechanical medial proximal tibial angle (mMPTA) and mechanical lateral distal femoral angle (mLDFA) and intra-articular alignment (JLCA). This is notable because and osteotomy is intended to correct bony deformities responsible for intra-articular symptoms. An abnormal mHKAA—outside the 180° ± 3° range—may therefore result solely from an intra-articular deviation. When planning is based only on the mHKAA, no distinction is made between malalignment caused by true bony deformity and that arising from intra-articular pathology.

Moreover, conventional planning is typically performed using a whole leg radiograph (WLRs), which provides a static representation of lower limb alignment under standardized positioning. While this approach ensures reproducibility[49], it fails to capture the dynamic nature of knee loading during gait. There is growing evidence that static malalignment is an oversimplification of the biomechanical reality, as dynamic knee alignment and loading patterns vary throughout the gait cycle[230,517–519]. Although patients briefly contact the ground with both limbs during heel strike and pre-swing, loading between the legs during these phases is not equally distributed. In fact, the majority of the gait cycle is spent in single-limb support. As a result, WLRs provide only a limited representation of the loading conditions actually experienced during walking. This raises the question: how representative is a WLR for true functional loading? Differences between static and dynamic alignment have been demonstrated particularly during the early and terminal stance phases—periods associated with increased pain in patients with KOA[230,232,517–519]. These insights raise the question of whether realignment correction should be planned based on individual gait characteristics rather than solely on static imaging. Although the first steps in this direction are being taken[520,521], the integration of patient-specific, gait-based alignment analysis into clinical practice remains a challenge for the future.

The Role of JLCA in Osteotomy Planning and Surgical Decision-Making

The JLCA represents a composite measure of intra-articular deformity and soft tissue laxity, which progressively increases with KOA progression[159,245]. In line with this, **Chapter 6** demonstrated that varus or valgus alignment of the JLCA was correlated with reduced cartilage quality in the affected compartment, further emphasizing its role as a marker of intra-articular disease severity. The JLCA directly affects lower limb alignment under weight-bearing conditions and has been associated with postoperative overcorrection following MOW-HTO[220,522–525]. To avoid overcorrection in MOW-HTO, a previous study proposed a simple equation in which JLCA-2/2 is subtracted from the planned correction[220]. For example, with a planned correction of 7° and a JLCA of 4°, 1° would be subtracted from the planned correction, resulting in an actual correction of 6°.

A shift in JLCA - known as the *seesaw effect* - occurs only when the pivot point of the knee joint, referred to as the *hypomochlion*, is reached[526]. Previous studies have estimated that this tipping point typically occurs when the mMPTA exceeds approximately 92°[159,527], suggesting that particular attention should be paid to the JLCA when planning a correction that will result in a postoperative mMPTA exceeding 92°.

Beyond its influence on osteotomy planning, JLCA also plays an important role in determining the most appropriate surgical strategy for varus knee deformity. Traditionally, factors such as age and activity level guided this decision – knee osteotomy for younger, active patients and UKA for older, low-demand individuals. However, recent evidence suggests that the location of deformity should be the primary criterion[528,529]. Ollivier *et al.*[526] defined intra-articular deformity as JLCA, bony deformity as the difference between the mLDFA and the mMPTA, and whole leg deformity as mLDFA - mMPTA + JLCA. When the intra-articular component exceeds 60% of the global deformity, UKA is preferred; when the bony deformity exceeds 60%, osteotomy is indicated[526]. In intermediate cases, where both contributions are below 60%, no clear superiority exists, and shared decision-making should consider factors such as age, sports participation, and the condition of the meniscus and cartilage[159,530]. As demonstrated in **Chapter 8**, a considerable number of osteotomies are performed in the absence of a true bony deformity. These findings underscore the importance of incorporating the JLCA into the decision-making process, as it provides valuable insight into the intra-articular component of the deformity and may help guide the selection of the most appropriate surgical strategy for varus knee correction.

In my view, osteotomies may at times be overused in cases of isolated intra-articular deformity. Conceptually, creating a deliberate extra-articular malalignment in an otherwise anatomically straight limb to address an intra-articular problem seems counterintuitive, and for such patients a UKA may be a more appropriate treatment option. However, robust evidence to support this assumption is currently lacking. Future research—ideally a randomized controlled trial with long-term follow-up or a well-designed matched-controlled study—is needed to directly compare outcomes of osteotomy versus UKA in patients with isolated intra-articular deformity.

Does Accuracy Matter?

The primary goal of a knee osteotomy is to shift load distribution from the affected to the unaffected compartment, thereby reducing pain and slowing KOA progression[531]. Preoperative planning is therefore aimed at achieving the intended correction accurately during surgery. However, a recent systematic review[516] concluded that the majority of osteotomies fall outside the intended, varying, and relatively wide target range, with a clear tendency toward undercorrection. Undercorrection fails to relieve symptoms, as the mechanical axis continues to pass through the medial compartment, whereas excessive overcorrection can result in poor functional outcomes and degenerative changes in the other compartment[532–535].

To improve accuracy, computer-assisted navigation and patient-specific instrumentation (PSI) have been introduced. Navigation may increase the proportion of osteotomies falling within the target range, but reported results remain inconsistent[536–538]. Similarly, PSI has been associated with slightly improved coronal alignment accuracy (approximately 1° more accurate), though the differences compared to conventional techniques are often not statistically significant[539,540].

Whether this degree of inaccuracy, over- or undercorrection, has a meaningful impact on long-term outcomes remains uncertain. Current evidence suggests that the postoperative mMPTA was associated with a higher risk of conversion to TKA[115], although another study reported greater treatment success with slight valgus overcorrection following MOWHTO[541]. One of the key remaining questions in the field is whether pursuing ever-greater surgical precision truly translates into improved clinical outcomes.

In my view, the accuracy of an osteotomy is unlikely to be so critical that it must be performed with absolute, degree-perfect accuracy. Instead, it appears to be a reasonable margin, approximately 2°, which alignment can still achieve favorable biomechanical and clinical outcomes. What may be more important is to avoid excessive joint line obliquity—particularly values exceeding 5°. Excessive obliquity can lead to medio-lateral femoro-tibial subluxation and altered compartmental contact pressures[461,528]. Furthermore, pronounced joint line obliquity can complicate subsequent conversion to total knee arthroplasty, as it often necessitates greater tibial bone resection to achieve proper prosthetic alignment. To confirm or refute these assumptions, large datasets with detailed postoperative weight-bearing WLRs and long-term follow-up are required to elucidate how correction accuracy and joint line orientation relate to functional and survival outcomes after osteotomy.

Deformity Analysis and Surgical Decision-Making

The indication for an osteotomy should be based on a precise analysis of the deformity origin and its contribution to intra-articular and bony deformity. The “ideal” indication for an osteotomy has been defined as the correction of a substantial bony deformity responsible for intra-articular symptoms[510]. Building upon the deformity framework proposed by Ollivier *et al.*[526], this analysis allows differentiation between predominantly intra-articular or bony deformities, thereby guiding surgical choice.

When the deformity originates primarily from intra-articular structures, UKA is generally preferred, as the pathology is largely confined to the joint (Figure 1). Conversely, when the bony component predominates, osteotomy is indicated to restore overall limb alignment (Figure 1)[526]. Nonetheless, the long-term implications of performing osteotomy in cases with a substantial intra-articular component remain unclear, emphasizing the need for further research to define optimal correction strategies and their impact on joint preservation outcomes.

When an osteotomy is indicated, the subsequent step is to identify the level of correction. This is achieved by calculating the relative femoral and tibial contributions to the bony deformity. When the femoral component accounts for more than 80% of the deviation, a distal femoral osteotomy is recommended; when the tibial component predominates (>80%), a high tibial osteotomy is indicated (Figure 1)[526]. In cases without a clear predominance, or when an isolated correction would result in excessive joint line obliquity—particularly when postoperative mMPTA > 93° in the presence of a femoral deformity (mLDFA > 90°)[526], a double-level osteotomy should be considered, in line with recent ESSKA consensus guidelines[96,542]. This flowchart serves as a practical first guideline to support clinical decision-making and subsequent osteotomy planning in varus knee correction, providing a structured framework to identify the most suitable candidates and the optimal site of correction based on the underlying deformity. However, this approach is not yet universally adopted among osteotomy surgeons, and substantial variation in clinical practice remains.

From Concern to Confidence: The Effect of Osteotomy on Subsequent TKA

Even in cases where TKA becomes inevitable after a previous knee osteotomy, implant survival appears reassuring. As demonstrated in **Chapter 15**, the subsequent implant survival following osteotomy was comparable to that of primary TKA patients. Most matched controlled studies—primarily from Europe and Asia—have similarly reported no significant differences in revision rates between HTO–TKA and TKA-only patients[483–486]. These findings suggest that persistent concerns among some surgeons regarding the potential of osteotomies to complicate future arthroplasty may be largely unfounded—provided that detailed preoperative planning is performed. Particular attention should be given to the joint line obliquity, to prevent the knee from being positioned obliquely in space[461,528]. Thus, with careful surgical planning, the conversion from osteotomy to arthroplasty should not be viewed as a limitation, but rather as an eventual continuation of personalized, joint-preserving knee care.

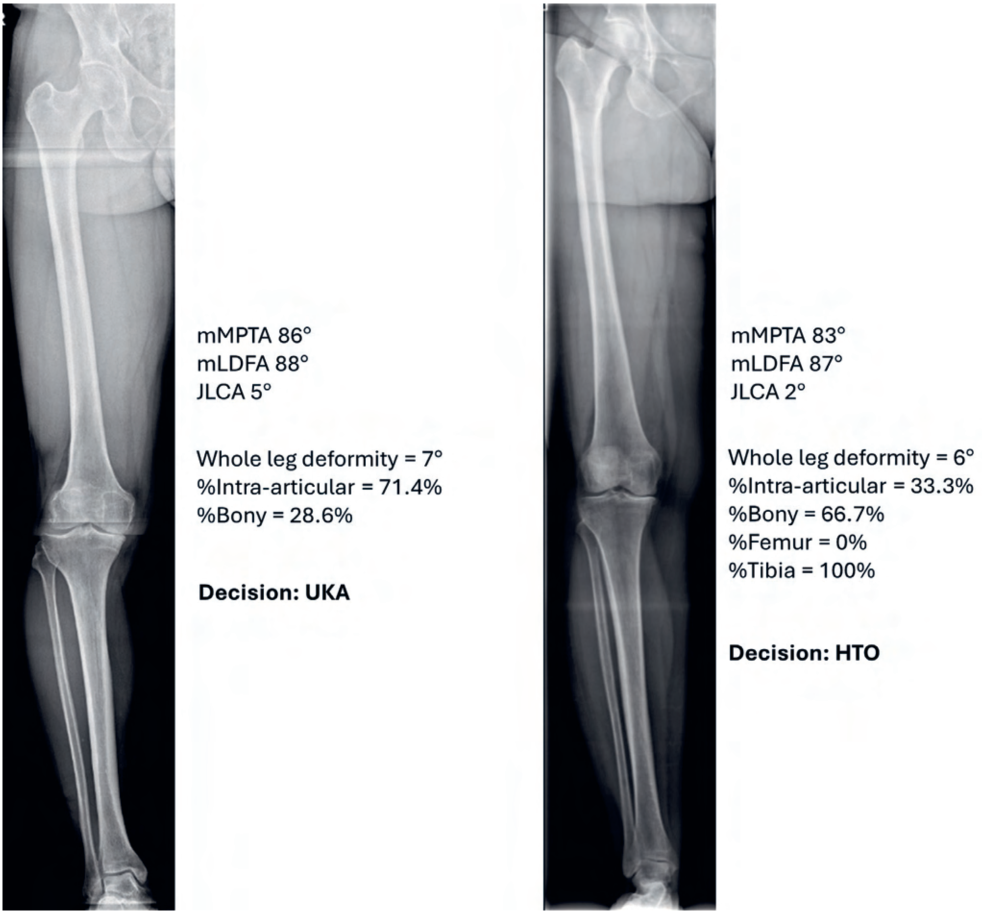

Figure 1 - Examples of varus deformity analysis and treatment decision-making based on deformity origin. In the first case, varus deformity is almost entirely intra-articular (% intra-articular > 60%), leading to an indication for UKA. In the second case, varus deformity is primarily located in the tibia (% bony > 60%, tibial contribution = 100%), indicating a high tibial osteotomy. JLCA = joint line congruency angle; mLDFA = mechanical lateral distal femoral angle; mMPTA = mechanical medial proximal tibial angle.

Effects of osteotomy on adjacent joints

While the primary goal of an osteotomy is to relieve knee pain by restoring mechanical alignment, it inevitably affects the entire kinetic chain of the lower limb, including the hip and ankle. An MOW-HTO may induce reorientation of the ankle joint[292–296], which can worsen alignment and increase pain[293]. New-onset ankle symptoms have been reported in up to 20% of patients[300,301], typically within two years postoperatively, particularly when the ankle joint line is no longer parallel to the ground[293]. These alignment changes are associated with increased pain, progression of ankle osteoarthritis, and reduced quality of life[293,297,303]. As demonstrated in **Chapter 8**, the geometry of the entire tibia appears to play a crucial role in these outcomes: a valgus tibial morphology (increased mechanical lateral distal tibial angle with a medially located CORA) predisposes to deterioration of the ankle joint after MOW-HTO.

In contrast, it may be reasoned that the impact of osteotomy on the hip is limited, given its ball-and-socket configuration, which allows compensatory motion and may attenuate the transmission of coronal or sagittal plane corrections through the lower limb. However, direct evidence supporting this assumption is scarce, as few studies have specifically investigated postoperative alterations at the hip following osteotomies. Although a significant correlation has been reported between the degree of correction and the mechanical greater trochanter angle, the clinical implications of this finding remain unclear and have yet to be substantiated[543].

Overall, I believe that lower limb realignment should be considered within the context of the entire kinetic chain rather than as an isolated joint intervention. In my view, current clinical practice places too much emphasis on knee-centered outcomes, while the potential biomechanical consequences for adjacent joints remain insufficiently explored. Further research should aim to clarify how changes in knee alignment influence load distribution and joint mechanics throughout the limb over time. Adopting a more comprehensive, kinetic-chain–oriented approach in both preoperative planning and postoperative evaluation may ultimately help prevent secondary degeneration and improve long-term functional outcomes after knee realignment surgery.

Beyond Knee Angles

While current alignment analyses primarily focus on the mLDFA and mMPTA, this narrow perspective overlooks the complex interplay within the entire lower limb[213]. As demonstrated in **Chapter 5**, our findings confirm that the mMPTA is often varus and the mLDFA is often valgus. Previous studies have demonstrated that a neutral hip–knee–ankle (HKA) alignment often results from a compensatory relationship between a varus proximal tibia and an opposing valgus distal femur[56], and that, in general, men tend to present with a more varus HKA, whereas women more frequently exhibit a valgus alignment[55,57].

However, focusing solely on knee-related angles may conceal compensatory mechanisms occurring proximally and distally within the limb. For instance, when considering both the mLDFA and the lateral proximal femoral angle, it remains unclear how varus–valgus alignment patterns distribute along the femur, and whether proximal varus and distal valgus act as balancing mechanisms within the same bone, similar to the tibial pattern observed in **Chapter 7 and Chapter 8**. To fully understand lower limb alignment and deformity, future research should move beyond isolated knee geometry and broaden its scope to include the alignment of the entire lower limb. By adopting a more comprehensive, whole-limb perspective, we can improve the classification of patients with lower limb malalignment, better identify compensatory patterns, and refine surgical planning. Ultimately, this integrated approach may lead to more personalized and anatomically accurate treatment strategies, improving both functional outcomes and long-term joint preservation.

Bridging Knowledge Gaps

An overarching theme emerging from this discussion is the potential benefit of gaining new insights into the mechanisms underlying KOA and lower limb malalignment[143,544,545]. To achieve this, a prospective cohort should be established in which biplanar standing whole-leg radiographs are obtained using the EOS® system[546], enabling detailed assessment of both coronal and sagittal alignment. Such a cohort would help address existing knowledge gaps and advance our understanding of the mechanisms and optimal management of lower limb malalignment and KOA—a need that will only become increasingly important in the coming years due to the rising incidence of KOA in younger patients.

To address key questions regarding osteotomy survival and the risk factors that influence long-term outcomes, the establishment of standardized, large-scale datasets is essential. In the Netherlands, a national arthroplasty registry - the Landelijk Register Orthopedische Implantaten[547] (LROI) - already exists and is widely accepted. Unfortunately, no equivalent registry is currently available for osteotomies. By incorporating a dedicated osteotomy module into the LROI, it would be possible to consolidate expertise and outcomes across the country. This is a collective effort that the Dutch orthopedic community must prioritize to advance the quality and consistency of osteotomy care.

Over the past decades, extensive research has been conducted in the search for a definitive biomarker capable of diagnosing patients before the onset of radiographic KOA[548], yet no breakthrough has been achieved —likely due to the heterogeneity of KOA pathophysiology and the absence of a single molecular pathway that consistently characterizes early disease across patient subgroups. What is often overlooked in many KOA cohorts[143,544,545] is the phenotypic driver of disease: lower limb malalignment. Future research should increasingly focus on biomechanically overloaded phenotypes and their corresponding endotypes, to better understand the mechanisms driving KOA progression. As a concluding perspective, this thesis advocates for greater recognition of lower limb malalignment as a critical determinant in KOA development and progression. To date, interventions such as osteotomy that directly correct malalignment have proven far more effective than relying solely on the search for pharmacological therapies. Even if an effective drug for KOA were developed, patients with significant lower limb malalignment would still require osteotomy first to restore proper mechanical alignment.

Reframing the Boundaries of Knee Osteotomy

This thesis highlights the continued relevance of osteotomy as a joint-preserving treatment in patients with unicompartmental KOA and a lower limb malalignment. Long-term results show 64–90% survival at 10 years without conversion to TKA[97], outperforming other joint-preserving treatments[549]. Yet even these data do not prove that an osteotomy truly delays TKA; answering that question would require a sham-controlled randomized trial—methodologically sound, but ethically and practically challenging.

At the same time, patient-reported outcomes consistently demonstrate substantial improvements in pain, function, and quality of life[103–107], underscoring the clinical value of the procedure. This raises the question of whether current indications are too narrow. If the primary goal of osteotomy is to shift mechanical load from the affected to the unaffected compartment, then even patients with minimal malalignment might derive benefit.

The argument extends further when considering prophylactic osteotomy. Varus alignment increases the risk of developing KOA by 1.5- to nearly 3-fold[20,21], and each 1° increase in varus elevates medial compartment loading by ~5% during walking[19]. Correcting malalignment *before* symptoms arise could theoretically reduce the likelihood of KOA onset. However, such an approach must be weighed against the risks of surgery.

Ultimately, I believe the future of osteotomy lies not only in refining surgical technique but in thoughtfully redefining when—and for whom—we should perform this procedure.

Conclusion

This thesis demonstrates that lower limb malalignment is a critical and unfavorable factor in the development and progression of unicompartmental KOA. It highlights the importance of accurate imaging, a deep understanding of mechanical alignment, and refined surgical techniques in preserving joint health. These findings support a more personalized and forward-looking approach to KOA, aiming to maintain function, mobility, and quality of life—especially in younger, active patients.

While joint-preserving procedures such as osteotomy can effectively mitigate symptoms and slow disease progression, the underlying mechanisms driving KOA remain complex and incompletely understood. Understanding *why* malalignment develops is essential for moving beyond treatment toward true prevention. This represents the overarching dream for future research and embodies the vision of *Realigning the Future:* if the mechanisms that drive lower limb malalignment can be identified, it may become possible to intervene early—during growth or in early adulthood—to prevent malalignment before structural joint damage occurs.

Nederlandse samenvatting

De wereldwijde toename van knieartrose, met name onder jonge en actieve mensen, benadrukt de noodzaak van behandelstrategieën die gericht zijn op het behoud van het eigen gewricht in plaats van vervanging ervan. Hoewel een totale knieprothese (TKA) een bewezen effectieve behandeling is bij vergevorderde knieartrose, is deze ingreep minder geschikt voor jongere, actieve patiënten met hoge functionele eisen en een lange levensverwachting. Vanuit dit perspectief biedt een osteotomie een waardevol alternatief: deze operatie maakt het mogelijk om bij jonge patiënten goede klinische resultaten te bereiken, terwijl het eigen gewricht langdurig behouden blijft.

Dit proefschrift richt zich op vier onderling samenhangende thema's binnen het onderzoeksgebied van knieartrose, die gezamenlijk het volledige traject bestrijken van diagnostiek tot chirurgische behandeling. Het centrale doel is het verfijnen van de diagnostiek en het verder optimaliseren van osteotomieën als gewrichtssparende behandeling. Hieronder worden de belangrijkste bevindingen per thema samengevat.

Thema 1 – Beeldvorming bij knieartrose

Het eerste deel van dit onderzoek richtte zich op het verbeteren van de radiologische evaluatie van knieartrose. Daarbij werd onderzocht hoe röntgen- en magnetic resonance imaging (MRI)-beelden op een betrouwbaardere manier kunnen worden ingezet om de gewrichtsstatus en de progressie van artrose te beoordelen, met specifieke aandacht voor de invloed van patiëntpositionering tijdens het maken van röntgenopnamen.

In **hoofdstuk 2** werd aangetoond dat de positie van de knie tijdens röntgenopnames — met name de mate van rotatie en flexie — een aanzienlijke invloed heeft op de gemeten minimale gewrichtsspleet (mJSW). Een kleinere gewrichtsspleet, wat doorgaans wordt geïnterpreteerd als een toename van knieartrose, bleek niet alleen het gevolg van daadwerkelijk kraakbeenverlies, maar ook van verschillen in positionering. Dit benadrukt het belang om bij het interpreteren van mJSW-metingen in longitudinale studies rekening te houden met deze positioneringseffecten.

In **hoofdstuk 3** werden radiologische metingen van de gewrichtsspleet (JSW) vergeleken met MRI-metingen van de morfologie van het kraakbeen en de meniscus. De resultaten toonden aan dat bicompartimentele metingen — waarbij beide gewrichtscompartimenten worden meegenomen — een sterkere correlatie vertonen met de Kellgren-Lawrence score dan unicompartimentele metingen. Deze bevinding benadrukt het belang van een gecombineerde beoordeling van beide compartimenten voor een nauwkeuriger en representatiever beeld van de structurele gewrichtsschade bij knieartrose.

Thema 2 – Invloed van beenasafwijkingen

Het tweede deel van dit proefschrift richtte zich op het onderzoeken van de invloed van beenasafwijkingen, aan de hand van zowel longitudinale als cross-sectionele analyses. Daarbij werd bestudeerd hoe afwijkingen in de beenas de gewrichtsgezondheid beïnvloeden en welke rol sportactiviteiten en mechanische belasting hierin spelen.

In **hoofdstuk 4** werd aangetoond dat een grotere alfa-hoek in de heup samenhangt met een varusstand van de tibia, met name bij mannen en bij personen die in hun jeugd intensief hebben gesport. Deze bevindingen suggereren dat zowel cam-morfologie als varus uitlijning kunnen ontstaan via vergelijkbare mechanismen — namelijk adaptieve reacties van de groeischijven op herhaalde mechanische belasting. Verdere studies zijn nodig om te onderzoeken in hoeverre aanpassingen van belasting tijdens de groei de ontwikkeling van dergelijke afwijkingen, en daarmee het risico op artrose, kunnen beperken.

In **hoofdstuk 5** werd onderscheid gemaakt tussen bot- en intra-articulaire uitlijning om de progressie van knieartrose beter te kunnen voorspellen. Over een periode van twee jaar bleek dat de meeste individuen een verschuiving richting varus vertoonden. Patiënten met een botvarus, maar een aanvankelijk normale intra-articulaire uitlijning, ontwikkelden progressieve gewrichtsvarus, passend bij mediale knieartrose. Deze resultaten tonen aan dat botgeometrie dynamisch is en onderstrepen de belangrijke rol van beenasafwijkingen bij het ontstaan van vroege intra-articulaire veranderingen.

In **hoofdstuk 6** werd dit onderscheid tussen bot- en intra-articulaire uitlijning verder toegepast om de relatie tussen kraakbeenkwaliteit (T2) en beenasafwijkingen te onderzoeken. Met behulp van MRI-gebaseerde T2-mapping — een techniek die gevoelig is voor veranderingen in de kraakbeensamenstelling — werd aangetoond dat malalignement, met name van intra-articulaire, samenhangt met een compartimentsspecifieke afname van de kraakbeenkwaliteit.

Thema 3 – Optimalisatie van osteotomieën bij knieartrose

Het derde deel van dit proefschrift richtte zich op het verbeteren van de zorg rondom osteotomieën door de preoperatieve planning te verfijnen, de beoordeling van botgenezing te verbeteren en chirurgische technieken verder te optimaliseren. Door nieuwe planningsmethoden, biomaterialen en gestandaardiseerde evaluatie-instrumenten te onderzoeken, heeft dit deel als doel de behandeling en uitkomsten voor patiënten die een osteotomie ondergaan, te verbeteren.

In **hoofdstuk 7** werd de traditionele preoperatieve planning uitgebreid door de positie van het rotatie- en angulatiecentrum (CORA) te analyseren bij patiënten met een tibiale deformiteit en KOA. De studie toonde aan dat het CORA zich vaak in de diafyse bevindt in plaats van in de metafyse, wat leidt tot secundaire translatieafwijkingen.

Hoofdstuk 8 onderzocht de gecombineerde invloed van de CORA-locatie, de distale tibiageometrie en de correctiegrootte op de postoperatieve enkeluitlijning bij patiënten die een valgiserende mediale open-wig osteotomie (MOW-HTO) ondergingen. Een valgusvormige distale tibia bleek geassocieerd met een verslechterde enkeluitlijning. Dit benadrukt het belang om bij de pre-operatieve planning niet alleen te focussen op het kniegewricht, maar de volledige beenas te beoordelen.

In **hoofdstuk 9** werden trends geanalyseerd in chirurgische technieken en fixatiemethoden bij proximale tibia-osteotomieën. Er werd een duidelijke verschuiving vastgesteld van laterale gesloten- naar mediale open-wig-technieken, van kram- naar plaatfixatie, en een toenemend gebruik van gecombineerde procedures, zoals osteotomieën die gelijktijdig worden uitgevoerd met kraakbeenherstel, meniscusreparatie of kruisbandreconstructie.

Hoofdstuk 10 presenteerde het studieprotocol van een gerandomiseerde gecontroleerde trial naar het gebruik van AttraX® Putty als synthetisch botvervangend materiaal bij open-wig osteotomie. Het protocol beschrijft hoe de effectiviteit van dit biomateriaal zal worden geëvalueerd met betrekking tot het verminderen van postoperatieve pijn en het bevorderen van botgenezing. Dit onderzoeksontwerp biedt een waardevol kader om de klinische meerwaarde van biomaterialen in het herstel en de revalidatie na osteotomie te beoordelen.

Voortbouwend op de evaluatie van botgenezing omvatte **hoofdstuk 11** een systematische review van radiologische beoordelingsmethoden voor botgenezing na osteotomie. De analyse toonde een aanzienlijke variatie en een gebrek aan consensus tussen studies, wat de noodzaak onderstreept van een gestandaardiseerde, betrouwbare en reproduceerbare beoordelingsmethode.

Als antwoord hierop introduceerde **hoofdstuk 12** de Unified Bone Union (UBU)-classificatie, een systeem dat is ontwikkeld om botgenezing na osteotomie op een consistente manier te beoordelen. De methode liet een hoge reproduceerbaarheid zien, zowel tussen als binnen beoordelaars, en een sterke correlatie tussen röntgen- en computed tomography (CT)-beoordelingen. De UBU-classificatie biedt daarmee een praktisch en reproduceerbaar instrument dat kan bijdragen aan meer uniformiteit in zowel klinische toepassing als wetenschappelijk onderzoek.

Tot slot onderzocht **hoofdstuk 13** de invloed van de positie van de hinge en de helling van de osteotomie op veranderingen in de posterior tibial slope (PTS) na MOW-HTO. De resultaten toonden aan dat met name de positie van de hinge bepalend is voor het behoud van de PTS. Een correcte hingepositie is daarom essentieel om een ongewenste toename van de PTS en de daarmee gepaard gaande verhoogde belasting op de voorste kruisband te voorkomen.

Thema 4 – Invloed van osteotomie op knieprothese-uitkomsten

Het laatste deel van dit proefschrift richtte zich op de invloed van een eerdere osteotomie op de resultaten van een eventueel latere knieprothese. Het doel was om beter te begrijpen hoe gewrichtssparende chirurgie, zoals een proximale tibia osteotomie, de uitkomsten van daaropvolgende ingrepen beïnvloedt.

In **hoofdstuk 14** werd aangetoond dat een TKA na een eerdere proximale tibia-osteotomie gepaard ging met een revisiepercentage van 6%. Een jongere leeftijd en een lage comorbiditeit waren geassocieerd met een hoger revisierisico, terwijl de gemiddelde overleving van de oorspronkelijke osteotomie ongeveer twaalf jaar bedroeg. Een belangrijke beperking van deze studie was echter het gebruik van niet-gematchte populatiedata, waardoor een directe vergelijking met primaire TKA niet mogelijk was.

Daarom onderzocht **hoofdstuk 15** in een gematchte studieopzet of een eerdere proximale tibia-osteotomie invloed had op de uitkomsten van een latere TKA. De resultaten toonden aan dat zowel de revisie- en infectiecijfers als de patiëntgerapporteerde uitkomsten vergelijkbaar waren met die van primaire TKA. Deze bevindingen bevestigen dat een voorafgaande osteotomie de resultaten van een latere knieprothese niet negatief beïnvloedt.

Conclusie

Dit proefschrift laat zien dat een standsafwijking een belangrijke factor is bij het ontstaan en de progressie van knieartrose. Het benadrukt het belang van nauwkeurige beeldvorming, inzicht in mechanische uitlijning en verfijnde chirurgische technieken voor het behoud van het kniegewricht. Deze inzichten ondersteunen een gepersonaliseerde en toekomstgerichte benadering van knieartrose, gericht op het behouden van functie, mobiliteit en kwaliteit van leven, vooral bij jonge, actieve patiënten.

Hoewel osteotomieën effectief symptomen kunnen verminderen en progressie vertragen, blijven de mechanismen van knieartrose complex en onvoldoende begrepen. Inzicht in het ontstaan van malalignement is essentieel om verder te gaan dan behandeling en toe te werken naar echte preventie. Dit vormt de ambitie van toekomstig onderzoek en sluit aan bij de visie van *Realigning the Future:* als de onderliggende mechanismen beter worden begrepen, kan vroegtijdig ingrijpen mogelijk voorkomen dat malalignement leidt tot structurele gewrichtsschade.

Addenda

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Addenda

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Colleagues at the Mayo Clinic, Rochester, Minnesota, USA. **Prof. dr. Daniel Saris**, dear Daniel. Thank you so much for your trust and for giving me the opportunity to spend part of my PhD at the Mayo Clinic. The confidence you placed in me, your encouraging words, and your valuable input on my research plans have played a significant role in my development. I am truly grateful for that. **Dr. Christopher Nagelli**, dear Chris. I would also like to sincerely thank you for my time at the Mayo Clinic. You made me feel at home from the very beginning. Your positivity, kindness, and hospitality are the reason I look back on my stay with such joy. Thank you for making my time in Rochester so memorable. **Dr. Mario Hevesi**. Thank you as well for the trust you placed in me during my stay. I greatly appreciated your input and your critical perspective during the Wednesday morning "dr. Hevesi meetings." I learned a lot from those discussions, and they have strongly influenced the way I approach research. I would also like to thank the members of the Dr. Saris lab: **Katy**, **Kyndra**, **Dunja**, and **Emi**. Thank you for the fun times, the outings, and for introducing me to American life (including, of course, plenty of fast food). Thanks to all of you, I had an amazing and unforgettable time.

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Opa Mees en **oma Eef**, ook jullie wil ik bedanken voor jullie zorgzaamheid en interesse in mijn werk, maar vooral voor de ontspanning die jullie me boden. In drukke periodes kon ik me altijd verheugen op de momenten dat ik naar jullie in Spanje op vakantie ging, één of twee keer per jaar. Heerlijk in het zonnetje, tapas eten, en volledig tot rust komen. Jullie zorgden altijd goed voor me—geen hotel dat daar ook maar bij in de buurt komt.

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Addenda

Curriculum vitae

Eva Bax was born in Zeist, the Netherlands, on the 29th of June 1998. She completed her secondary education at the Christelijk Lyceum Zeist in 2016, after which she began her bachelor's programme in Technical Medicine at the University of Twente, the Netherlands. During her bachelor studies (2016–2019), she developed a strong interest in the interface between technology and clinical practice. She completed her bachelor thesis with distinction, earning a grade of 9.

Following the successful completion of her bachelor's degree, she continued in the master's programme in Technical Medicine at the University of Twente, specializing in Medical Imaging & Interventions (2019–2022). For her graduation internship, she joined the Department of Orthopedics at the University Medical Center (UMC) Utrecht, where she combined scientific research with clinical practice. She completed her master's graduation research under the supervision of dr. Roel Custers and dr. Nienke van Egmond, and finished this project with distinction, earning a grade of 9.

During this period, she developed a particular interest in knee osteoarthritis, lower limb malalignment, and osteotomies. Motivated by the clinical relevance and scientific potential of these topics, she continued within the Orthopedics Department of UMC Utrecht as a PhD candidate. Before starting her doctoral trajectory, she spent three weeks volunteering at St. Elisabeth Hospital in Arusha, Tanzania.

In December 2022, she formally started her PhD at Utrecht University, supervised by prof. Harrie Weinans, prof. Moyo Kruyt, dr. Roel Custers, and dr. Nienke van Egmond**.** Throughout her PhD, she remained actively involved in clinical activities, including outpatient clinics. She presented her work at multiple national and international conferences, including several editions of International Cartilage Regeneration & Joint Preservation Society (ICRS), Nederlandse Orthopaedische Vereniging (NOV), and International Cartilage Regeneration & Joint Preservation Society (OARSI). She also contributed to organizing educational activities, including osteotomy courses, the Knee Joint Preservation Course, and the Joint Preservation Course, and she supervised several bachelor's and master's students.

In the final year of her PhD, she spent three months as a Research Fellow at the Mayo Clinic in Rochester, Minnesota, USA**,** where, under the guidance of prof. Daniel Saris and dr. Mario Hevesi, she further deepened her passion for clinical research and knee joint preservation.

In the final phase of her PhD, she became actively involved in the PROBE consortium, a large collaborative initiative focused on knee osteoarthritis. During this period, she was also involved in obtaining several major research grants, which further strengthened the scientific foundation of the projects and allowed the research line to be continued.

Three years after beginning her doctoral journey, her PhD thesis was completed. Following the defense of her dissertation, she continued her academic career as a postdoctoral researcher, maintaining her focus on clinical research and knee joint preservation.

Addenda

List of Publications

Included in this thesis

Peer reviewed publications

Bax, E. A., Nguyen, H. C., Custers, R. J. H., Arbabi, V., Rayegan, H., Gielis, W. P., Lindner, C., Cootes, T. F., Kloppenburg, M., Blanco, F. J., Haugen, I. K., Berenbaum, F., Jansen, M. P., Mastbergen, S. C., Roemer, F. W., Eckstein, F., Wirth, W., Kruyt, M. C., & Weinans, H. (2025). Impact of quantified knee positioning on the measurement of minimal joint space width using statistical shape models: A cross-sectional and longitudinal analysis in the IMI-APPROACH. Osteoarthritis Imaging, 100357. https://doi.org/10.1016/j.ostima.2025.100357

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Nguyen, H. C., Bax, E.A., Custers, R. J. H., van Egmond, N., Kuiper, R. J. A., Arbabi, V., Rayegan, H., Gielis, W.-P., Sakkers, R. J. B., Kloppenburg, M., Blanco, F. J., Haugen, I. K., Berenbaum, F., Jansen, M. P., Mastbergen, S. C., Lindner, C., Cootes, T. F., Weinans, H. (2026). Progression of Bone and Joint Space Deformity in Patients with Mild Knee Osteoarthritis: Data from the IMI-APPROACH Cohort. Osteoarthritis and Cartilage Open. https://doi.org/10.1016/j.ocarto.2026.100762

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Janssen Y, Nguyen HC, Custers RJH, van Egmond N, Kruyt MC, Sakkers RJB, Thooft J, Kloppenburg M, Blanco FJ, Haugen IK, Berenbaum F, Mastbergen SC, Weinans H, Bax E.A. (2026). Uncovering the Impact of Center of Rotation of Angulation Location on High Tibial Osteotomy in Knee Osteoarthritis: A Potential Pathway for Improved Outcomes. Cartilage. doi:10.1177/19476035261420279.

Bax, E. A., Harlianto, N. I., Custers, R. J. H., van Egmond, N., Foppen, W., & Kruyt, M. C. (2024). Radiographic Assessment of Bone Union in Proximal Tibia and Distal Femur Osteotomies. JBJS Open Access, 9(4). https://doi.org/10.2106/JBJS.OA.24.00101

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Submitted for publication

Dorst, S., Custers, R. J. H., van Egmond, N., Sakkers, R. J. B., Weinans, H. H., Bax, E. A. What Is the Effect of a High Tibial Osteotomy on the Ankle Joint? In Most Patients, Ankle Alignment Worsens Due to a Valgus-Shaped Tibia.
Under review

Manuscript in preparation

Bax, E. A., Rohdenburg, J. E., Ahmad, R. A., van Egmond, N., Stuart, M. J., Krych, A. J., Hevesi, M., Saris, D. B. F. Four Decades of High Tibial Osteotomy: Trends in Technique, Fixation, and Concomitant Procedures.

Not included in this thesis

Bax E.A., Fuller C, Thooft J, Spaans AJ, Sakkers R, Mastbergen SC, Kloppenburg M, Blanco FJ, Berenbaum F, Weinans H, Nguyen HC. Three-Dimensional Leg Alignment Analysis: Do We Need a Consensus?
Under review

Bax E.A., Ahmad RA, Clark SC, van Egmond N, Taunton MJ, Pagnano MW, Sierra RJ, Hevesi M, Saris DBF. Comparable Total Knee Arthroplasty Function Following High Tibial Osteotomy or Unicompartmental Knee Arthroplasty: More Than 10 Years of Follow-Up.
Under review

Fuller CB, Spaans AJ, Custers RJH, Nijhuis WH, van Egmond N, Sakkers RJB, Bax E.A. Cutting to the Truth: Are We Measuring Osteotomy Parameters Correctly?
Under review