Population-based effect of total knee arthroplasty alignment on simulated tibial bone remodeling

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\textbf{A B S T R A C T}

Periprosthetic bone loss is an important factor in tibial implant failure mechanisms in total knee arthroplasty (TKA). The purpose of this study was to determine the effect of postoperative knee alignment and population variation on tibial bone remodeling, to assess long-term stability of a knee replacement. Strain-adaptive finite element (FE) remodeling simulations were conducted following kinematic and mechanical alignment of a cemented fixed-bearing implant after TKA; kinematic TKA alignment was assumed to be more consistent with the preoperative varus alignment, while mechanical alignment was defined according to the neutral mechanical axes. To account for the effect of tibial variation on the outcome, bone remodeling was considered over a population of 47 subjects. Bone mineral density (BMD) was analyzed over three regions of interest (ROIs); medial, lateral and distal. The two proximal ROIs showed an average decrease in BMD in both alignments after two years. Greater overall proximal bone loss was found in the mechanical postoperative knees in comparison with kinematically aligned implants. Bone resorption was also concentrated more medially in mechanical alignment: increased medial ROI bone loss was found in every subject compared to kinematic alignment; while in the lateral ROI, higher regional two-year BMD was found in 39 of the 47 cases (82.9%) following mechanical alignment. Two distinct remodeling pathways were identified over both alignments, based on the variance in density change over the population; displaying predominant bone apposition either around the distal tip of the keel or at the lateral cortex. This study demonstrates that correction of native varus alignment to neutral mechanical alignment leads to an increase in medial bone resorption. Large variation between specimens illustrates the benefit of population-based FE analyses over single model studies.

1. Introduction

Total knee arthroplasty (TKA) is one of the most successful surgical interventions, but despite reduced revision rates, the number of primary TKA failures is increasing as a result of the aging population and the acceptance of TKA in younger patients (Sharkey et al., 2013). Two common causes of long-term implant failure are aseptic loosening and periprosthetic fracture (Sharkey et al., 2013; Schroer et al., 2013), which are linked to stress shielding-related osteolysis as observed in longitudinal bone density studies (Jaroma et al., 2016; Petersen et al., 1995; Martin et al., 2017). Tibial varus collapse, a mode of periprosthetic fractures, has been associated with preoperative varus alignment, subsequent valgus postoperative alignment and severe obese patients with small tibial components (Fehring et al., 2017; Martin et al., 2018).

Medial bone loss has been observed in the vast majority of failed cases (Martin et al., 2018), and increased medial bone resorption has been found to be related to the mechanical correction of anatomical varus knees towards neutral or valgus alignment following TKA (Jaroma et al., 2016; Martin et al., 2017; Yoon et al., 2018), indicating extensive bone remodeling could increase the risk of catastrophic varus collapse. These clinical findings are in line with Wolff’s law and the strain-adaptive bone remodeling theories (Huiskes et al., 1987), since all indicated factors are also related to greater stress reduction in the medial proximal tibia.

Implant alignment is considered one of the important factors in successful TKA outcome, since it largely determines functional outcome and long-term survivorship (Berend et al., 2004). Traditionally, implants have been placed according to mechanical alignment, in which the knee was aligned in a neutral biomechanical way despite any preoperative alignment being in a varus position.

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deformities. However, this technique has been challenged in recent years by the kinematic alignment (Rivièr et al., 2017; Cherian et al., 2014), which would result in alignment more consistent to the preoperative knee.

The effect of both alignment techniques on postoperative bone remodeling was simulated in this study over a population of tibiae, in order to identify factors in extensive periprosthetic bone resorption and related risk of potential implant failure. Since large variability can be found between tibiae in terms of size, geometry and bone density, the population-based approach enabled us to relate tibial characteristics to remodeling outcome, and to identify different remodeling pathways. It was hypothesized that mechanically aligned postoperative knees would lead to increased medial bone loss over kinematically aligned implants in each of the tibiae following preoperative varus loading, irrespective of geometry, density or implant size.

2. Materials and methods

FE models of tibiae from 47 different subjects were automatically created using a custom made workflow, consisting of the following consecutive steps: (1) tibial bone segmentation, (2) implant placement, (3) material property assignment, and (4) application of boundary and loading conditions. Each subject was assumed to have a constitutional varus alignment preoperatively. Two different postoperative alignments were modeled following two alignment philosophies: consistent kinematic alignment and neutral mechanical alignment.

In the initial step in the model setup, the bones in lower limb CT scans of completely anonymized cardiovascular patients, diagnosed with Fontaine stage III/IV peripheral artery disease, were automatically segmented based on boundary enhancement filtering and graph cut optimization (Krcah et al., 2011). Use of the anonymized CT data was approved by an internal medical ethics review committee. The tibiae were identified by bone volume and relative orientation, and surface meshes were created based on the binary voxel masks (Fang and Boas, 2009) and smoothed using curvature flow (Desbrun et al., 1999).

The resulting meshes were then aligned according to the mechanical axis (Grood and Suntay, 1983), with the largest inertial axis being defined as the longitudinal axis and neutral rotational alignment referencing the medial third of the tibial tubercle (Lützner et al., 2010).

Implant alignment, resection planning and tray size determination were performed relative to this reference frame. For each tibia, a size-matched cemented cruciate-retaining, fixed-bearing, cobalt-chromium Attune implant (DePuy Synthes, Warsaw, IN, USA) was placed according to the two alignment strategies. This Attune knee system was used since it is a modern device with successful results following mechanical alignment in terms of tibial coverage (Clary et al., 2014), and clinical outcome (Porter et al., 2019; Heckmann et al., 2019), therefore providing a useful clinical benchmark. A preoperative hip-knee-ankle (HKA) angle of 3° varus between the femoral and tibial mechanical axes was assumed for all subjects, in line with constitutional varus knee alignment found over cohorts of asymptomatic subjects (Bellemans et al., 2012; Moreland et al., 1987) and arthritic patients (Vic et al., 2014). The kinematic alignment technique was aimed at reconstructing the patient-specific HKA alignment and joint line orientation, restricted by a predefined safe range to undercorrect patients with severe knee deformities. The resulting HKA angle was limited between 3° varus and 3° valgus; independent femoral and tibial cuts were made within ±5° of their respective mechanical axes in the coronal plane following a published technique based on the accuracy of computer assisted surgery (Almawiai et al., 2017; Hunt et al., 2016), or were aimed to be within ±3° to allow for a surgical error of 2° with manual instruments (Barrett et al., 2014). The preoperative 3° varus HKA angle was retained in the used kinematic alignment. The tibial component was placed in a 5° varus angle relative to the tibial mechanical axis to account for the additional 2° tibial varus offset in recreating the anatomical joint line (Hungerford and Krackow, 1985), which is not affected by the overall constitutional varus angle (Vic et al., 2014). The femoral rotation was 0° relative to the posterior condyles. Mechanical postoperative alignment was achieved by placing the implant according to the mechanical axes, resulting in 0° of postoperative HKA and tibial varus angles, regardless of constitutional deformity and anatomical joint line orientations. We accounted for 3° external rotation of the femoral component relative to the posterior condyles in the mechanical loading conditions, which was adopted to compensate for flexion and extension gaps (Insall et al., 1985). A posterior tibial slope of 3° was defined in both alignments.

The resection level was defined 8 mm below the lowest point of the highest condyle for both alignments independently, and the corresponding size was set to be the largest size in which the tray could be placed on the resection surface with a maximum overhang below 2 mm, corresponding with a reported tibial coverage study (Clary et al., 2014). Bone coverage following to the established implant position was defined as the relative resection plateau surface area covered by the baseplate, and was computed to validate implant position against clinical and computational measure outcomes (Clary et al., 2014; Meier et al., 2018; Ishii et al., 2018).

A cement layer was generated based on a 0.75 mm offset over the entire bone-contact surface of the tibial component, and used as outline for resection of the tibia by applying a Boolean operation (HyperMesh, Altair Engineering, MI, USA). The tibiae were distally resected 150 mm beneath the proximal resection level. The proximal tibia was fixed distally in order to reduce computational cost in the final FE simulations. All parts in the assembly were (re)meshed using first order tetrahedral elements with a size of 2 mm and connected using fixed node contact, meaning the entire implant fixation interface is perfectly bonded to the bone by the cement layer.

Consistent pre- and postoperative tibial bone meshes were used by reconstructing the preoperative models out of the two resected proximal bone parts, to allow for element-wise evaluation of TKA-related strain differences. The difference in resected geometry required the use of separate preoperative models, despite the use of the kinematic alignment definition over all preoperative cases. This constitutional varus alignment was assumed over all intact tibiae, regardless of native subject-specific knee alignment, in order to consider the effect of structural tibial differences on consistent alignment change. Hence, in case of mechanical implant alignment, the preoperative models were rotated to the kinematic alignment, in order to apply preoperative loading conditions consistently with the kinematic models, as depicted in Fig. 1. There was no difference in initial strain between both preoperative models.

Bone material properties of the tibial meshes were assigned per element using corresponding CT intensities (Powell and Abel, 2015). The scan-specific linear function between Hounsfield units and BMD was determined using a recently published calibration method based on the intensities of air, fat and muscle tissue (Eggermont et al., 2019); linear elastic properties of the calibrated bone densities were subsequently assigned using reported modulus–density relationships of cortical and trabecular bone, respectively (Keller, 1994; Morgan et al., 2003). Elastic moduli used for the CoCr tray, the polyethylene (PE) insert and the bone cement were 210 GPa, 588 MPa, and 2551 MPa, respectively.

Implant- and alignment-specific knee loading during physiological activity cycles was simulated using inverse dynamics at University of Denver (Fitzpatrick and Rullkoetter, 2014), based on in vivo loading and kinematics (Kutzner et al., 2010). Tibiofemoral activity peak forces of guilt, step down (SD) and deep knee bend (DKB) load cycles (Table 1) were applied at the centers of pressure (COPs) of the lateral and medial femoral condyles on the insert contact surface (Fig. 2).

The instances of peak loading during the dynamic load cycles occurred at the same moment in time within kinematic and mechanical alignment for all three activities. In the preoperative models, the COPs of the kinematic alignment forces were connected to the closest nodes on the proximal tibial surface using springs; the number of connected nodes was determined as function of the total related contact area, and spring constants were
individually assigned based on distance and a compressive modulus of 9 GPa representing the intermediate articular cartilage (Peña et al., 2006).

The average strain energy density (SED) after application of the three peak loads was considered as measure for bone strains during daily living. Subsequent iterative bone density changes were simulated using strain adaptive remodeling, with the difference between local preoperative and postoperative SED per unit bone mass, $S_{\text{ref}}$ and $S$, respectively, considered as stimulus for density change in time $\frac{d\rho}{dt}$ (Huiskes et al., 1987). If the relative local difference was lower than 35%, the stimulus fell into the so-called ‘dead zone’ and no remodeling was assumed. Outside of the dead zone, the rate of local bone apposition or resorption was also dependent on its available free bone surface $a$, representing the porosity and specific surface and determined based on the corresponding bone density $\rho$ (Martin, 1984). Bone associated with greater free surface density $a$ was assumed to be more responsive to changes in SED, since remodeling activity takes place at these free surfaces.

$$\frac{d\rho}{dt} = \begin{cases} 0 & \text{if } |S/S_{\text{ref}} - 1| < 0.35 \\ a(\rho)\left(S - 1.35S_{\text{ref}}\right) & \text{if } S/S_{\text{ref}} - 1 \geq 0.35 \\ a(\rho)\left(S - 0.65S_{\text{ref}}\right) & \text{if } S/S_{\text{ref}} - 1 \leq -0.35 \end{cases}$$

**Equation 1.** Definition of the local bone remodeling rate $|d\rho/dt|$ following the strain adaptive theory (Huiskes et al., 1987), as incorporated in the iterative postoperative FE simulations.

Simulations were time-scaled using computer time units (CTU) defined relative to the maximum stimulus per iteration; each postoperative year was considered to correspond to 30 CTU. Used dead zone and time conversion values were established in a study by Tarala et al. (2011), in which simulated periprosthetic bone adaptations around a femoral hip implant were fitted to clinical data of a two-year clinical
follow-up study (Akhavan et al., 2006). Simulations incorporating the custom remodeling algorithms were conducted in MSC.MARC (MSC Software Corporation, Santa Ana, CA, USA).

Two-dimensional anteroposterior (AP) projections were made by mapping the element numbers of each FE model in a three-dimensional matrix with a voxel size of 0.25 cm$^3$ (Fang and Boas, 2009), and subsequently taking the sum of the associated bone mineral content (BMC) values in AP direction. This method allowed us to efficiently compute virtual projections over a large number of time points. Two-dimensional AP projections were used as they allowed for density analysis in line with clinical remodeling measurements performed in densitometry studies (Jaroma et al., 2016; Petersen et al., 1995; Martin et al., 2017), are generally less prone to tibial geometry variations than three-dimensional analyses, and the greatest differences in remodeling outcome were expected to be found in the coronal plane. Three different regions of interest (ROIs) in the proximal tibia were used to compare relative local BMD change over time between the 47 subjects and both alignments. The ROIs were defined relative to the position of the distal tip of the keel, as depicted in Fig. 3; bone anterior and posterior relative to the keel was included in the proximal ROIs to cover the entire proximal bone and reduce relative difference in regional bone volume between alignments; hence, this is different from an actual X-ray projection, in which the keel would obscure anteriorly and posteriorly located bone.

The Pearson linear correlation coefficient was used to test significance in the statistical relationship between remodeling outcome in the ROIs and various zero time point measures. Regional preoperative BMD, ROI bone volume, implant size and bone coverage were the factors considered in studying the effect on remodeling outcome over tibiae with various geometries and density distributions. Remodeling rate following the initial CTU (≈11.2 days) was considered short-term remodeling; long-term remodeling was captured in the relative bone loss after two years and remodeling rate at the two-year time point.

In order to identify different remodeling patterns over the population, the AP projections of the proximal tibiae were transformed to the average tibial frontal outline including implant position using an existing nonrigid registration algorithm based on affine registration and free-form deformations (Rueckert, 1999). Registered scans enabled use of pixel-wise comparison between all tibiae to determine local mean and variance BMD values, and therefore distinguish between divergent distributions. Different remodeling pathways were identified by local sites displaying increased variance in two-year BMD, since it is much easier to group different outcome distributions based on local, more distinct differences.

3. Results

Average bone coverage in the postoperative FE models of the 47 tibiae following automatic setup was 82.8% and 84.8% in kinematic and mechanical alignment, respectively. Median tray size over the population was implant size 6 (mediolateral (ML): 74 mm, AP: 49 mm), with used implants ranging from size 2 to size 10 (ML: 62–86 mm, AP: 41–56 mm); the implant following mechanical alignment was found to be one size greater than in kinematic alignment for the majority of subjects (53.2%). In two cases, the implant was planned to be two sizes greater in mechanical alignment, while the implant was one size smaller compared to the kinematic case in one instance. In the remaining tibiae (40.4%), a single implant size was used over both alignments.

At a simulated time point of two years after TKA, a general BMD decrease was observed in the two proximal ROIs, while structural bone formation was seen distally for kinematic alignment (Fig. 4). Paired comparisons between the two alignment strategies revealed more bone loss in the medial ROI (mean: −24.8% vs. −7.0%) and distal ROI (mean: 15.8% vs. −2.6%) for every mechanically aligned tibia as compared to their corresponding kinematically aligned model (Fig. 5). In 39 cases (82.9%), a reduction of bone loss in the lateral ROI was found for mechanical TKA alignment; total bone loss over the two proximal ROIs together was greater in mechanical alignment for 93.6% of the subjects (ranging from −15.3% to +3.3% BMD difference). For each ROI, the difference in relative density change between both alignments was normally distributed and significant for $p<0.05$.

Although intrasubject effect of alignment on postoperative remodeling was quite consistent over the population (Fig. 5), large variation between different tibiae was found in the extent of bone remodeling (Fig. 4), the course of density change over time (Fig. 6) and local redistribution patterns (Fig. 9).

Fig. 6 shows that on average, most of the density changes take place in the initial months after operation, with the remodeling rate gradually

Fig. 3. Schematic AP view of the ROI definitions, including relevant measures and the tibial outline in both alignments; the cumulative BMC in AP direction is considered for each pixel within the ROIs.

Fig. 4. Bar graph of regional mean relative BMD change in both alignments after two years, including related standard deviation.
increased variance in absolute bone change found over the population after two years. Increased variance relative to mean local density change was found in both alignments around the distal tip of the keel, and at the lateral cortex, as indicated on the variance heatmaps of Fig. 8. BMD changes at both sites were found to be significantly negatively correlated to each other, for both alignments separately, indicating that bone formation at one site is associated with bone resorption at the other site. Based on these findings, two separate remodeling pathways were defined: a pattern of bone densification around the distal tip of the keel (‘Distal keel site/pathway’), and a distribution with bone formation at the lateral cortex (‘Lateral cortex site/pathway’).

Density distributions associated with these two pathways were illustrated in Fig. 9 based on the top 10% of cases showing the highest bone increase at the indicated sites within mechanical alignment. Relative two-year bone changes at the two sites were significantly related to mean regional preoperative BMD, with denser bones being linked to distal keel formation and low BMD tibiae associated with lateral cortex formation. However, Pearson coefficients were found to be lower than those for the density changes over the entire ROIs, as reported in Table 2.

Table 2

| Outcome measure | Alignment | ROI | Pearson correlation coefficient ρ |
|-----------------|-----------|-----|---------------------------------|
| Initial remodeling rate (d[%]/dt) | Kinematic | Medial | 0.642* |
|                  | Kinematic | Lateral | 0.457* |
|                  | Mechanical | Medial | 0.786* |
|                  | Mechanical | Lateral | 0.308* |
|                  | Distal | Medial | 0.289* |
|                  | Distal | Lateral | 0.520* |
| Two-year remodeling rate (d [%]/dt) | Kinematic | Medial | -0.757* |
|                  | Kinematic | Lateral | -0.807* |
|                  | Mechanical | Medial | -0.875* |
|                  | Mechanical | Lateral | -0.843* |
|                  | Distal | Medial | 0.697* |
|                  | Distal | Lateral | 0.669* |
| Two-year bone change (%) | Kinematic | Medial | -0.576* |
|                  | Kinematic | Lateral | -0.523* |
|                  | Mechanical | Medial | -0.378* |
|                  | Distal | Medial | 0.714* |

Mean initial BMD (g/cm³)

| Outcome measure | Alignment | ROI |
|-----------------|-----------|-----|
| Mean initial BMD (g/cm³) | Medial | 0.637* |
|                  | Lateral | 0.478* |
|                  | Distal | 0.530* |

Fig. 5. Box-whisker plot of intrasubject remodeling difference over the ROIs, indicating median, 25th and 75th percentiles and outliers. Intrasubject difference is defined as the difference in relative BMD change (%) between mechanical and kinematic outcome of the same tibia. Negative values indicate greater intrasubject bone loss following mechanical alignment compared to kinematic alignment.

Fig. 6. Course of relative BMD change over time for both alignments in each ROI, indicating the course of mean values, the range and the cases with extreme rates at the initial and two-year time points.
4. Discussion

In this study, the effect of postoperative alignment and kinematic variation on bone remodeling was investigated in strain-adaptive FE simulations of a population of tibiae. The current results demonstrate that correction of native varus alignment to neutral mechanical alignment increases the long-term bone loss in the medial ROI in each of the 47 subjects, relative to more consistent kinematic alignment outcome. This finding is in line with our hypothesis that mechanical correction would lead to greater medial resorption, and with clinically reported long-term outcomes (Jaroma et al., 2016; Petersen et al., 1995), which found significantly more bone loss within the tibial condyle which had been unloaded following knee alignment change due to TKA, over the entire population. The shift in force distribution from the medial to the lateral condyle in mechanical alignment relative to kinematic loading, as shown by the implant-specific load cases (Table 1), was considered the main reason behind this finding. In line with this finding, more bone was generally preserved in the lateral ROI following mechanical alignment due to increased lateral loading, although this effect was not as extensive and was not found in every subject after two years. Over the total volume of both of the proximal ROIs, more bone loss was observed following mechanical alignment in almost all cases, suggesting implant placement according to constitutional varus alignment is beneficial in terms of long-term preservation of bone density in the proximal tibia. Within the distal ROI, additional bone loss was structurally encountered in mechanical alignment over kinematic alignment.

Although kinematically aligned TKA was found to be superior in terms of proximal tibial bone preservation, implant loading following kinematic alignment showed increased peak loads and less evenly distributed compressive forces over the mechanical load cases in the instances of maximum loading (Table 1). This could potentially lead to increased wear of the PE insert and reduced implant fixation, which has also been used by some authors to argue as to why mechanical alignment would be beneficial (Insall et al., 1985). On the other hand, significant advances have been made in recent years to reduce incidences of PE wear as the major cause of TKA failure: while PE wear was the main cause of primary failure in patients in 2002 (25%), it only accounted for 4.3% of the revision procedures performed in 2012 (Sharkey et al., 2013), despite the increasing usage of the kinematic alignment technique. Similar early revision rates have been found clinically comparing both alignments, while quicker recovery, better functional outcomes and lower rates of residual pain have been reported following kinematic alignment (Riviére et al., 2017).

In both alignment philosophies, initial tibial density values were found to be related to the course of bone remodeling over time; high initial bone resorption rates were typically found in tibiae with low BMD, while high density bones showed prolonged and increased bone loss after two years. This finding indicates that initial strain difference, which drives the initial bone remodeling rate and is commonly used to assess stress shielding (Au et al., 2007; Zhang et al., 2016), may not be a reliable measure for long-term bone remodeling. Bone remodeling simulations were chosen to cover a period of two years, as a compromise between simulated postoperative time, and the associated computational time required. Although an imaging study based on single photon emission CT uptake suggested implant-induced remodeling to only take place within the first two years after TKA (Soininvaara et al., 2008), some dual-energy X-ray absorptiometry (DEXA) studies observed
ongoing bone loss or restorative bone formation beyond two years (Jaroma et al., 2016; Petersen et al., 1995; Saari et al., 2007). Within our study, we found the average regional BMD over the population to remain almost stable after two years (Fig. 6), but progressive remodeling after this period was still encountered in individual cases, with regional bone loss of up to a rate of ~7% per year in higher density bones (Fig. 7). Although simulated bone remodeling was still ongoing after two years, a predictable slow and steady decline in absolute rate was already seen after the first year in all cases. This was in line with reported clinical results that most rapid bone changes occurred in the initial year after TKA (Jaroma et al., 2016; Soininvaara et al., 2008; Saari et al., 2007). Therefore, we considered the rate at the two-year time point a suitable measure for extended remodeling beyond this point, even though the average time from primary TKA to revision due to medial tibial collapse was reported to be seven years (Fehring et al., 2017; Martin et al., 2018).

A large variation in remodeling results was found over the simulated population, even though all tibiae were loaded following the same configurations. Most of the variation was likely due to the vast differences encountered in initial BMD values and preoperative density distributions over the population. Although subject information was not available for the used anonymized data set, it is likely that initial differences in overall densities were caused to a large extent by supposed variation in patient factors like age, sex, BW and activity levels, while differences in density distributions were largely subject to variation in patient-specific native knee alignments. Several studies in osteoarthritis (OA) patients have reported greater relative medial densification of the proximal tibia related to varus alignment (Hulet et al., 2002; Thorp et al., 2006; Li and Nilsson, 2000a). Patient-specific preoperative alignment was not considered in the current study since no weight-bearing clinical scans were available to determine the native joint alignment. In addition, alignment-specific loading data was only available for the two studied alignment definitions, while patient-specific preoperative alignment would require individual loading configurations. Mild varus preoperative alignment was therefore assumed for all subjects, to be able to study the effects of a consistent and frequent mechanical alignment correction following TKA, since constitutional varus deformity is frequently found in asymptomatic subjects and arthritis patients (Bellemans et al., 2012; Moreland et al., 1987; Victor et al., 2014). Current FE models were created from a data set of cardiovascular patients, which may be different from an actual TKA patient population in terms of bone density (Stewart and Black, 2000; Karvonen et al., 1998), and constitutional varus alignment (Victor et al., 2014). Not only an increased varus HKA angle was found in arthritis patients in comparison to asymptomatic controls (mean: 6.0° vs. 1.3° varus, respectively), also the tibial joint line orientation was affected in the arthritis group (Victor et al., 2014). These structural differences might change the strain distribution throughout the tibia, but also the remodeling response in local bone density affected by OA might differ from generic bone response. Initially denser bone as a result of OA could lead to increased relative bone resorption outcome, suggesting decreased implant stability, while it might still be beneficial in terms of absolute bone densities compared to an identical knee which was not affected by OA. The relative effect of OA classification on postoperative remodeling could be assessed using a clinical validation study. No data about the OA status of the used subjects was available. Based on the results, it could be assumed greater long-term medial bone resorption following mechanical alignment is generally associated with knees in increasingly varus native alignment, even without consideration of the larger related force shifts, due to the associated higher initial medial density values. Because of the large interindividual differences in tibial geometry and density distributions, it is very likely that structural effects found over the population would be reflected in simulations of a native varus TKA cohort.

Use of a statistical shape and intensity model (SSIM) could increase tibial variation within a population by covering most of the variance in geometry and bone density in a limited number of models. Principal modes of a SSIM could also enable a more controlled statistical analysis of geometrical features and distributions on remodeling outcome,
potentially providing more reproducible characteristics for specific remodeling patterns. This could potentially help guide clinical practice by being able to identify cases in which tibiae would display reduced proximal bone loss following deformity correction to mechanical alignment.

Although the use of AP projections allows for comparison with clinical DEXA scans, defined ROIs can not be used in single clinical scans since bone densities directly surrounding and in the line of sight of the keel and baseplate have to be excluded due to metallic reflection and scattering. This bone area was considered in the computational ROIs in order to cover the entire proximal tibia and to reduce effect of alignment on relative differences in regional bone volume. No single clinical standard on ROI definitions in tibial remodeling is available, which complicates direct comparison between outcomes of different clinical studies. To validate simulational outcome and incorporate tibia-specific material behaviour, patient-specific bone remodeling using CT scans of longitudinal periprosthetic tibial remodeling studies could be used in future studies. The sensitivity and responsiveness of current bone adaption were based on such a remodeling study around a femoral hip implant (Tarella et al., 2011), but bone response might differ in the proximal tibia. The modulus-densitiy relationship used for assigning the moduli to trabecular bone was tibia-specific, as this relation was found to deviate between anatomic sites (Morgan et al., 2003).

The relative tibial coverage of the trays in kinematic and mechanical alignment was found to be in line with numbers reported in clinical and computational studies (Clary et al., 2014; Meier et al., 2018; Ishii et al., 2018), indicating realistic postoperative models were achieved following the automatic workflow. However, multiple simplifications limit use of current FE simulations on a patient-specific level. Preoperative alignment was assumed to be in varus without considering native alignment of the individual tibiae, intact knee loading was based on the implant-specific loading profile, and perfectly consistent alignment replication was assumed in postoperative kinematic models. In both postoperative alignments, perfectly fixed contact between bone, cement and implant was defined. Only tibiofemoral peak loads of three repetitive activities were applied pre- and postoperatively, neglecting effects of entire loading cycles, soft tissue, variation between movement cycles and relative contributions of (other) physiological activities on proximal tibial stresses. Simplification in physiological loading was made mainly in order to limit total simulation time, by computing iterative strain distributions more efficiently. The applied peak loads were based on a body weight (BW) of 75 kg and not scaled to the subject’s BW. Furthermore, the load cases were not size-specific; loading profiles of tibial and femoral components in a single, medium size were used regardless of the size of the actual implant or tibia. This was done to ensure consistent intact loading between kinematic and mechanical model setups of the same subject, despite potential implant size differences between both postoperative alignments. Effects of load simplification, BW scaling and size-specific loading on strain-adaptive remodeling are limited since bone adaptations are driven by relative SED differences, which remain fairly constant as long as pre- and postoperative load configurations are consistent. Change in activity levels and in relative activity contribution after TKA has greater potential effect on long-term remodeling, as well does general age- and gender-related BMD decrease, especially in postmenopausal women. Apart from the fact that there was no information available about BW, age, gender and activity levels of used subjects, these factors were not considered in order to study only the implant-induced effects on bone adaptation.

5. Conclusions

Based on this computer simulation study we can conclude that the correction of constitutional varus alignment to neutral mechanical postoperative alignment leads to an increase in medial tibial bone resorption compared to more consistent kinematic alignment, independent of initial tibial geometry and bone density. In mechanical alignment, increased resorption was also found distally of the keel, while reduced bone loss was found laterally. The course of bone remodeling over time showed rapid initial remodeling rates for low density bones, while high density bones generally had increased and prolonged relative proximal bone loss after two years. The latter trend has also been displayed in a clinical DEXA study comparing remodeling in low- and high-BMD groups (Li and Nilsson, 2000b). These results indicate that, when considering bone remodeling, it may be beneficial to align the implant according to constitutional varus alignment rather than to adopt neutral mechanical alignment, since greater initial medial densification and medial condyle unloading have both been found to increase bone resorption. Density distributions revealed different bone remodeling pathways, with most bone apposition either near the distal keel tip or at the lateral cortex, irrespective of the chosen alignment. The variations seen between specimens illustrate the benefit of population-based FE analyses over single model studies.

Credit author statement

Thomas Anijs: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Review & Editing, Visualization. David Wolson: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding acquisition. Nico Verdonschot: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision. Dennis Janssen: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This study was funded by DePuy Synthes Joint Reconstruction, Leeds, UK. One of the authors is an employee of DePuy Synthes.

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Credit author statement

Thomas Anijs: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft, Review & Editing, Visualization. David Wolson: Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision. Dennis Janssen: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

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