Original Article

Analysis of the correlation between postoperative effects of total knee arthroplasty and angles of axial alignments of the lower extremities

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Abstract: Background: An appropriate angle of implantation in total knee arthroplasty (TKA) plays a pivotal role in the survival rate of implants and clinical outcomes. In previous studies, the hip-knee-ankle angle (HKA) was used to predict surgical efficacy. However, the correlation between HKA and clinical function has been questioned. Objective: This study aimed to investigate whether HKA can be utilized to evaluate postoperative efficacy of TKA, exploring the correlation between postoperative outcomes of TKA and angles of multiple axial alignments of the lower extremities. Methods: In this retrospective study, clinical data of patients that underwent primary TKA, between April 2013 and April 2017, were analyzed. Femoral posterior condylar offset (FCO) and angles of axial alignments of the lower extremities, including HKA, femoral interior angle (FIA), distal femoral valgus resection (DFVR), coronal tibiofemoral angle (CTA), sagittal tibial angle (STA), sagittal femoral angle (SFA), coronal femoral angle (CFA), mechanical lateral distal femoral angle (mLDFA), mechanical medial proximal tibial angle (mMPTA), and ankle angle (AA), were measured via postoperative X-ray images. Each of these factors or angles was subjected to linear regression analysis, along with postoperative knee function, which was assessed by Knee Society Scores (KSS), Oxford Knee Scores (OKS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. Standardized regression coefficients were compared. Results: Seventy patients, with an average age of 66.03 ± 9.80 years, that underwent 101 primary TKAs were included. The HKA angle was 0° ± 3° in 58 cases (57.43%) and 0° ± 1° in 17 cases (16.83%), respectively. Correlation analysis demonstrated that FIA, DFVR, HKA, and mLDFA were significantly correlated with postoperative function (all P < 0.05). Absolute values of correlation coefficients, after normalization, were statistically compared, finding that the sequence of correlation coefficients was mLDFA (0.344) > DFVR (0.334) > FIA (0.292) > HKA (0.288). Conclusion: HKA can be utilized for evaluation of the surgical quality of TKA. Among angles of other axial alignments of the lower limbs, FIA, DFVR and mLDFA have been proven to be associated with postoperative function. They can be used to predict postoperative efficacy. Moreover, mLDFA is the most intimately correlated with postoperative function. It is a reliable parameter in predicting postoperative outcomes. Intensive attention should be paid to the angle of femoral implants in the coronal plane.

Keywords: Total knee arthroplasty, alignment, surgical outcomes, lower limb axial alignment

Introduction

Total knee arthroplasty (TKA) has been commonly applied to treat knee joint diseases. However, 15-30% of patients are still dissatisfied with clinical outcomes after TKA [1-3]. After TKA, some patients present with different persistent complications, such as pain, ankylosis, and joint clicking [3, 4].

Surgical efficacy of TKA is affected by various factors, including axial alignment of the lower extremities, rotation angle of the implant, soft tissue balance status, and patellofemoral tracking [5-8]. Previous studies have demonstrated that an appropriate angle of implantation plays a pivotal role in the survival rate of implants, as well as short-term, mid-term, and long-term clinical efficacy [6, 9-11].

The hip-knee-ankle angle (HKA) of lower extremities within 3° and tibial and femoral implants perpendicular to their respective anatomical axes on the sagittal plane have been
considered determining factors affecting the success of surgery [12]. Mechanically aligned TKA yields a high survival rate of implants [13-15]. However, numerous recent investigations have questioned the effects of HKA on restoration of affected limb function after TKA [6, 16, 17]. Parratte et al. performed a subsequent follow-up in 398 patients with valgus deformity prior to TKA, finding that when HKA was 0° ± 3°, it did not exert any significant effects on 15-year survival rates of implants [18]. Van Lommel et al. retrospectively analyzed the clinical data of 132 patients with preoperative varus alignment, demonstrating that function in patients with mild varus (3° and 6°) was better restored, compared with that in counterparts with a neutral angle (0°). No statistical significances were observed in survival rates of implants between the two groups [19]. In addition, different from the concept of “mechanically aligned TKA”, the current concept of “kinematically aligned TKA” aims to make the angle between the joint line and femoral and tibial implants similar to that in the collateral knee joint [20]. Based on outcomes of mid-term follow-ups, currently reported clinical outcomes of “kinematically aligned TKA” are better than those of “mechanically aligned TKA” [20-23]. To the best of our knowledge, none of these studies have statistically compared the effects of HKA and angles of other axial alignments of the lower extremities on surgical outcomes.

Therefore, the objectives of this study were as follows: 1) To determine whether HKA can be utilized to evaluate postoperative efficacy of TKA; 2) To evaluate and compare the correlation between postoperative efficacy of TKA and angles of multiple axial alignments of the lower limbs. This study attempted to identify the angle of axial alignment that is the most significantly correlated with postoperative outcomes. Thus, it aimed to provide guidance for implant fixation and prediction of surgical effects.

Materials and methods

This study was performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave provided informed consent prior to inclusion in the study.

Materials

This was a single-center retrospective study. Patients that underwent primary TKA, between April 2013 and April 2017, were included in this investigation. All cases were categorized into the same treatment group.

Inclusion criteria and exclusion criteria

Inclusion criteria were as follows: Patients aged > 18 years; Patients that had osteoarthritis or rheumatoid arthritis; Patients with complete imaging data of the frontal and lateral knee X-rays and full-length radiographs. Exclusion criteria were as follows: Patients with a medical history of ipsilateral femoral lesions, knee joint fracture, or neuromuscular disease that affected knee joint function; Patients that lacked preoperative or postoperative imaging data of the knee joint; Patients implanted with a highly constrained prosthesis. A flow diagram of the study design is shown in Figure 1.

Clinical data

Angles of all axial alignments of the lower extremities were quantitatively measured by the same researcher. Angles of 10 axial alignments of the lower extremities, including HKA, femoral interior angle (FIA), distal femoral valgus resection (DFVR), coronal tibiofemoral angle (CTA), sagittal tibial angle (STA), sagittal femoral angle (SFA), coronal femoral angle (CFA), mechanical lateral distal femoral angle

Figure 1. Flow chart of the study design.
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(mLDFA), mechanical medial proximal tibial angle (mMPTA), and ankle angle (AA), were measured via postoperative X-ray images.

Measurement methods are defined as follows. Anatomical axis of the femur (FAA) is defined as the line between the midpoint of the connecting line between the cortical inner membrane at the femoral isthmus and the midpoint of the connecting line between the cortical inner membrane, 10 cm proximal to the knee joint line of the femur. Anatomical axis of the tibia (TAA) is defined as the connecting line between the midpoint of the cortical inner membrane at 1/2 of the tibia and the tibial midpoint 10 cm from the joint line. Mechanical axis of the femur (FMA) refers to a straight line connecting the center of the hip joint and the center of the knee joint. Mechanical axis of the tibia (TMA) is defined as the connecting line between the center of the knee joint and the center of the ankle joint. CTA refers to the angle between FAA and TAA. HKA is defined as the angle between FAA and TMA. FIA represents the angle between the connecting line of the center of the femoral head and the center of the ankle joint and FAA. DFVR refers to the angle between TMA and proximal tibial joint line. mLDFA refers to the lateral angle between FAA and distal femoral joint line. mMPTA is defined as the medial angle between TMA and proximal tibial joint line. AA represents the medial angle between TAA and ankle joint line. STA refers to the angle between TAA and the joint line on lateral images. SFA is defined as the angle between FAA and the longitudinal axis of the femoral implant on lateral images [24]. CFA represents the medial angle between FAA and distal femoral joint line [24]. Femoral posterior condylar offset (FCO) was evaluated on true lateral radiographs by measuring the maximal thickness of the posterior condyle, projected posteriorly to the tangent of the posterior cortex of the femoral shaft [25] (Figures 2 and 3).

Figure 2. Radiological measurements. FIA, femoral interior angle; DFVR, distal femoral valgus resection; HKA, hip-knee-ankle angle; CTA, coronal tibiofemoral angle; CFA, coronal femoral angle; mLDFA, mechanical lateral distal femoral angle; mMPTA, mechanical medial proximal tibial angle; and AA, ankle angle.
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Other data, including age, gender, follow-up time, and type of deformity (varus and valgus), were also recorded. Postoperative function of the knee was assessed by Knee Society Scores (KSS), Oxford Knee Scores (OKS), and WOMAC scores. Regression equations were obtained when they reached statistical significance and normal distribution. Standardized regression coefficients were recorded and subsequently compared after normalization. Analysis of the correlation between other data and postoperative clinical outcome was done. Pearson correlation analysis was used for continuous variables and Kendall correlation analysis was used for unordered categorical variables. \( P \) values less than 0.05 indicate statistical significance.

**Results**

Seventy patients that underwent 101 TKAs for the first time, between April 2013 and April 2017, were included in this study. Thirty-one patients underwent bilateral TKA and 39 patients underwent unilateral TKA. Of these, 62 patients (90 TKAs) were female and 8 patients (11 TKAs) were male, with an average age of 66.03 ± 9.80 years. The mean follow-up time was 12.77 ± 6.68 months (range: 6-46 months). HKA was 0° ± 3° in 58 cases (57.43%) and 0° ± 1° in 17 cases (16.83%) (Table 1). No severe postoperative complications requiring revision TKA were observed during subsequent follow-ups. Measurement results of the angles of 10 axial alignments of the lower extremities and clinical outcomes are illustrated in Table 2 and Figure 4.

HKA and KSS scores, after TKA, were subjected to linear regression analysis. \( P = 0.004 < 0.05 \) indicates statistical significance. Thus, results suggest that HKA was correlated with KSS scores.

One-dimensional linear regression analyses were performed between the angles of lower

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**Table 1. General data**

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>11 (11)</td>
<td>Age 66.03 ± 9.80</td>
</tr>
<tr>
<td>Female</td>
<td>90 (89)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HKA</td>
<td>0° ± 3°</td>
<td>58 (57) Follow-up 12.77 ± 6.68</td>
</tr>
<tr>
<td></td>
<td>0° ± 1°</td>
<td>17 (17) time</td>
</tr>
</tbody>
</table>

HKA, hip-knee-ankle angle; N, number of cases. No significant correlation was observed between general data, including gender, age, and follow-up time, as well as postoperative function of the knee joint.

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**Figure 3.** A lateral radiograph of the right knee shows the measurement of the sagittal alignment of the femoral and tibial components \( x = \) SFA, sagittal femoral angle, \( y = \) STA, sagittal tibial angle, and \( z = \) FCO, femoral posterior condylar offset) [24].

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**Statistical analysis**

SPSS 23.0 statistical software was used for statistical analysis (SPSS Inc., Chicago, IL, USA). One-dimensional linear regression analyses were performed. Independent variables included FCO, angles of axial alignments of the lower limbs, and other data. Dependent variables were clinical function scores, including KSS, OKS, and WOMAC scores. Regression equations were obtained when they reached statistical significance and normal distribution. Standardized regression coefficients were recorded and subsequently compared after normalization. Analysis of the correlation between other data and postoperative clinical outcome was done. Pearson correlation analysis was used for continuous variables and Kendall correlation analysis was used for unordered categorical variables. \( P \) values less than 0.05 indicate statistical significance.
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Table 2. Results of the angles of 10 axial alignments of the lower extremities and clinical outcomes

<table>
<thead>
<tr>
<th>FIA</th>
<th>DFVR</th>
<th>HKA</th>
<th>CTA</th>
<th>STA</th>
<th>SFA</th>
<th>CFA</th>
<th>mLDFA</th>
<th>mMPTA</th>
<th>AA</th>
<th>KSS</th>
<th>OKS</th>
<th>WOMAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td>Mean</td>
<td>1.84</td>
<td>5.86</td>
<td>3.26</td>
<td>3.87</td>
<td>86.03</td>
<td>0.63</td>
<td>95.30</td>
<td>91.34</td>
<td>89.41</td>
<td>89.45</td>
<td>179.22</td>
<td>17.09</td>
</tr>
<tr>
<td>Median</td>
<td>1.57</td>
<td>5.61</td>
<td>2.76</td>
<td>3.61</td>
<td>87.83</td>
<td>0.00</td>
<td>95.07</td>
<td>91.27</td>
<td>89.23</td>
<td>90.00</td>
<td>179.00</td>
<td>17.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.03</td>
<td>1.74</td>
<td>0.00</td>
<td>0.01</td>
<td>0.10</td>
<td>-9.41</td>
<td>88.92</td>
<td>84.70</td>
<td>82.70</td>
<td>79.33</td>
<td>165.00</td>
<td>13.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>5.95</td>
<td>13.13</td>
<td>10.51</td>
<td>10.51</td>
<td>95.73</td>
<td>8.80</td>
<td>102.87</td>
<td>102.15</td>
<td>96.48</td>
<td>99.30</td>
<td>193.00</td>
<td>24.00</td>
</tr>
</tbody>
</table>

N, number of cases; FIA, femoral interior angle; DFVR, distal femoral valgus resection; HKA, hip-knee-ankle angle; CTA, coronal tibiofemoral angle; STA, sagittal tibial angle; SFA, sagittal femoral angle; CFA, coronal femoral angle; mLDFA, mechanical lateral distal femoral angle; mMPTA, mechanical medial proximal tibial angle; AA, ankle angle; KSS, knee society score; OKS, Oxford knee score; and WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 4. Measurement results of HKA and mL DFA. HKA, hip-knee-ankle angle; mL DFA, mechanical lateral distal femoral angle.

Table 3. Significance test for correlation between the angles of axial alignment of the lower extremities and KSS, OKS, and WOMAC

<table>
<thead>
<tr>
<th>P value</th>
<th>FIA</th>
<th>DFVR</th>
<th>HKA</th>
<th>CTA</th>
<th>STA</th>
<th>SFA</th>
<th>CFA</th>
<th>mLDFA</th>
<th>mMPTA</th>
<th>AA</th>
<th>KSS</th>
<th>OKS</th>
<th>WOMAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>KSS</td>
<td>0.003</td>
<td>0.001</td>
<td>0.004</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>&lt; 0.001</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>OKS</td>
<td>n.s.</td>
<td>0.019</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0.043</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0.021</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s., no statistical significance; FIA, femoral interior angle; DFVR, distal femoral valgus resection; HKA, hip-knee-ankle angle; CTA, coronal tibiofemoral angle; STA, sagittal tibial angle; SFA, sagittal femoral angle; CFA, coronal femoral angle; mL DFA, mechanical lateral distal femoral angle; mMPTA, mechanical medial proximal tibial angle; and AA, ankle angle.

When KSS scores were utilized to evaluate postoperative function, linear regression analysis revealed statistical significance between the angles of multiple axial alignments of the lower extremities, including FIA, DFVR, HKA, and mL DFA, and postoperative function (all P < 0.05). No significant correlation was observed between the angles of other axial alignments of the lower extremities, including CTA, STA, SFA, mMPTA, AA, and CFA, as well as postoperative function of the knee joint.

When KSS scores were utilized, according to the absolute values of correlation coefficients after normalization, the sequence of correlation coefficients was mL DFA (0.344) > DFVR (0.334) > FIA (0.292) > HKA (0.288) (all P < 0.05) (Figure 5).

When OKS and WOMAC scores were used, DFVR and mL DFA were significantly correlated with OKS scores. However, only mL DFA was significantly correlated with WOMAC scores (P < 0.05). No statistical significance was detected.
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between the angles of other axial alignments and postoperative function scores.

Regarding other data, follow-up times were significantly related to KSS and there was a statistically significant correlation between age and postoperative function, including KSS, OKS, and WOMAC. Moreover, differences in individual FCO values and gender did not correlate with postoperative function scores. The absolute value of Kendall correlation coefficient between the type of deformity and OKS was 0.189 < 0.2, indicating that the correlation was very weak.

Discussion

TKA is an efficacious treatment of knee joint diseases. However, the optimal angle of axial alignment after TKA remains controversial. Previous investigations have demonstrated that neutral HKA and femoral and tibial components perpendicular to their respective mechanical axes yield optimal clinical outcomes and high survival rate of implants [1, 26]. However, a short knee X-ray with a relatively constrained range was mainly employed in previous studies, significantly differing from full-length radiographs [27]. With an unceasing increase in the number of TKA cases and a large proportion of patients dissatisfied with postoperative effects, more and more surgeons have realized that the angle of implants during TKA should be investigated further [28]. Traditionally, the criterion if HKA is with 0° ± 3° has been utilized to evaluate surgical quality. Parratte et al. suggested that when HKA is within 0° ± 3°, it does not exert any significant effects on 15-year survival rates of implants. This is inconsistent with traditional ideas [18]. Bellemans et al. proposed the concept of “constitutional varus” in 2012. They considered that an important fraction of the normal population has a natural alignment at the end of growth of 3° varus or more [29]. Howell et al. demonstrated that kinematically aligned TKA yields higher clinical efficacy, compared with mechanically aligned TKA [30]. However, Ishikawa et al. found that patellofemoral and tibiofemoral contact stresses were increased more in kinematically aligned TKA, compared with mechanically aligned TKA. After kinematically aligned TKA procedures, long-term survival of implants might be shortened [31]. According to the proposed concept of “constitutional varus”, a slight under-correction following TKA can result in superior clinical outcomes in varus knees [19]. However, the concept of “kinematically aligned TKA” considered that it is of the utmost priority to restore the axial alignments of affected lower limbs in place of the collateral alignment axis [23]. The current study demonstrates that HKA is correlated with surgical outcomes of TKA. The objective of subsequent investigations should be to identify the optimal range of HKA angles following TKA.

The current study also found that correlation between mLDFA and postoperative restoration of knee junction was strongest among all angles of lower limb axial alignments. This finding probably overturns the viewpoint that HKA...
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plays the most pivotal role among angles of all axial alignments of the lower extremities. At present, the effects of HKA on surgical effects of TKA are widely debated. The conclusion derived from this study possibly guides the research direction towards a correlation between mL DFA and postoperative function after TKA. Similar to HKA, the optimal mL DFA remains to be elucidated by subsequent investigations. Carroll et al. demonstrated that TKA with mL DFA of 87° ± 3° yields superior postoperative outcomes, compared with mL DFA of 90° ± 3°, according to a cohort of 110 patients. However, they failed to statistically compare surgical outcomes among more ranges of mL DFA. Thus, insufficient evidence was obtained to determine whether the mL DFA of 87° ± 3° was the optimal range [32].

Maximal correlation was found between mL DFA and postoperative function in the current study, indicating the significance of the angle of femoral implants in the coronal plane intraoperatively. mL DFA is subject to the influence of multiple intraoperative procedures, such as the angle of intramedullary rod positioning during femoral implantation and the rotating angle between the implant and resected femoral surface. Maderbacher et al. divided 40 knees into six groups, including DFVR measured by the surgeon group, DFVR calculated by the computer software group, and 5°, 6°, 7°, and 8° valgus pre-set groups. They found that mL DFA of 90° could be easily achieved with a valgus pre-set of 7° [33]. However, the sample size of that investigation was only 40. As mentioned above, the optimal range of mL DFA is still unclear. In other words, it is uncertain whether the mL DFA of 90° is the optimal target angle. Consequently, the best valgus pre-set needs to be investigated further.

Moreover, previous studies have demonstrated that FCO and baseline characteristics of patients, such as body mass index (BMI) and gender, are not correlated with surgical outcomes of knee joint arthroplasty. In this study, there was no significant correlation between FCO and postoperative outcome, which is in accord with findings in previous studies [34-36]. This study focused on the relationship between angles and post-operative outcomes, so there was not much exploration on baseline characteristics of patients, such as the impact of BMI on post-operative clinical outcomes.

Several limitations of this study should be acknowledged. First, this retrospective study determined the correlation between angles of different postoperative axial alignments and clinical efficacy, but failed to prove the cause-effect relationship. Second, the number of patients receiving full-length X-rays of bilateral lower extremities was limited, restricting the sample size of this experiment. To the best of our knowledge, correlation between so many angles of multiple axial alignments of the lower extremities and surgical effects has never been investigated before. Third, similar to other studies that measured angles of axial alignment of the lower extremities on imaging radiographs, rotation of the lower extremity might have affected measurement results during image acquisition [37, 38]. In this study, unified standards were adopted to obtain each image to minimize image variability. It was considered that a full-length radiograph of bilateral lower extremities in the standing position was the most accurate approach for measuring angles of axial alignment of the lower extremity. Fourth, the maximal duration of follow-up was only 4 years. Therefore, this study failed to evaluate the effects of angles of different axial alignments on survival rates of implants. The primary objective of this study was to assess the impact of the angle of axial alignment on postoperative function. In previous studies, the effects of the angles of partial axial alignments of the lower extremities on survival rates of implants have been investigated [38, 39]. However, a comprehensive comparison of the effects of the angles of multiple axial alignments on survival rates of implants has not been explored. Fifth, the current study only assessed correlation between the angle of axial alignment of the lower extremities and postoperative function. The optimal range of the angle of axial alignment of the lower extremities, such as the optimal range of mL DFA, will be the objective of subsequent research. Sixth, OKS and WOMAC scores revealed no statistical significance in the correlation between FIA, HKA, and postoperative function. It was considered that the main reason for this occurrence was that OKS and WOMAC scales are more subjective, compared with KSS, due to more open-ended questions. In addition, the sample size of this study was only 101 knees, leading to the occurrence of type II errors.
Methods for improving postoperative function of TKA have captured widespread attention of surgeons. Results of this study revealed that mLDFA, DFVR, FIA, and HKA were correlated with surgical outcomes of TKA. Kim et al. investigated 3,048 cases of TKA, finding that the survival rate of implants was relatively high when CTA was within 3°-7.5° valgus, mLDFA was within 2°-8.0° valgus, SFA was within 0°-3°, mMPTA was 90°, and STA was within 0°-7° [24]. However, they failed to classify and compare the effects of more ranges of angles. They did not evaluate postoperative function. Therefore, to the best of our knowledge, the optimal range of angles of axial alignments of the lower extremities has yet to be investigated.

In conclusion, angles of different axial alignments of the lower extremities should be considered and balanced when performing TKA. According to present findings, surgeons should attach importance to the four above-mentioned angles of axial alignments of the lower extremities. However, the four above-mentioned angles of axial alignments of the lower extremities are merely one of the factors affecting clinical efficacy. Other parameters, including ligament balance and variables that can enhance surgical outcomes of TKA, should also be considered.

Conclusion

HKA can be utilized for evaluation of surgical outcomes of TKA. Among angles of other axial alignments of the lower limbs, FIA, DFVR and mLDFA have been proven to be associated with postoperative function. They can be used to assess postoperative efficacy. mLDFA is the most intimately correlated with postoperative function. Intensive attention should be paid to the angle of femoral implants in the coronal plane. Moreover, mLDFA is a relatively reliable parameter for evaluation and prediction of postoperative outcomes of TKA.

Acknowledgements

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Disclosure of conflict of interest

None.
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[34] Baker P, Petheram T, Jameson S, Reed M, Gregg P and Deehan D. The association be-


