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REVIEW ARTICLE

Changes in femoral bone mineral density after total knee arthroplasty: a systematic review and meta-analysis

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Abstract

Background Bone loss after total knee arthroplasty (TKA) may lead to periprosthetic fractures that are associated with significant costs (morbidity, economic, etc.) and pose a challenge to operative fixation. This meta-analysis quantifies the change in bone mineral density (BMD) of the distal femur after primary TKA.

Methods A systematic review of six databases was performed by two independent reviewers. Studies that reported bone density after knee arthroplasty were identified and inclusion/exclusion criteria was applied. Data were extracted and analyzed using the Comprehensive Meta-Analysis Software.

Results Fourteen studies were included in the analysis. The average decrease in BMD was 0.09 [0.05, 0.13], 0.14 [0.08, 0.20], 0.16 [0.10, 0.23], and 0.16 [0.12, 0.20] g/cm^2 at 3, 6, 12, and 24 months, respectively, corresponding to a 9.3%, 13.2%, 15.8%, and 15.4% BMD loss. A high degree of heterogeneity existed between the studies ($I^2 > 90\%$ at most time points).

Conclusion In summary, there is a rapid and significant 15% decrease in BMD in the first 6 months after TKA that is sustained to 24 months. Better understanding regarding how perioperative optimization of bone health may affect BMD loss and the incidence of periprosthetic fracture is essential.

Level of evidence Therapeutic Level II.

Keywords Bone mineral density · Bone loss · Femur · Total knee arthroplasty · Meta-analysis · Periprosthetic fracture

Introduction

Currently over 7 million people in the USA have knee or hip joint arthroplasties [1], and unfortunately, there is a rise in periprosthetic fractures. The majority of these cases are fragility fractures which are difficult to manage surgically and are associated with high costs, prolonged length of stay, and poorer outcomes [2]. Major risk factors for fracture are older age, female gender, and presence of osteoporosis which are common in those undergoing total knee arthroplasty (TKA) [3, 4]. A potential strategy to reduce periprosthetic fracture risk is to identify suboptimal bone status and provide appropriate treatment if indicated [5].

Approximately one quarter of patients with osteoarthritis awaiting lower extremity arthroplasty have concomitant osteoporosis as assessed by dual-energy x-ray absorptiometry (DXA) [6–8]. Several imaging modalities can quantify bone mineral density (BMD) including dual photon absorptiometry (DPA), but DXA remains the gold standard providing accurate and reproducible measurements with minimal radiation exposure [9]. DXA is also the ideal modality for measuring periprosthetic BMD as it is less by the metal implants unlike other modalities, e.g., CT. However, DXA is rarely routinely performed in distal aspect of the femur prior to TKA, and standard methods to quantify BMD do not exist for the region. In a patient population with a high baseline prevalence of

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osteoporosis performing arthroplasty prior to bone quality optimization may further increase the risk of postoperative fractures.

In our experience, postoperative fragility fractures after TKA occur almost exclusively on the ipsilateral side. The etiology of these fractures is likely multifactorial (e.g., altered gait mechanics increasing ipsilateral falls); however, these events may be related to post-surgical weight-bearing changes through an implant leading to decreased ipsilateral BMD. Previous studies with small sample sizes have reported a decrease in ipsilateral distal femur BMD ranging from 1 to 44% [10, 11]. However, there are no large studies that report results from multiple patient populations, surgeons, and implant designs.

The senior author is associated with the American Orthopaedic Association's Own the Bone Program focused on addressing the fragility fracture epidemic by disseminating preventive measures aimed to reduce future fractures (e.g., counseling regarding nutrition, physical activity, and lifestyle), bone active pharmacotherapy when indicated, and informed risk/benefit communication. DXA testing is important after a fragility fracture; it is reasonable that preoperative BMD screening and appropriate interventions could reduce morbid periprosthetic fractures. Moreover, knowledge of BMD change after arthroplasty may identify those patients who could benefit from bone active therapy and thereby reduce periprosthetic fracture risk.

We hypothesize that there is a significant decrease in BMD after knee arthroplasty. This study is a systematic literature review and meta-analysis devised to quantify the change in BMD of the distal femur after primary TKA.

Methods

A systematic review was independently performed by two authors (JP and JB) querying PubMed, CINAHL, Cochrane, Scopus, Web of Science, and Google Scholar for articles published up until June 2017 (Fig. 1). Searches were conducted using the Medical Subject Headings (MeSH) 'bone density' and 'arthroplasty, replacement, knee' as defined by the National Library of Medicine. The initial inclusion criterion was studies reporting measurements of lower extremity BMD following primary knee arthroplasty. Upon a more thorough second review of these initially screened articles, those measuring BMD of the distal femur after TKA were included. Exclusion criteria applied upon this second review included tibial and hip BMD reported without femoral measurements, revision total knee or unicompartmental arthroplasty, contralateral knee pathology, patient populations with medical conditions altering bone density (e.g., inflammatory arthritis, cancer, chronic steroid use, etc.), computational studies, and bisphosphonate use.

The quality of each study was appraised using a modified version of the Downs and Black checklist, a methodology with high internal consistency (KR-20: 0.89) used to quantify study quality based on 27 mostly binary items [12]. With the exceptions of items 5 and 27, a score of 1 is awarded for an answer of 'yes' whereas 0 represents 'no' or 'unable to determine.' Item 27 was modified to a binary answer: one point was awarded if a power calculation was present. The maximum possible calculated score was 28.

BMD measurements were extracted from text, figures and tables, while ImageJ Software (NIH) was used to extract data points from digitized graphs [13]. If more than one site of BMD was reported in the study, they were categorized based on location on the distal femur: supracondylar or intracondylar. Supracondylar was defined as being proximal to the superior aspect of the anterior flange of the femoral component. Intracondylar was defined as being distal to the superior aspect of the anterior flange but within the confines of the implant. The plane of imaging (coronal or sagittal) was also recorded. Subgroups within individual studies were pooled prior to analyzing the change in BMD at several time points: baseline, 3 months, 6 months, 12 months, and greater than 12 months. Only data from these exact time points were included in the analysis as often times other time points were reported. Comprehensive Meta-Analysis Software (version 3) was used to calculate individual standardized mean difference (Hedge's g) statistics and the absolute difference in means. A pooled Hedge's g was calculated using random effects modeling weighting studies based on inverse variance. A percent change in BMD was calculated by comparing the difference in means to the baseline BMD. Standard deviation data was imputed for studies where it was not reported by inserting the pooled standard deviation. A Pearson correlation coefficient was used for the pre-post correlation. Forest plots were constructed to include the calculated pooled effect sizes and 95% confidence intervals (CI). The Q-statistic and I^2 were used to evaluate study heterogeneity. I^2 values less than 25% signify low between-study variance and homogeneity of the studies while studies with I^2 greater than 75% represent high variance and heterogeneity. Significance was defined as a p value of less than 0.05.

To calculate statistical changes over time, an artificial variable based on Hedge's g was calculated for each time point from baseline and compared using ANOVA. If a significant relationship was observed, the artificial variable was compared between successive time points using Chi squared [14].

Publication bias was visually assessed with Funnel plots. The Classic Fail-safe N, Orwin's Fail-safe N, and Duval and Tweedie's Trim and Fill were utilized to quantify the bias. For Orwin's test, a trivial effect size was

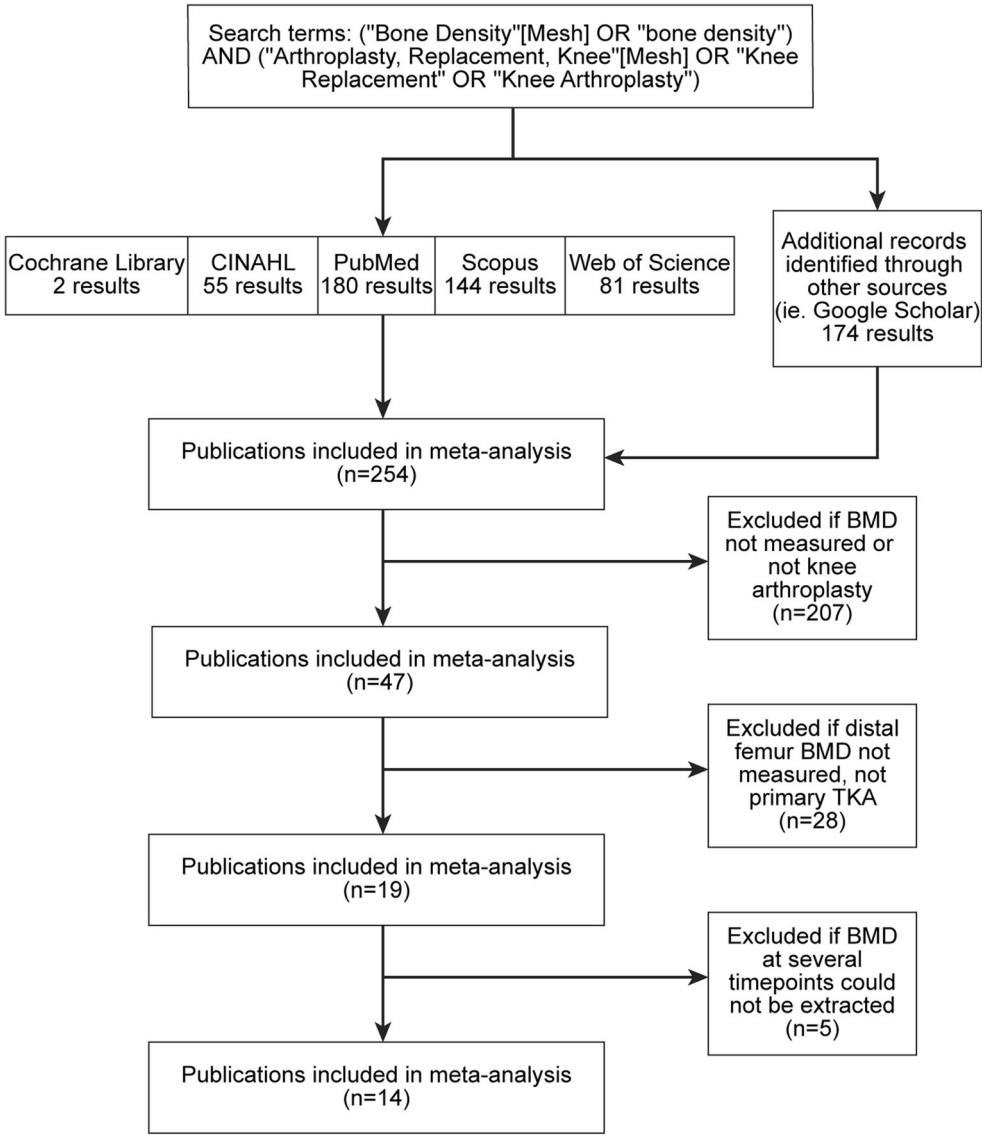

Fig. 1 Systematic review search strategy

defined as half of the calculated effect size, and the mean effect size of the missing studies was defined as the smallest calculated effect size. We evaluated sources of heterogeneity between the studies by performing a sensitivity analysis at 12 months. This was done through single study deletion and moderator comparisons: pre-post correlation coefficient, use of cement, region of interest (ROI) measured, country, imaging modality, imaging plane, and use of imputated data.

Results

Systematic review summary

Nineteen studies were identified that measured distal femur BMD after primary TKA (Fig. 1). Five of these studies were excluded as the absolute BMD could not be extracted. Details of the remaining studies included in the meta-analysis are shown in Table 1 (see Appendix for an in-depth summary of the studies) [10, 15–27]. Overall, BMD was reported for 547 patients on the operative side.

Quality assessment of studies

Using the Downs and Black checklist, the range of calculated quality index scores for the included studies was 10 to 20 with the mean quality score being 14.9 ± 3.4. While the Downs and Black checklist is validated for assessment of both randomized and non-randomized studies, often points were not awarded for the several items addressing randomization and blinding as most of the studies were longitudinal studies.

Table 1 Details of the remaining studies included in the meta-analysis

Study	*n*	Side	Mean age (SD or range)	Mean BMI	Males (%)	Time points	Country	Continent	Implant(s)	Modality	Cement
Gazdzik	106	Operative	69.8 (± 9.37)	31.71 (± 4.84)	0.0	3, 6, and 12 months*	Poland	Europe	AGC II Biomet Merck PFC Sigma Johnson & Johnson Scorpio type Stryker	DXA	+
Järvenpää	69	Operative	67.7 (± 6.2)	29.8 (± 5)	17.4	3, 6, 12, 24, 48, and 84 months	Finland	Europe	Duracon Nexgen AMK AGC	DXA	+
Karbowski	12 12	Operative Contralateral	70.5 (58–80)	†	16.7	3 and 9 months	Germany	Europe	PFC knee	DXA	†
Liu	28 28	Operative Contralateral	65.4 (54–78)	Mean height 157 (± 6 cm) Mean weight 64.6 (± 9.1 kg)	0.0	3, 6, and 12 months	Taiwan	Asia	Osteonics Whiteside	DXA	–
Mau-Moeller	23	Operative	67.7 (± 8.3)	29.8 (± 2.4)	65.2	3 months	Germany	Europe	Multigen Plus	DXA	†
Minoda	56	Operative	72.9 (57–85)	Mean height 150.7 (135–172 cm) Mean weight 57.4 (33–79 kg)	21.4	3, 6, 12, 18, and 24 months	Japan	Asia	NexGen LPS-flex; cemented fixed-bearing posterior-stabilized prosthesis, Zimmer; cemented mobile-bearing PFC Sigma RP posteriorly stabilized prosthesis, DePuy	DXA	+
Petersen 1995	8	Operative	70 (51–77)	†	25.0	24 months	Denmark	Europe	PCA Primary	DPA	–
Petersen 1996	29	Operative	70.9 (51–83)	†	34.5	3, 6, and 12 months	Denmark	Europe	PCA Modular, Modified PCA Modular, and Duracon	DPA	–
Saari	47	Operative	71.0 (50–82)	†	27.7	12, 24, and 60 months	Sweden	Europe	AMK	DXA	+
Shibuki	22	Operative	76.0 (5.7)	24.9 (4.0)	9.1	3, 6, 12, and 24 months	Japan	Asia	LCS Complete, DepuySynthes	DXA	–
Soininvaara 2004	69	Operative	67 (± 6.8)	29.5 (± 4.7)	29.0	3, 6, and 12 months	Finland	Europe	Duracon, Nexgen, AMK	DXA	+
Soininvaara 2008	16	Operative	66 (± 4.9)	29.5 (± 5.0)	31.3	6, 12, and 24 months	Finland	Europe	Duracon modular (Howmedica Inc., Divsion of Pfizer), Nexgen (Zimmer) and AMK (DePuy)	DXA	+
van Loon	12	Operative	62 (41–80)	†	33.3	3, 6, and 12 months	Netherlands	Europe	Press Fit Condylar, Johnson & Johnson	DXA	+
Windisch	50	Operative	66 (58–83)	†	26.0	3 and 6 months	Germany	Europe	LCS-Knie Fa.	DXA	–

Table 2 Baseline BMD observed between studies

Study	*n*	ROI	BMD	
			Mean [95% CI]	SD
Operative leg				
Gazdzik	106	Supracondylar	0.674 [0.638, 0.710]	0.190
Järvenpää	69	Intracondylar and supracondylar	1.395 [1.353, 1.437]	0.179
Karbowski	12	Intracondylar	0.690 [0.558, 0.823]*	0.234*
Liu	28	Intracondylar and supracondylar	0.746 [0.709, 0.783]	0.101
Mau-Moeller	23	Supracondylar	0.980 [0.935, 1.025]	0.110
Minoda	56	Distal femur	1.150 [1.104, 1.196]	0.175
Petersen 1995	8	Intracondylar	0.696 [0.592, 0.800]	0.149
Petersen 1996	29	Intracondylar	1.164 [1.090, 1.239]	0.205
Saari	47	Intracondylar and supracondylar	0.970 [0.899, 1.041]	0.249
Shibuki	22	Intracondylar and supracondylar	0.630 [0.583, 0.677]	0.112
Soininvaara 2004	69	Intracondylar and supracondylar	1.415 [1.372, 1.458]	0.184
Soininvaara 2008	16	Intracondylar and supracondylar	1.365 [1.288, 1.442]	0.158
van Loon	12	Intracondylar and supracondylar	0.950 [0.849, 1.050]	0.178
Windisch	50	Supracondylar	0.890 [0.801, 0.979]*	0.321*
Overall			0.980 [0.818, 1.143]	0.310

Meta-analysis results

Baseline date

The overall mean baseline BMD was 0.989 g/cm^2 [95% CI 0.810, 1.167], Table 2. The standard deviation for the Windisch and Karbowski studies was imputed as the pooled mean standard after excluding the Peterson studies which used DPA for BMD measurements.

Change in BMD

The average decrease in BMD was 0.09 [0.05, 0.13], 0.14 [0.08, 0.20], 0.16 [0.10, 0.23], and 0.16 [0.12, 0.20] g/cm^2 at 3, 6, 12, and 24 months, respectively. This corresponded to a 9.3%, 13.2%, 15.8%, and 15.4% BMD loss. Both Hedge's g and the difference in means are reported (Table 3) based on ROIs: distal femur combined, intracondylar, and supracondylar. Heterogeneity

Table 3 Hedge's g and the difference in means

Time point	ROI	Studies (*n*)	Patients (*n*)	Hedge's g [CI]	I^2	Mean/difference in means [CI]	Percent change (%)	I^2
Baseline	Combined	12	510	–	–	0.989 [0.810, 1.167]	0	99.30
	Supra	10	442	–	–	0.981 [0.793, 1.168]	0	99.02
	Intra	8	275	–	–	1.052 [0.802, 1.302]	0	98.74
3 months	Combined	11	476	− 0.382 [− 0.537, − 0.226]	96.25	− 0.089 [− 0.131, − 0.046]	− 9.32	97.84
	Supra	8	379	− 0.232 [− 0.280, − 0.184]	23.29	− 0.057 [− 0.074, − 0.040]	− 5.98	65.92
	Intra	7	241	− 0.541 [− 0.871, − 0.211]	97.18	− 0117 [− 0.186, − 0.047]	− 11.68	97.88
6 months	Combined	10	437	− 0.585 [− 0.807, − 0.363]	97.85	− 0.135 [− 0.195, − 0.076]	− 13.19	98.93
	Supra	8	352	− 0.365 [− 0.570, − 0.159]	95.04	− 0.097 [− 0.161, − 0.033]	− 11.01	97.98
	Intra	7	245	− 0.840 [− 1.195, − 0.485]	97.01	− 0.189 [− 0.245, − 0.134]	− 16.93	95.78
12 months	Combined	11	504	− 0.594 [− 0.790, − 0.397]	97.73	− 0.160 [− 0.225, − 0.096]	− 15.75	99.13
	Supra	9	419	− 0.423 [− 0.633, − 0.222]	95.70	− 0.129 [− 0.204, − 0.055]	− 13.18	98.54
	Intra	8	292	− 0.792 [− 1.149, − 0.434]	97.92	− 0.203 [− 0.296, − 0.111]	− 18.43	98.72
24 months	Combined	6	218	− 0.464 [− 0.624, − 0.304]	94.02	− 0.160 [− 0.204, − 0.115]	− 15.42	94.36
	Supra	4	154	− 0.591 [− 0.895, − 0.287]	93.99	− 0.186 [− 0.287, − 0.085]	− 18.08	96.39
	Intra	5	162	− 0.507 [− 0.834, − 0.181]	96.59	− 0.188 [− 0.307, − 0.070]	− 17.88	97.69

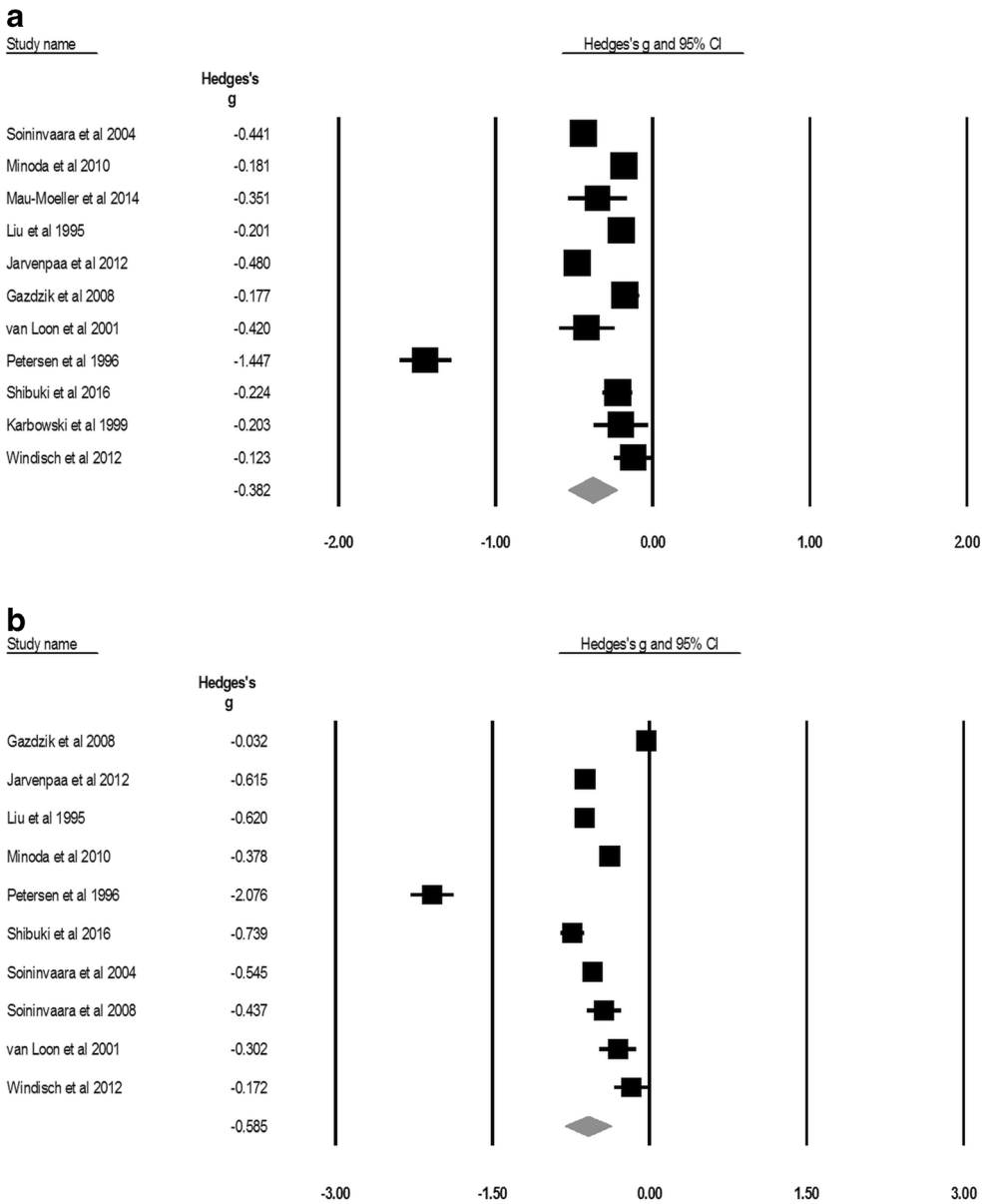

Fig. 2 Forest plots of Hedge's g for the absolute decrease in BMD at **a** 3 months, **b** 6 months, **c** 12 months, and **d** 24 months postoperatively. The size of the squares reflects the weight of the study, and the horizontal lines represent the 95% confidence interval. The diamond is the mean effect size

was large with the I^2 statistic being greater than 90% for most of the time points. Forest plots of Hedge's g for the combined ROIs demonstrate a significant decrease in BMD from baseline at each of the time points (Fig. 2a–d). Figure 3 displays the percentage decline from baseline in BMD. This was calculated from the difference between the mean BMD at a particular time point and the baseline divided by the mean baseline BMD. It approaches an asymptote of approximately 15% loss by 2 years. A statistically significant decrease in BMD was observed in the combined, intracondylar, and supracondylar ROIs from baseline to 24 months and at each time point (between baseline and 3 months, 3 and 6 months, 6 and 12 months, and 12 and 24 months).

Publication Bias

A representative funnel plot shown in Fig. 4 demonstrates that publication bias exists among the studies. There are several studies with smaller or larger effect sizes than predicted, but they remain symmetric about the mean effect size despite the relative absence of smaller studies with larger standard errors. At 12 months, Duval and Tweedie's trim and fill revealed that only four trimmed studies to the left of the mean and 0 to the right of the mean were required to make the funnel plot symmetric. With the four trimmed studies, the effect size increased to -0.797 [-1.048, -0.547] from -0.594 [-0.790, -0.397]. The classic and Orwin's fail-safe N tests resulted

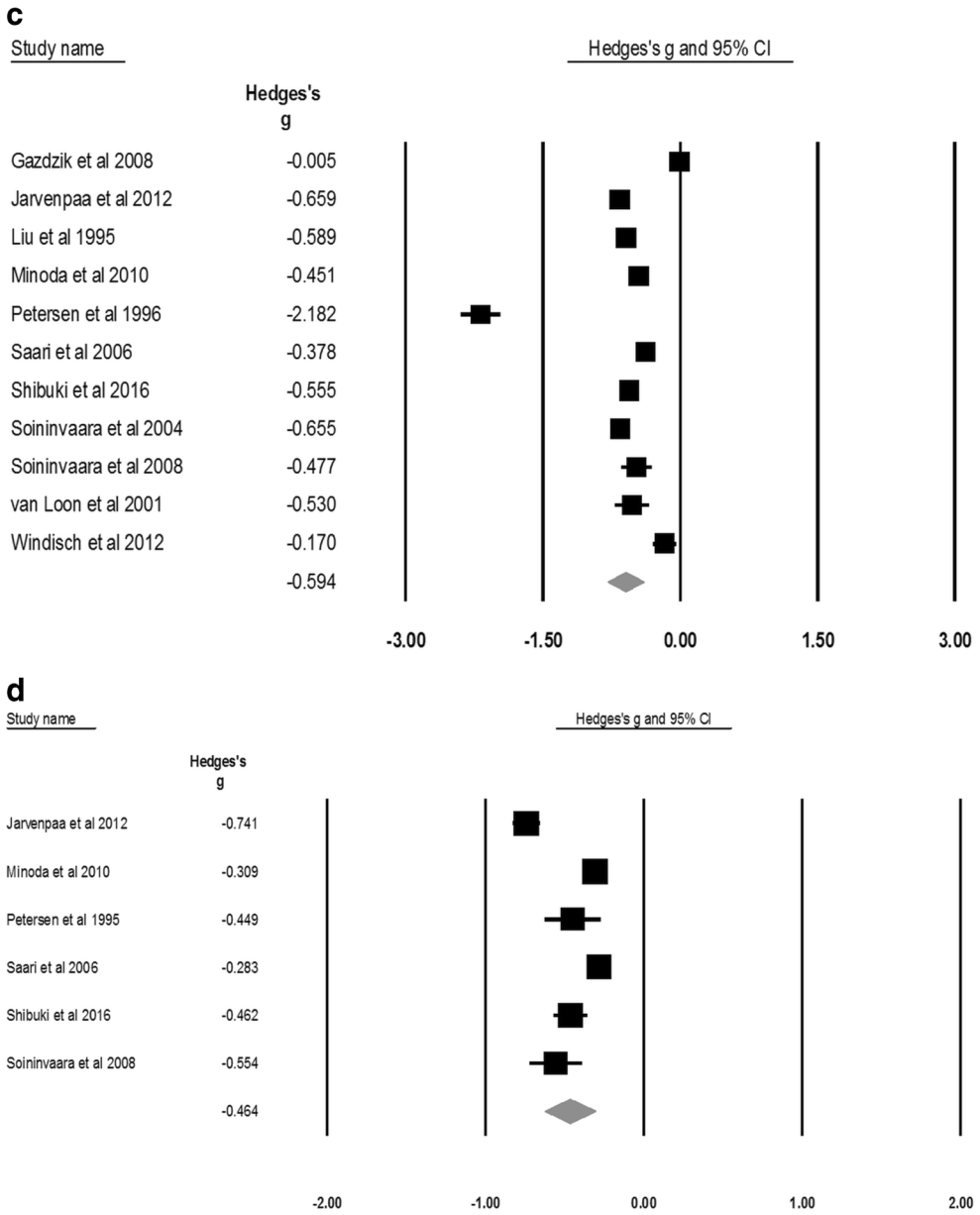

Fig. 2 continued.

3220 and 12 missing studies, respectively, required to change the effect size to nonsignificant.

Sensitivity analysis

To identify potential sources of heterogeneity, sensitivity analysis was performed on the 12-month data. Several moderator variables did not significantly contribute to study heterogeneity. Low between study variance was seen when varying the pre-post correlation coefficient ($p = 0.968$), use of cement ($p = 0.164$), country ($p = 0.536$), and imputed data ($p = 0.176$) in addition to single-study deletion. ROIs measured ($p < 0.0001$) and imaging plane ($p < 0.0001$) contributed most significantly to the heterogeneity. Imaging modality was also significant ($p < 0.0001$); however, only one study at 12 months was in the DPA group.

Discussion

The prevalence of TKA in the US population has risen over several decades with 4.7 million individuals living with a TKA in 2010 [1]. Increased demand among an aging population, greater implant longevity, and patients undergoing knee replacement at younger ages are all contributing factors to this rise. The incidence of periprosthetic fractures has also

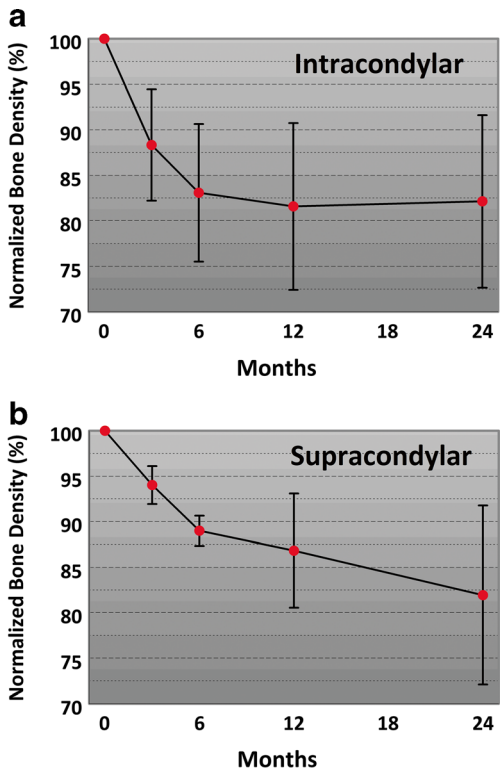

Fig. 3 Percent change in BMD of the femoral intracondylar (**a**) and supracondylar (**b**) regions from baseline over 24 months postoperatively

dramatically risen: noted to be 0.3–5.5% for primary TKA and as high as 30% for revision arthroplasty [28, 29]. Abdel et al. reported a similar effect after total hip arthroplasty (THA): a 3.5% 20-year cumulative risk of postoperative fracture after primary THA rising to a 11.4% 20-year cumulative risk after revision THA [30, 31]. Implying a linkage to poor bone quality, the risk of postoperative fracture was significantly higher in uncemented femoral stems and in females [30]. Although bone status is a major consideration in revision arthroplasty, it is currently not commonly assessed in clinical practice when risk stratifying a candidate for primary arthroplasty surgery. Knowledge of postoperative BMD loss following arthroplasty might lead to improved protocols for preoperative bone health optimization aimed to reduce periprosthetic fracture [5].

Our meta-analysis found that a rapid and significant decrease in BMD occurs after TKA that does not recover by 2 years. The observed 15% decrease occurs in the first 6 months after TKA (Fig. 3). The nadir in BMD is reached by 12 months and appears to be sustained to 24 months. Sensitivity analysis demonstrated a larger effect size in cemented compared to uncemented femoral components. Although the difference found was not statistically significant, it is consistent with previous finite-element computer modeling predicting less bone loss of the distal femur with an uncemented femoral component, positing this as a potential protective factor for periprosthetic fractures [32].

The observed BMD decline is comparable to widely recognized causes of "acute rapid and severe bone loss [33]: stroke patients have 9% spine and hip bone loss after 1 year while renal transplant patients may have up to 18% spine and 4% hips bone loss annually. Unfortunately, these rapid bone loss disorders are associated with an increased risk of fracture. One meta-analysis evaluating commonly screened sites found that for every one standard deviation change in BMD (equivalent to 10–12% change in BMD), the relative risk of fracture increased by 1.5–2.6% [34]. The exact clinical implication of postoperative femoral BMD decline is unknown, but the decrease in bone quality likely increases the risk of periprosthetic fracture. In patients with low BMD preoperatively (i.e., osteopenia), this 15% decrease may bring the ipsilateral leg into the range of osteoporotic BMD. However, if TKA patients are screened preoperatively for low BMD and their bone health is optimized prior to surgery, this may mitigate the effects of the observed 15% BMD loss in the postoperative period [5].

Several investigations show promising results for this approach of preoperative optimization. A meta-analysis by Teng et al. [35] demonstrated a 50% reduction in revision TKA

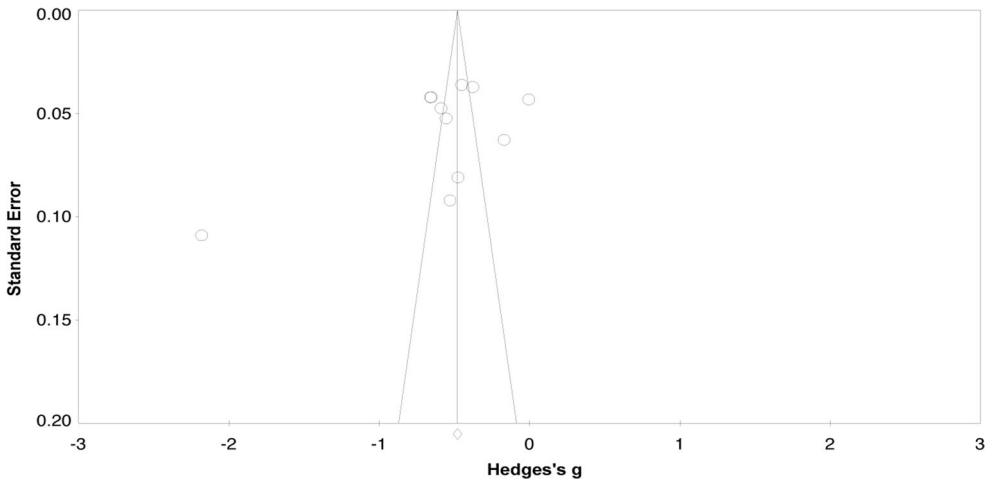

Fig. 4 Funnel plot of standard error by Hedge's g for the change in BMD at 12 months

among patients with bisphosphonate use for at least 6 months prior to primary TKA. Fu et al. [36] published a large cohort study of osteoporotic patients with newly diagnosed osteoarthritis and found a 24–34% reduction in the requirement for TKA and a significant decrease in the amount of pain medications consumed among bisphosphonate users.

Meta-analysis is a tool to investigate a given effect among studies with similar methods. Heterogeneity, within and between study variance, is measured using an I^2 statistic. While using random effects modeling, I^2 was consistently greater than 90% in our review signifying a high degree of heterogeneity. Sensitivity analysis was performed to determine what variations in methodology and techniques most likely contributed to this. Three factors were significant: ROI measured, imaging plane, and imaging modality.

A limitation of this report is that there is no standard ROI defined at which to measure distal femoral BMD following TKA. As such, to simplify analysis, ROIs were grouped into supracondylar or intracondylar measurements which likely contributed to the heterogeneity observed. Unsurprisingly, limb rotation can greatly affect the DXA precision and most studies did not report methods to improve precision [37, 38]. A coefficient of variation as high as 20% has been reported with varying degrees of internal and external rotation with supracondylar measures being least effected by rotation [38, 39]. Another contributor to heterogeneity within our study was the large variation in baseline BMD observed between studies (Table 2) which was likely in part due to differing BMD measurement methods and patient populations. Data collected sooner postoperatively generally had higher baselines. Studies with lower BMD baselines also appeared to have older populations with higher rates of osteopenia. While these differing methods certainly affected the heterogeneity observed among the studies, they should not confound the calculated effect sizes. Future studies should focus on developing standardized methods and ROIs for DXA imaging of extremities. Studies have evaluated strategies to improve reproducibility by mitigating rotation and flexion using soft foam cast or braces [40, 41]. These strategies need to be routinely applied to move this science forward.

We identified evidence of publication bias. The trim and fill analysis identified four theoretical missing studies in the absence of bias. The missing studies were left of the calculated mean and resulted in an increased effect size. Despite funnel plot asymmetry, which could be due to random variation, the risk with the trim and fill analysis is that it could be adjusting for non-existent studies.

There are several limitations to our meta-analysis. These include heterogeneity, unidentified bias, and confounding factors within individual studies, and only including studies from the databases searched. Many studies did not report patient comorbidities, and few presented multivariable analysis evaluating the effect of population characteristics, especially those known to affect BMD such as gender. We were also limited in drawing any meaningful conclusion about the effect of TKA on BMD of the contralateral distal femur due to too few studies reporting this data.

Future research should focus on evaluating the contralateral limb BMD change due to compensatory mechanics and weight-bearing. Examining the cause of postoperative femoral BMD loss and if the observed BMD loss is sustained beyond 24 months is also of interest. The correlation between decreased postoperative femoral BMD to periprosthetic fracture risk is unknown. Additionally, further study is needed on the effect of bisphosphonate use and other medications affecting bone metabolism in the perioperative period, particularly on the rate of periprosthetic fracture. The rate of periprosthetic fracture in individuals preoperatively screened and treated for osteoporosis in comparison to those who are not is another avenue of study.

DXA measurements are only one aspect of determining a patient's fracture risk. Several other factors such as age, fall risk, and prior fracture history help define the absolute fracture risk for fragility fractures [42]. Periprosthetic fractures, with arguably more associated morbidity, likely have analogous risk factors but may be affected by the type of prosthesis, use of cement, and surgical placement and misadventures. This meta-analysis highlights the periprosthetic BMD loss observed 2 years after TKA and calls to attention the need for perioperative bone health optimization with continued postoperative evaluation.

Compliance with ethical standards

Conflict of interest None.

Appendix

Summary of investigations

Fourteen studies were included in the meta-analysis. Two of the first studies prospectively measuring BMD after TKA were by Petersen et al. [10, 15] using DPA. Petersen et al. [15] 1995 measured BMD in three areas of the distal femur (anterior to the fixation lugs, proximally to the lugs and posteriorly to the lugs) 2 years after TKA in 8 patients. The 1996 Petersen et al. [10] study measured and compared the BMD at similar regions (behind the anterior flange of femoral component and above the fixation lugs) for 29 patients at 1 year after implantation with different femoral components in hopes to reduce the previously observed loss in BMD. Another earlier study published, Liu et al. [16], was a case-control study measuring mostly supracondylar BMD bilaterally in 48 females, comparing two different implants to age-matched controls.

Several studies focused on quantifying supracondylar BMD changes. Gazdzik et al. [17] is a prospective

longitudinal study that reported the BMD of an area proximal to the superior border of the femoral components in 106 postmenopausal females. In a similarly designed study, Mau-Moeller et al. [18] measured BMD three months postoperatively at the same femoral ROIs in 23 patients (65% male). Windisch et al. [19] also measured supracondylar femur BMD prospectively in 50 patients at several time points in the first postoperative year. In the Minoda et al. [20] study, twenty-eight patients with fixed-bearing TKA were matched with 28 patients with mobile-bearing TKAs, and the BMD of the anterior, central and posterior distal femur ROIs (spanning metaphyseal and intracondylar regions) were measured for 24 months. Van Loon et al. [21] studied the 1-year postoperative changes in BMD of the femoral neck, lumbar spine, and distal femur (distal anterior area of the femur behind the anterior flange and supracondylar area just superior to the anterior flange of the femoral component).

Soininvaara et al. [22, 23] developed standardized ROIs of the distal femur (anterior metaphyseal, central metaphyseal, posterior metaphyseal, total metaphyseal and diaphyseal). One of their studies in 2004 measured the changes in BMD of the operative leg in 69 patients over the course of a year [22]. Karbowski et al. [24] conducted a smaller longitudinal study measuring BMD of the same ROIs in the operative knee of 12 patients. Soininvaara et al. [23] 2008 studied the changes in BMD detected by DXA along with attempting to correlate single photon emission computed tomography measurements in the standard ROIs prospectively 2 years after TKA in 16 patients. Järvenpää et al. [25] compared the BMD at these standard ROIs defined by Soininvaara between 61 obese and nonobese patients over a period of 7 years. Shibuki et al. [26] retrospectively studied 22 patients collecting BMD at Soininvaara's recommended ROIs over a 2-year postoperative period. In 2006, Saari et al. [27] reported 83 patients randomized into four groups based on varus/valgus alignment: a flat or a concave tibial plateau with the posterior cruciate ligament (PCL) retained and a concave or a posterior-stabilized tibial component with the PCL resected. They measured three intracondylar ROIs over 5 years.

References

1. Maradit Kremers H, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA, Jiranek WA, Berry DJ (2015) Prevalence of Total hip and knee replacement in the United States. J Bone Joint Surg Am 97:1386–1397. https://doi.org/10.2106/JBJS.N.01141
2. Bozic KJ, Kamath AF, Ong K, Lau E, Kurtz S, Chan V, Vail TP, Rubash H, Berry DJ (2015) Comparative epidemiology of revision arthroplasty: failed THA poses greater clinical and economic burdens than failed TKA. Clin Orthop Relat Res 473:2131–2138. https://doi.org/10.1007/s11999-014-4078-8
3. Singh JA, Jensen M, Lewallen D (2013) Predictors of periprosthetic fracture after total knee replacement. Acta Orthop 84:170–177. https://doi.org/10.3109/17453674.2013.788436
4. Canton G, Ratti C, Fattori R, Hoxhaj B, Murena L (2017) Periprosthetic knee fractures. A review of epidemiology, risk factors, diagnosis, management and outcome. Acta Biomed 88:118–128
5. Lin T, Yan S-G, Cai X-Z, Ying Z-M (2012) Bisphosphonates for periprosthetic bone loss after joint arthroplasty: a meta-analysis of 14 randomized controlled trials. Osteoporos Int 23:1823–1834. https://doi.org/10.1007/s00198-011-1797-5
6. Labuda A, Papaioannou A, Pritchard J, Kennedy C, DeBeer J, Adachi JD (2008) Prevalence of osteoporosis in osteoarthritic patients undergoing Total hip or Total knee arthroplasty. Arch Phys Med Rehabil 89:2373–2374. https://doi.org/10.1016/j.apmr.2008.06.007
7. Lingard EA, Mitchell SY, Francis RM, Rawlings D, Peaston R, Birrell FN, McCaskie AW (2010) The prevalence of osteoporosis in patients with severe hip and knee osteoarthritis awaiting joint arthroplasty. Age Ageing 39:234–239. https://doi.org/10.1093/ageing/afp222
8. Chang CB, Kim TK, Kang YG, Seong SC, Kang S-B (2014) Prevalence of osteoporosis in female patients with advanced knee osteoarthritis undergoing total knee arthroplasty. J Korean Med Sci 29:1425–1431. https://doi.org/10.3346/jkms.2014.29.10.1425
9. Mazess RB, Barden HS (1988) Measurement of bone by dual-photon absorptiometry (DPA) and dual-energy X-ray absorptiometry (DEXA). Ann Chir Gynaecol 77:197–203
10. Petersen MM, Lauritzen JB, Pedersen JG, Lund B (1996) Decreased bone density of the distal femur after uncemented knee arthroplasty. A 1-year follow-up of 29 knees. Acta Orthop Scand 67:339–344. https://doi.org/10.3109/17453679609002327
11. Seki T, Omori G, Koga Y, Suzuki Y, Ishii Y, Takahashi H (1999) Is bone density in the distal femur affected by use of cement and by femoral component design in total knee arthroplasty? J Orthop Sci 4:180–186
12. Downs SH, Black N (1998) The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 52:377–384. https://doi.org/10.1136/jech.52.6.377
13. Abràmoff MD, Magalhães PJ, Ram SJ (2004) Image processing with Image. J Biophoton Int 11:36–42
14. Borenstein M, Hedges L, Higgins J, Rothstein H (2009) Multiple outcomes or time-points within a study. Introd. to meta-analysis, Pennsylvania
15. Petersen MM, Olsen C, Lauritzen JB, Lund B (1995) Changes in bone mineral density of the distal femur following uncemented total knee arthroplasty. J Arthroplast 10:7–11
16. Liu TK, Yang RS, Chieng PU, Shee B (1995) Periprosthetic bone mineral density of the distal femur after total knee arthroplasty. Int Orthop 19:346–351. https://doi.org/10.1007/BF00178346
17. Gazdzik TS, Gajda T, Kaleta M (2008) Bone mineral density changes after Total knee arthroplasty: one-year follow-up. J Clin Densitom 11:345–350. https://doi.org/10.1016/j.jocd.2008.04.007
18. Mau-moeller A, Behrens M, Felser S, Bruhn S, Mittelmeier W, Bader R et al (2015) Modulation and Predictors of Periprosthetic Bone Mineral Density following total knee arthroplasty. Biomed Res Int 2015:418168. https://doi.org/10.1155/2015/418168
19. Windisch C, Windisch B, Kolb W, Kolb K, Grützner P, Roth A (2012) Osteodensitometry measurements of periprosthetic bone

using dual energy X-ray absorptiometry following total knee arthroplasty. Arch Orthop Trauma Surg 132:1595–1601. https://doi.org/10.1007/s00402-012-1601-9
20. Minoda Y, Ikebuchi M, Kobayashi A, Iwaki H, Inori F, Nakamura H (2010) A cemented mobile-bearing total knee replacement prevents periprosthetic loss of bone mineral density around the femoral component: a MATCHED COHORT STUDY. J Bone Jt Surg Br 92-B:794–798. https://doi.org/10.1302/0301-620X.92B6.23159
21. van Loon CJ, Oyen WJ, de Waal Malefijt MC, Verdonschot N (2001) Distal femoral bone mineral density after total knee arthroplasty: a comparison with general bone mineral density. Arch Orthop Trauma Surg 121:282–285
22. Soininvaara TA, Miettinen HJA, Jurvelin JS, Suomalainen OT, Alhava EM, Kröger HPJ (2004) Periprosthetic femoral bone loss after total knee arthroplasty: 1-year follow-up study of 69 patients. Knee 11:297–302. https://doi.org/10.1016/j.knee.2003.09.006
23. Soininvaara T, Nikola T, Vanninen E, Miettinen H, Kröger H (2008) Bone mineral density and single photon emission computed tomography changes after total knee arthroplasty: a 2-year follow-up study. Clin Physiol Funct Imaging 28:101–106. https://doi.org/10.1111/j.1475-097X.2007.00782.x
24. Karbowski A, Schwitalle M, Heine A, Eckardt J (1999) Periprosthetic bone remodelling after total knee arthroplasty: early assessment by dual energy X-ray absorptiometry. Trauma 119: 324–326
25. Järvenpää J, Soininvaara T, Kettunen J, Miettinen H, Kröger H (2014) Changes in bone mineral density of the distal femur after total knee arthroplasty: a 7-year DEXA follow-up comparing results between obese and nonobese patients. Knee 21:232–235. https://doi.org/10.1016/j.knee.2013.03.004
26. Shibuki T, Sukezaki F, Suzuki T, Toyoshima Y, Nagai T, Inagaki K (2016) Periprosthetic bone mineral density changes after cementless Total knee arthroplasty. Showa Univ J Med Sci 28: 155–161
27. Saari T, Uvehammer J, Carlsson LV, Regner L, Karrholm J (2006) Posterior stabilized component increased femoral bone loss after total knee replacement. 5-year follow-up of 47 knees using dual energy X-ray absorptiometry. Knee 13:435–439. https://doi.org/10.1016/j.knee.2006.08.002
28. Della Rocca GJ, Leung KS, Pape H-C (2011) Periprosthetic fractures: epidemiology and future projections. J Orthop Trauma 25(Suppl 2):S66–S70. https://doi.org/10.1097/BOT.0b013e31821b8c28
29. Frenzel S, Vécsei V, Negrin L (2015) Periprosthetic femoral fractures—incidence, classification problems and the proposal of a modified classification scheme. Int Orthop 39:1909–1920. https://doi.org/10.1007/s00264-015-2967-4
30. Abdel MP, Houdek MT, Watts CD, Lewallen DG, Berry DJ (2016) Epidemiology of periprosthetic femoral fractures in 5417 revision total hip arthroplasties: a 40-year experience. Bone Jt J 98B:468–474. https://doi.org/10.1302/0301-620X.98B4.37203
31. Abdel MP, Watts CD, Houdek MT, Lewallen DG, Berry DJ (2016) Epidemiology of periprosthetic fracture of the femur in 32 644 primary total hip arthroplasties: a 40-year experience. Bone Joint J 98–B:461–467. https://doi.org/10.1302/0301-620X.98B4.37201
32. vanLenthe GH, Malefijt MCD, Huiskes R (1997) Stress shielding after total knee replacement may cause bone resorption in the distal femur. J Bone Joint Surg Br 79B:117–122. https://doi.org/10.1302/0301-620X.79B1.6808
33. Epstein S, Inzerillo AM, Caminis J, Zaidi M (2003) Disorders associated with acute rapid and severe bone loss. J Bone Miner Res 18:2083–2094. https://doi.org/10.1359/jbmr.2003.18.12.2083
34. Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312:1254–1259. https://doi.org/10.1136/bmj.312.7041.1254
35. Teng S, Yi C, Krettek C, Jagodzinski M (2015) Bisphosphonate Use and Risk of Implant Revision after Total Hip / Knee Arthroplasty : A Meta-Analysis of Observational Studies. PLoS One 10(10):e0139927. https://doi.org/10.1371/journal.pone.0139927
36. Fu S-H, Wang C-Y, Yang R-S, Wu F-LL, Hsiao F-Y (2017) Bisphosphonate use and the risk of undergoing Total knee arthroplasty in osteoporotic patients with osteoarthritis. J Bone Joint Surg 99:938–946. https://doi.org/10.2106/JBJS.16.00385
37. Goh JC, Low SL, Bose K (1995) Effect of femoral rotation on bone mineral density measurements with dual energy X-ray absorptiometry. Calcif Tissue Int 57:340–343
38. Therbo M, Petersen MM, Schroder HM, Nielsen PK, Zerahn B, Lund B et al (2003) The precision and influence of rotation for measurements of bone mineral density of the distal femur following total knee arthroplasty: a methodological study using DEXA. Acta Orthop Scand 74:677–682. https://doi.org/10.1080/00016470310018199
39. Spittlehouse AJ, Getty CJ, Eastell R (1999) Measurement of bone mineral density by dual-energy X-ray absorptiometry around an Uncemented knee prosthesis. J Arthroplast 14:957–963
40. Sepriano A, Roman-Blas JA, Little RD, Pimentel-Santos F, Arribas J, Largo R et al (2015) DXA in the assessment of subchondral bone mineral density in knee osteoarthritis-a semi-standardized protocol after systematic review. Semin Arthritis Rheum 45:275–283. https://doi.org/10.1016/j.semarthrit.2015.06.012
41. Tjørnild M, Søballe K, Bender T, Stilling M (2011) Reproducibility of BMD measurements in the prosthetic knee comparing knee-specific software to traditional DXA software: a clinical validation. J Clin Densitom 14:138–148. https://doi.org/10.1016/j.jocd.2011.01.002
42. McClung MR (2005) The relationship between bone mineral density and fracture risk. Curr Osteoporos Rep 3:57–63