



Contents lists available at ScienceDirect

Journal of ISAKOS

journal homepage: www.elsevier.com/locate/jisakos

Original Research

Changes in coronal knee-alignment parameters during the osteoarthritis process in the varus knee

William Colyn^{a,b,c,*}, L. Bruckers^d, L. Scheys^e, J. Truijen^f, K. Smeets^g, J. Bellemans^{b,f,h}

^a Dept. of Orthopedic Surgery, AZ Turnhout, Turnhout, 2300, Belgium

^b UHasselt, Faculty of Medicine and Life Sciences, Diepenbeek, Belgium

^c Ziekenhuis Oost-Limburg, Dept. Future Health, Genk, Belgium

^d I-BioStat, University Hasselt, Hasselt, Belgium

^e Dept. of Orthopedic Surgery, University Hospitals Leuven, Leuven, Belgium

^f Dept. of Orthopedic Surgery, ZOL Genk, Genk, Belgium

^g Dept. of Orthopedic Surgery, AZ Vesalius, Tongeren, Belgium

^h GRIT Belgian Sports Clinic, Leuven, Belgium

ARTICLE INFO

Keywords:

Constitutional varus
Knee alignment
Prediseased
Osteoarthritis
Coronal

ABSTRACT

Objectives: The idea to aim for an “individualized” alignment, whereby the constitutional alignment is restored, has gained much interest among knee surgeons. This requires insight into the prediseased, natural alignment of our patients' knees. The aim of this study is (1) to determine how the hip–knee–ankle (HKA) angle is influenced during the arthritic process and (2) to investigate the correlation between joint line changes and the progression of osteoarthritis (OA). It is our hypothesis that the most pronounced coronal parameter changes appear at the proximal tibia and at the joint line.

Methods: One hundred sequential full-length X-rays with a minimum follow-up of 1 year were retrospectively reviewed from a radiographic joint database. Patients had to be at least 50 years of age needed to have an HKA angle of more than 1.3° varus to be included. Patients with ipsilateral total hip arthroplasty, femoral or tibial fracture, osteotomy, or ligamentous repair were excluded. Fifteen alignment parameters were investigated on the sequential full-length X-rays. Moreover, the relationship between the alignment parameters and the Kellgren–Lawrence grade (KL grade) was determined by using linear mixed models.

Results: A progressive KL grade is associated with an increase of the HKA ($p < 0.001$). Mostly, HKA differs due to decrease of the medial tibial plateau (MPTA) angle (0.93°) and an increase of the joint line angle (JLCA) (0.86°). The mL DFA demonstrated the most pronounced changes in the beginning of OA (KL grade 1–2) ($p = 0.049$). In particular, the MPTA becomes considerably smaller ($p = 0.004$) in the later stage of OA (KL grade 3). Also, a progressive increase of the JLCA ($p < 0.001$) is observed upwards of KL grade 3.

Conclusion: By comparing consecutive full-length X-rays in the same patients, it is possible to define the coronal alignment changes during the arthritic process. The HKA angle increases according the arthritic progression, whereby the most pronounced changes appear at the proximal tibia (MPTA) and at the joint line (JLCA). The alignment changes in varus OA knees can be divided in three stadia: (1) erosion of the distal medial femoral condyle, (2) erosion of the medial tibial plateau, and (3) a progressive increase of the joint line angle.

Level of evidence: Therapeutic Study, Level III.

* Corresponding author. Orthopaedic Department, AZ Turnhout, Steenweg Op Merksplas 44, 2300, Turnhout, Belgium

E-mail address: william_colyn@hotmail.com (W. Colyn).

<https://doi.org/10.1016/j.jisako.2022.12.002>

Received 22 July 2022; Received in revised form 1 November 2022; Accepted 7 December 2022

Available online xxx

2059-7754/© 2023 The Author(s). Published by Elsevier Inc. on behalf of International Society of Arthroscopy, Knee Surgery and Orthopedic Sports Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

What are the new findings

This is the first article whereby sequential X-rays of patients were used. Therefore, it was possible to clarify the radiographic changes during the arthritic process of the knee.

We found that the first alterations towards increasing varus occur at the femoral site, whereby an erosion of the medial femoral condyle appears. Second, an erosion of proximal medial tibial plateau occurs and finally a lateral ligamentous laxity causes an increased lateral joint opening.

Introduction

Restoring the alignment to neutral in total knee arthroplasty (TKA) could be perceived as unnatural for a substantial fraction of the population [1]. Further research has indeed shown that a mild under-correction of the varus deformity during TKA was associated with better clinical and functional outcome scores [2]. A study by Parratte suggests a patient-specific ideal target for postoperative alignment, which does not necessarily lie within $0^\circ \pm 3^\circ$ [3]. This supports Howell's idea to aim for an "individualized" alignment, whereby the prearthritic or native limb alignment is restored [4,5]. However, restoring the natural, subject-specific alignment requires insight in the original, prediseased natural alignment of the patient.

Previous studies have suggested using the unaffected contralateral limb as a template for the arthritic limb but have failed to prove sufficient reliability [6]. Hence, the use of the contralateral limb to reconstruct the prediseased alignment is not encouraged [2]. Therefore, if it is only reliable to use the affected limb, the changes on the overall knee alignment through the arthritic process have to be understood to determine the prediseased alignment.

Through the process of osteoarthritis, the cartilage thickness reduces, and erosion of the subchondral bone increases. As a consequence, leg alignment will change over time. A previous study by Thienpont et al. already mentioned the correlation between the varus alignment and MPTA, as well as the JLCA [8]. Other studies have also confirmed the strong correlation between the MPTA and the HKA [1,7,9]. Also, some studies have suggested that varus deformity increases as a result of distal femoral wear. Victor et al. have noted that progressive varus OA is also associated with changes in the tibial joint line angle. However, none of these studies could rely on longitudinal assessments within patients as cross-sectional comparisons were only made between different patients at different arthritic stages. By using such study design within subject evolutions cannot be fully elucidated. Moreover, all these studies relied on X-ray assessments without correcting for potential rotational errors, which is a well-known limitation of two-dimensional full-length X-rays [2,10,11].

The aim of this study was (1) to longitudinally investigate the changes in hip-knee-ankle (HKA) angle throughout the different arthritic stadia at mid-term follow-up and (2) to investigate the correlation between joint line changes and progression of OA. It was our hypothesis that the most pronounced coronal parameter changes appear at the proximal tibia and at the joint line.

Patients and Methods

Patient selection

Using the (A) radiographic joint database, all full-length X-rays between 2014 and 2019 were retrospectively reviewed. The study was admitted by the Ethics Committee of (A) (internal ref nr 18/0088R). Inclusion required sequential full-length X-rays with a minimum follow-up of 1 year, patients were at least 50 years of age, and had an HKA angle of more than 1.3° varus at the time of the first available X ray as 1.3° was

determined as the mean HKA angle in a young healthy population in earlier research [1]. Full-leg radiographs had to be obtained while the patellae were facing forward [1,12,13]. Patients presenting with an ipsilateral total hip arthroplasty (THA), preoperative femoral or tibial fracture, osteotomy, or ligamentous repair were excluded.

From the 948 patients extracted from the database, 341 were excluded for insufficient varus, 36 for age, 268 for inadequate follow-up, 93 for extreme mispositioning, 76 for ipsilateral THP, and 34 for fracture or ligamentous repair. 100 patients were included for measurement analysis. Information from two X-rays was available for every patient. Of these, 31 were excluded because of less than 0.5° difference between the measurements, which can be explained by rotational or measurement errors. Finally, 69 patients were included for statistical analysis.

Radiographic measurements

All radiographic measurements were performed by the same person (B) using the AGFA PACS software package (Agfa-Gevaert; Mortsel, Belgium), with a documented measurement accuracy up to 0.1° [2]. In total, 14 alignment parameters were measured using previously described techniques. (1) The HKA angle was formed by the mechanical femoral axis and the mechanical tibial axis. (2) The mechanical axis deviation (MAD) was measured as the distance between the mechanical axis line and the centre of the knee. (3) The mechanical lateral distal femoral angle was defined as the lateral angle formed between the mechanical femoral axis and the knee joint line of the distal femur. (4) The medial angle formed between the mechanical tibial axis and the knee joint line of the proximal tibia was defined as the medial proximal tibial angle (MPTA). (5) The joint line convergence angle (JLCA) is the angle between the knee joint lines of the distal femur and the proximal tibia. (6) The angle between the parallel of the floor and the joint line of the distal femur was defined as the femoral joint line angle (FJLA). (7) The tibial joint line angle (TJLA) was formed between the proximal tibial joint line and the parallel of the floor [14]. (8) A lateral open angle was expressed by a positive value and a medial open angle by a negative value. (9) The medial opening was measured as the distance between the medial tibial plateau and the surface of the medial femoral condyle. (10) This distance at the lateral side was determined as the lateral opening. (11) The medial neck-shaft angle (MNSA) was formed by the anatomic axis of the femur and the bisector of the femoral neck. (12) The angle formed by the mechanical and anatomic axis of the femur was called the knee valgus proximal angle (KVPA). (13) The angle between the line connecting the tip of the greater trochanter with the centre of the femoral head and the mechanical femoral axis was defined as the lateral proximal femoral angle (LPFA). (14) The lateral angle formed by the mechanical axis of the tibia and the joint line of the proximal talus was defined as the lateral distal tibial angle (LDTA). (15) The distance measured between both medial malleoli was defined as the intermalleolar distance (IM-distance).

The degree of osteoarthritis was determined based on the Kellgren-Lawrence scale (KL scale) [5]. The formula of Maderbacher was used to correct possible rotational errors due to the use of two-dimensional full-length X-rays [10]. Therefore, some additional measurements were performed: the assessment of the lower limb rotation was based on the proximal fibular width (C), the distance between the lateral fibular cortex and the lateral tibial cortex (visible part of the fibula (E)), the distance between the tip of the fibula and the lateral tibial cortex (overlapped part of the fibular tip (B)) and the distance between the lateral fibular cortex and the fibular tip (B + E). The rotation was calculated using following formula [10]: $\text{rotation} = -14.20 - 0.17 \times 100 \times \text{EC} + 0.35 \times 100 \times \text{BC} + 0.31 \times 100 \times (\text{B} + \text{E})\text{C}$. For each increase with one degree of rotation, measured femoral parameters (mLDFA, KVPA, MNSA, LPFA, and FJLA) increased by a factor of 0.0824, tibial measurements (MPTA, LDTA, and TJLA) by a factor of 0.0504, and JLCA by a factor of 0.0664. The HKA was corrected by the rotation multiplied by

0.0697 in fully extended knees. Only patients with an increase of $>0.5^\circ$ in HKA between two measurements were included for statistical analysis.

Statistical methods

Linear mixed models were used to investigate the association between (1) HKA or IM distance and the other angles and (2) the angles and the KL scale [15]. More specifically, the following models were fitted. Models with either HKA or IM distance as dependent variable and one of the other alignment parameters as independent variable (predictor). Models with one of the angles as dependent variable and KL grade as a categorical predictor, allowing for nonlinear associations between the alignment parameters and degree of arthrosis. Every patient contributes data for both knees. This correlation between these two measurements needs to be taken into account in the statistical model. Therefore, a random patient effect was included in the linear mixed models (Verbeke & Molenberghs, 2000). The alignment parameters corrected for rotation were used in these models. And only those patients with an increase of $>0.5^\circ$ in (for rotation corrected) HKA between the two measurements were included in the statistical analysis.

Results

In total, 55 patients equalling 110 knees were finally included. Of those knees, 14 had a KL grade of I, 31 were a KL grade II, 41 a KL grade III, and 24 knees were rated as KL grade IV.

The mean follow-up between two sequential X-rays was 2 years (1.0 yrs. – 4.5 yrs). The mean change Δ in HKA in this period was 1.69° (SD, 1.20°). For mL DFA, MP TA, JL CA, and LD TA, the mean change Δ was 0.27° (SD, 1.19°), -0.46° (SD, 1.09°), 0.96° (SD, 1.26°), and -1.32° (SD, 3.44°), respectively. An increase in KL grade leads to an increase in HKA angle ($p < 0.001$), JL CA ($p < 0.001$) and FJ LA ($p = 0.001$), and lateral opening ($p < 0.001$). In contrast, the MP TA ($p = 0.004$), LD TA ($p = 0.012$), and the medial opening ($p < 0.001$) all decreased when the KL grade increased (Fig. 1). The associations between KL grade and mL DFA, KV PA, and TJ LA were not statistically significant, unless a linear

trend is assumed (mL DFA ($p = 0.049$), KV PA ($p = 0.021$), and TJ LA ($p = 0.038$)). mL DFA and TJ LA showed the most pronounced changes between KL grade I to KL grade II. The opposite was observed for MP TA and FJ LA, whereby the greatest decrease occurred between KL grade II and IV (Fig. 2). There was no association between MNSA ($p = 0.258$) or LP FA (0.292) and a more advanced KL grade.

The most pronounced changes in JL CA angle were also observed between KL grade 2 and 4 (Fig. 3). Changes in the medial opening were most consistently seen in KL grades 2–3. The lateral opening began to increase progressively from KL grade 1 onwards. In comparison, there was a decrease in the medial opening (slope = -0.3347 ; $p = 0.257$) and a sharper increase in the lateral opening (slope = 0.6308 , $p = 0.007$), where the KL grade was above 3. The IM distance was only associated with FJ LA ($p < 0.001$; $r^2 = 12.$) and TJ LA ($p < 0.001$; $r^2 = 18.2$). IM distance and HKA angle showed no association with each other. The association between the HKA angle and the other alignment parameters was described by means of linear mixed models (Fig. 4). There was a positive association between HKA and FJ LA ($p < 0.001$; $r^2 = 9.1$), mL DFA ($p < 0.0001$; $r^2 = 11.4$), and JL CA ($p < 0.001$; $r^2 = 29.6$). Conversely, a negative association was found between the HKA angle and MP TA ($p < 0.001$; $r^2 = 37.6$).

An increase of 1° in MP TA resulted in a decrease in the HKA by 0.93° . An increase of 1° in FJ LA, mL DFA, and JL CA was associated with an increase in the HKA of 0.45° , 0.61° , and 0.86° , respectively.

Discussion

The main objective of this study was to better understand the radiographic changes of a varus knee during arthritic evolution. In the mild arthritic stage, the knee alignment changes due to an erosion of the distal medial femoral condyle. In a more progressive arthritic stage, erosions of the medial tibial plateau will progressively change the knee alignment. The joint line angle becomes progressively higher during the arthritic process: the lateral opening, a radiographic sign of the ligamentous laxity, progressively rises during the arthritic process. The change in the overall knee alignment of varus OA knees was mostly determined by a

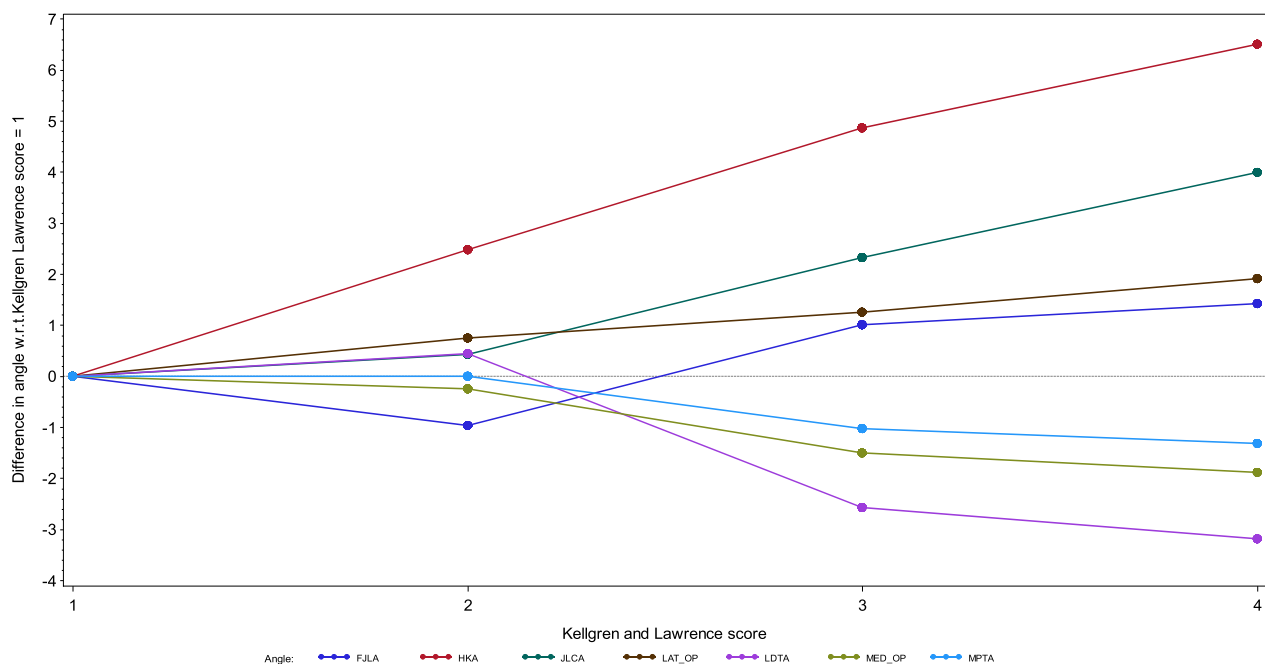


Fig. 1. Association between all significant alignment parameters and Kellgren–Lawrence scale. A progression of arthrosis will strongly influence the medial tibial plateau (MP TA) ($p = 0.004$), lateral distal tibial angle (LD TA) ($p = 0.011$), lateral opening (lat_op) ($p < 0.001$), medial opening (med_op) ($p < 0.001$), and the joint line (FJ LA ($p = 0.001$) and JL CA) ($p < 0.001$). The overall HKA angle is correlated to the KL grade ($p < 0.001$).

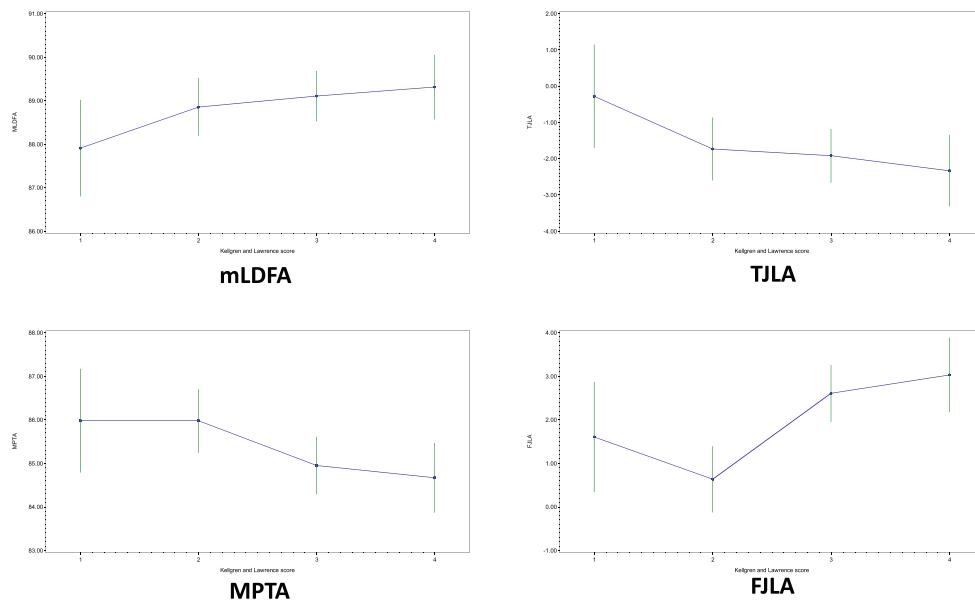


Fig. 2. An illustration of the changes of mLDFA, TJLA, MPTA, and FJLA correlated with the progression of KL grade. mLDFA and TJLA changes in the beginning of the curve, in contrast of MPTA and FJLA who changes at the end of the curve.

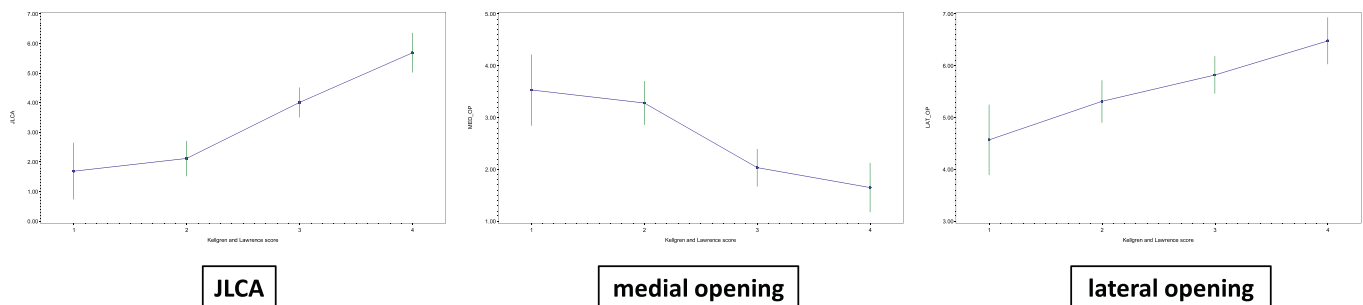


Fig. 3. An illustration of the joint line changes correlated with the progression of KL grade. The steepest slope of the curve is observed between KL grade 2 and 4 for JLCA and the medial opening. The lateral opening increases progressively.

decrease of the medial tibial plateau angle and an increasing joint line convergence angle.

These findings confirm earlier conclusions made by Thienpont et al. [7]. They included 96 patients with a preoperative OA knee on one side and a nonarthritic knee on the contralateral side. Other studies also confirmed the strong correlation between the MPTA and the HKA [1,7,9]. Although none of them used sequential X-rays, reliable alignment changes could not be investigated. By using several radiographs at a different stage of the arthritic process, it was possible to investigate the influence of arthrosis on the overall knee alignment. A previous study on the patterns of the femoral cartilage loss had already concluded that the correlations between cartilage thickness changes and the HKA angle were stronger for the tibia than for the femur in varus knees [8]. These findings support our findings of higher estimated changes in MPTA in comparison with the mLDFA.

Based on our findings, the change of alignment during the arthritic process can radiographically be divided into three stages: first, an increase of mLDFA and TJLA occurs. Second, the MPTA becomes smaller and the FJLA increases. Third, JLCA increases importantly. This means that the first alterations towards increasing varus occur at the femoral site, whereby an erosion of the medial femoral condyle appears. Second, an erosion of proximal medial tibial plateau occurs and finally a lateral ligamentous laxity causes an increased lateral joint opening.

Based on the findings of Cooke, Victor et al. already suggested that 220 bone losses occurred at the level of the distal femur [14]. We only observed this phenomenon in the earlier first stadium of arthrosis. When OA proceeds to KL grade III-IV, the femoral changes become less important. On the contrary, the changes at the tibial side become more determinant. Victor also described that the resulting varus deformity would push the knee outwards.

Thereby, the position of the tibial mechanical axis will change with respect to the floor, which explains the changes of the TJLA [14]. Previous research mentioned a progressive insufficiency of the lateral ligamentous complex appears to be associated with the end stage of varus OA knees [7,8,14,16]. We found that the lateral opening of the joint increases progressively from the beginning of the arthritic process.

At the end of this process, changes of the lateral opening are more prominent than the decrease in the medial opening. The decrease in medial opening is caused by the loss of medial cartilage. Due to the KL classification, the medial opening will diminish since a KL grade I is classified by a doubtful narrowing of the joint space and a KL grade IV for means that there is a severe narrowing of the joint space. So, the gradual decrease in medial opening mentioned that the KL scale was used adequately. The increase of the lateral opening can only be declared by the progressive laxity of the lateral ligamentous complex.

The most important clinical relevance of this study lies in the

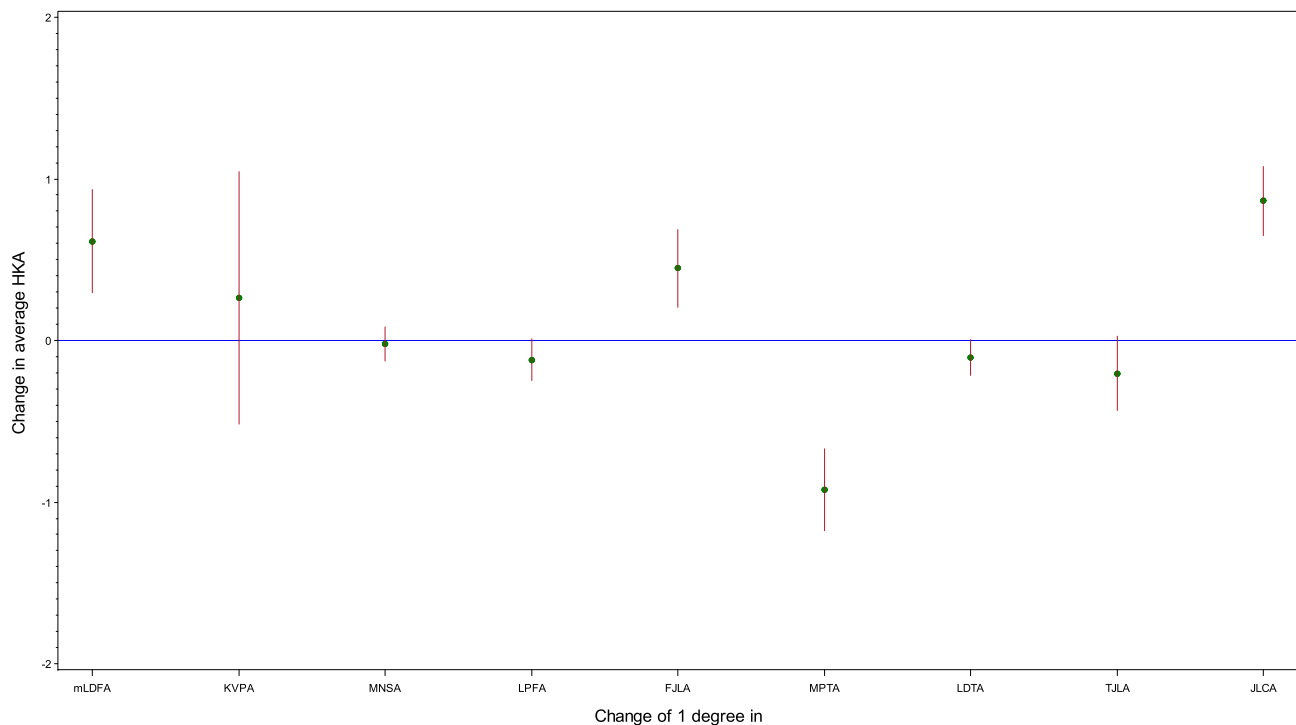


Fig. 4. An increase of 1° in MPTA decreased the HKA by 0.93° . An increase of 1° in FJLA, mL DFA, and JLCA was associated with an increase of the HKA of respectively 0.45° , 0.61° , and 0.86° .

possibility to determine the prediseased knee phenotype. This is increasingly recognized as the most relevant feature to restore the constitutional alignment and to develop customized knee components.

This study has several limitations. First, weight-bearing full-leg radiographs were used. The three-dimensional geometry of the limb is projected in two dimensions, whereby the rotational position of the lower extremities may influence the outcome of the measurement. Especially, when comparing consecutive X-rays of one patient, the consequences of rotation on the alignment have to be known. A perceived varus could in fact be a more external rotation of the limb. To tackle this issue, rotational corrections were calculated based on the formula of Maderbacher et al. [10]. Second, all the measurements were observed by one single investigator. The results could be influenced by the accuracy of the investigator. However, a single observer assures consistency. Third, the time interval between the sequential radiographs is relatively short (maximum 4.5 years). The reason for this is that older radiographs were performed by different digital radiography systems and so had to be excluded to ensure the accuracy of the X-ray images.

By using sequential X-rays of the patients, it was possible to investigate the effect of the intermalleolar distance on the HKA angle as well as the joint line. Only positive correlations were found between the IM distance and the TJLA as well as the FJLA. There is no association between the HKA angle and the IM distance although clinicians perceived a more varus alignment when patients were standing with both feet together. This can be explained by the fact that the HKA and other alignment parameters such as mL DFA, MPTA, MNSA, and KVPA represent the intrinsic geometry of the bone relative to a mechanical axis. We observed that only the relative orientation of the joint line to the floor is influenced by the IM distance.

5. Conclusion

A clarification of the radiographic changes was given by using consecutive X-rays during different arthritic stadia of our patients. The alignment changes in varus OA knees can be divided in three stadia: (1) erosion of the distal medial femoral condyle, (2) erosion of the medial

tibial plateau, and (3) a progressive increase of the joint line angle whereby at the end of the arthritic process, changes of the lateral opening become more prominent.

Funding

This study is part of Limburg Clinical Research Center supported by Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital.

Conflict of interest

None to declare.

Authors' contributions

WC: designed the study, performed the radiographic measurements, analysed and interpreted the data, prepared the manuscript. LB: performed the statistical analysis, analysed and interpreted the data. LS: analysed and interpreted the data, reviewed the manuscript. JT: analysed and interpreted the data, reviewed the manuscript. KS: designed the study, analysed and interpreted the data, reviewed the manuscript. JB: designed the study, analysed and interpreted the data, reviewed the manuscript.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Acknowledgements

The authors wish to acknowledge Dr. Elizabeth Flesher for her help in reviewing and revising the manuscript for grammar and syntax.

References

- [1] Bellemans J, Colyn W, Vandenuecker H, Victor J. The Chitranjan Ranawat Award: is neutral mechanical alignment normal for all patients? The concept of constitutional varus. *Clin Orthop Relat Res* 2012;470:45–53. <https://doi.org/10.1007/s11999-011-1936-5>.
- [2] Beckers L, Colyn W, Bellemans J, Victor J, Vandekerckhove P-J. The contralateral limb is no reliable reference to restore coronal alignment in. *TKA Knee Surg Sports Traumatol Arthrosc* 2020. <https://doi.org/10.1007/s00167-020-06152-9>. Epub 2020 Jul 21.
- [3] Parratte S, Pagnano MW, Trousdale RT, Berry 282 DJ. Effect of mechanical axis alignment on fifteen-year survival of modern, cemented total knee replacement. *J Bone Joint Surg Am* 2010;92:2143–9. <https://doi.org/10.2106/JBJS.I.01398>.
- [4] Vanlommel L, Vanlommel J, Claes S, Bellemans J. Slight undercorrection following total knee arthroplasty results in superior clinical outcomes in varus knees. *Knee Surg Sports Traumatol Arthrosc* 2013. <https://doi.org/10.1007/s00167-013-2481-4>.
- [5] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16(4):494–502. <https://doi.org/10.1136/ard.16.4.494>.
- [6] Vandekerckhove P-JTK, Matlovich N, Teeter MG, MacDonald SJ, Howard JL, Lanting BA. The relationship between constitutional alignment and varus osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc* 2017;25:2873–9. <https://doi.org/10.1007/s00167-016-3994-4>.
- [7] Thienpont E, Schwab PE, Cornu O, Bellemans J, Victor J. Bone morphotypes of the varus and valgus knee. *Arch Orthop Trauma Surg* 2017;137:393–400. <https://doi.org/10.1007/s00402-017-2626-x>.
- [8] Eckstein F, Wirth W, Huldemaier M, Stein V, Lengfelder V, Cahue S, et al. Patterns of femorotibial cartilage loss in knees with neutral, varus, and valgus alignment. *Arthritis Rheum* 2008;59(11):1563–70. <https://doi.org/10.1002/art.24208>.
- [9] Shetty GM, Mullaji A, Bhayde S, Wook Nha K, Keun Oh H. Factors contributing to inherent varus alignment of lower limb in normal Asian adults: role of tibial plateauinclination. *Knee* 2014;21:544–8. <https://doi.org/10.1016/j.knee.2013.09.008>.
- [10] Maderbacher G, Baier C, Benditz A, Wagner F, Greimel F, Grifka J. Presence of rotational errors in long leg radiographs after total knee arthroplasty and impact on measured lower limb and component alignment. *Int Orthop* 2017;41:1553–60. <https://doi.org/10.1007/s00264-017-3408-3>.
- [11] Nam D, Shah RR, Nunley RM, Barrack RL. Evaluation of the 3-dimensional, weight307 bearing orientation of the normal adult knee. *J Arthroplasty* 2014;29(5):906–11. <https://doi.org/10.1016/j.arth.2013.10.024>.
- [12] Moreland JR, Basset LW, Hanke GJ. Radiographic analysis of the axial alignment of the lower extremity. *J Bone Joint Surg Am* 1987;69:745–9. PMID: 3597474.
- [13] Paley D. *Principles of deformity correction*. Heidelberg, Germany: Springer-Verlag; 2003. p. 1–60.
- [14] Victor JMK, Bassens D, Bellemans J, Gürsu S, Dhollander AAM, Verdonk P. Constitutional varus does not affect joint line orientation in the coronal plane. *Clin Orthop Relat Res* 2014;472:98–104. <https://doi.org/10.1007/s11999-013-2898-6>.
- [15] Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data*. New York: Springer-Verlag; 2000.
- [16] Cooke TDV, Scudamore A, Greer W. Varus knee osteoarthritis: whence the varus? *J Rheumatol* 2003;30:2521–3. PMID: 14719187.