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Autologous versus synthetic bone grafts for the surgical management of tibial plateau fractures: a systematic review and meta-analysis of randomized controlled trials

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Aims

Our objective was to conduct a systematic review and meta-analysis, to establish whether differences arise in clinical outcomes between autologous and synthetic bone grafts in the operative management of tibial plateau fractures.

Methods

A structured search of MEDLINE, EMBASE, the online archives of Bone & Joint Publishing, and CENTRAL databases from inception until 28 July 2021 was performed. Randomized, controlled, clinical trials that compared autologous and synthetic bone grafts in tibial plateau fractures were included. Preclinical studies, clinical studies in paediatric patients, pathological fractures, fracture nonunion, or chondral defects were excluded. Outcome data were assessed using the Risk of Bias 2 (ROB2) framework and synthesized in random-effect meta-analysis. The Preferred Reported Items for Systematic Review and Meta-Analyses guidance was followed throughout.

Results

Six studies involving 353 fractures were identified from 3,078 records. Following ROB2 assessment, five studies (representing 338 fractures) were appropriate for meta-analysis. Primary outcomes showed non-significant reductions in articular depression at immediate postoperative (mean difference -0.45 mm, $p = 0.25$, 95%confidence interval (CI) -1.21 to 0.31, $I^2 = 0\%$) and long-term (> six months, standard mean difference -0.56, $p = 0.09$, 95% CI -1.20 to 0.08, $I^2 = 73\%$) follow-up in synthetic bone grafts. Secondary outcomes included mechanical alignment, limb functionality, and defect site pain at long-term follow-up, perioperative blood loss, duration of surgery, occurrence of surgical site infections, and secondary surgery. Mean blood loss was lower (90.08 ml, $p < 0.001$, 95% CI 41.49 to 138.67) and surgery was shorter (16.17 minutes, $p = 0.04$, 95% CI 0.39 to 31.94) in synthetic treatment groups. All other secondary measures were statistically comparable.

Conclusion

All studies reported similar methodologies and patient populations; however, imprecision may have arisen through performance variation. These findings supersede previous literature and indicate that, despite perceived biological advantages, autologous bone grafting does not demonstrate superiority to synthetic grafts. When selecting a void filler, surgeons should consider patient comorbidity, environmental and societal factors in provision, and perioperative and postoperative care provision.

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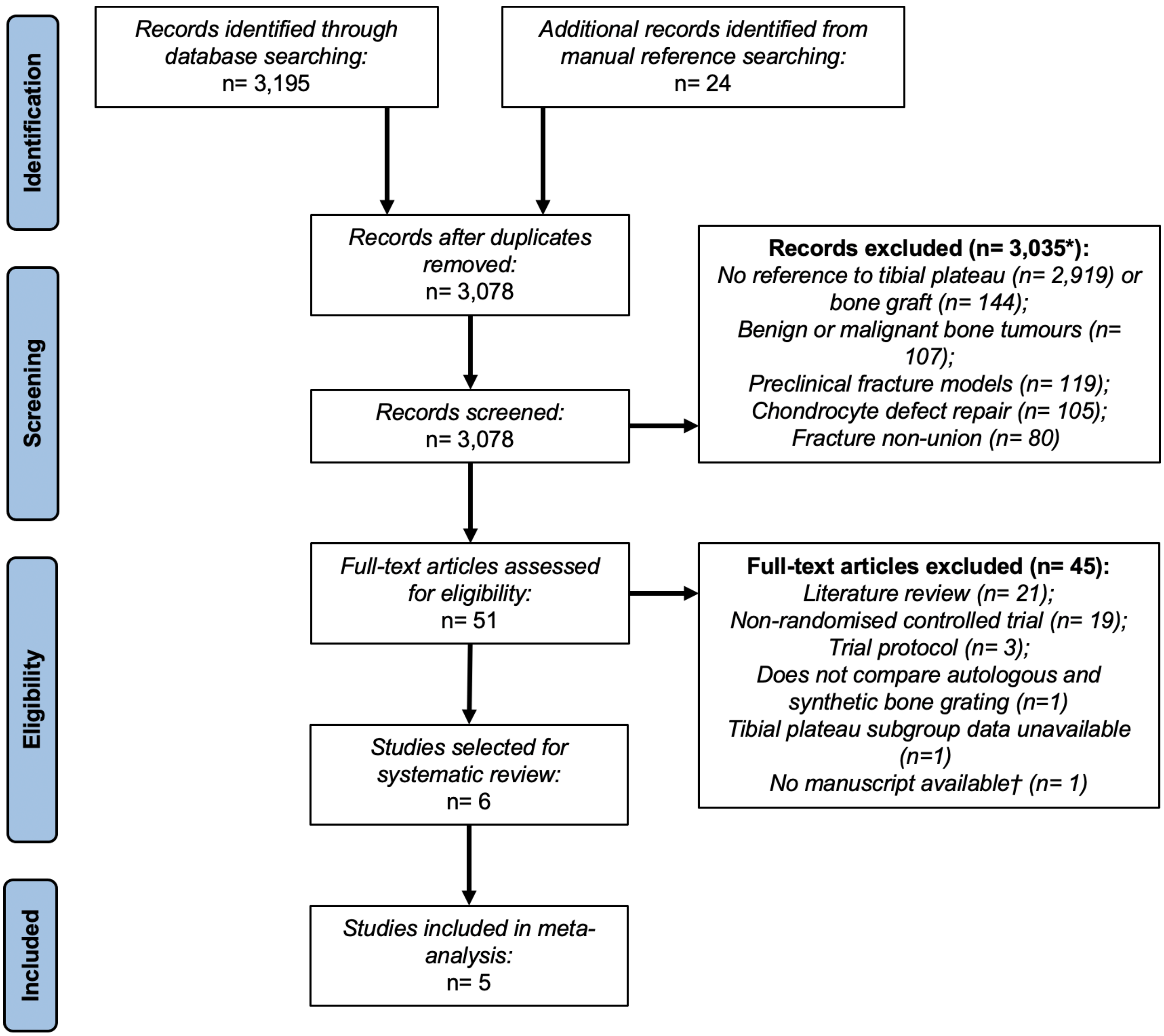

Fig. 1

A Preferred Reported Items for Systematic Review and Meta-Analyses flow diagram summarizing the selection of studies for systematic review and meta-analysis. Five studies were suitable for meta-analysis from 3,078 identified records. *Studies could be excluded for multiple reasons. †This conference abstract was excluded due to a lack of available data after contacting the corresponding author(s).

Introduction

Fractures of the tibial plateau, although relatively uncommon with a global yearly incidence of 10.3 per 100,000 people, have substantial and deleterious impacts on patients' quality of life.[1-3] Two distinct mechanisms of injury are observed: high-energy trauma in younger patients and low-energy trauma in osteopenic patients.[1-3] In both settings, there is significant risk of malunion, early osteoarthritis, and deep infection, which is severely debilitating in younger patients.[4-6]

Classification of tibial plateau fracture patterns, most commonly with Schatzker or AO/OTA nomenclature, indicate the degree of anatomical stability, and thus inform management strategies.[6-10] The span of injury patterns, both bony and soft-tissue, results in a wide variety of treatment methods and outcomes. Operative managements of complex fractures (AO/OTA 41 C1,2,3; Schatzker IV-VI) include uni-/bicondylar fixation, arthroplasty, or external fixation in soft-tissue injury.[6,9,11-13] Treatment seeks to achieve a stable, mechanically aligned leg with restoration of the joint surface.[2,3] Subsequently, in these complex fractures, bone grafting may support this reduction.[3]

Bone grafting is indicated to augment the open reduction and internal fixation of intra-articular tibial plateau fractures, improving the mechanical environment and promoting bone growth within the fracture defect void.[14-16] Historically, autologous bone grafting

Table I. Summary characteristics of randomized controlled trials included in meta-analysis and systematic review.

	Study setting			Patient population (treatment group, control group)					Treatment groups		
Study name	**Period**	**Country**	**Study centres, n**	**Patients, n**	**Tibial plateau fractures, n**	**Mean patient age, yrs (SD)**	**Patient sex, n (% female)**	**Mean follow-up, mths (SD)**	**Treatment void filler**	**Control void filler**	**Outcomes included in review**
Bucholz et al (1989)[31]	1981 to 1985	USA	1	20, 20	20, 20	37.5 (N/A), 36.7 (N/A)	9 (45), 7 (35)	34.5 (N/A), 15.4 (N/A)	CPC	ABG (Cancellous)	A, D, E
Russell et al (2008)[32]	1999 to 2002	USA, Canada	12	119	82, 38	43.0 (N/A), 43.0 (N/A)	46 (39)	12* (N/A)	CPC	ABG (Anterior Iliac Crest)	B, C, D, E
Heikkilä et al (2010)[33]	1995 to 1999	Finland	1	14, 11	14, 11	57.0 (N/A), 50.0 (N/A)	7 (50), 6 (55)	12* (N/A)	BG	ABG (Anterior Iliac Crest)	A, B, C, G
Pernaa et al (2011)[34]	1995 to 2010	Finland	1	5, 10	5, 10	52.0 (N/A), 58.0 (N/A)	8 (53)	132 (N/A)	BG	ABG (Anterior Iliac Crest)	A, B, C, D, F
Jónsson and Mjöberg (2015)[35]	2008 to 2012	Sweden	1	11, 9	11, 9	48.7 (19.3), 49.4 (15.5)	6 (55), 5 (56)	12*	PTG	ABG (Unspecified)	A, B, D, E, F, H
Hofmann et al (2019)[36]	2013 to 2017	Germany	20	65, 68	65, 68	47.0 (12.4), 46.3 (11.2)	36 (55%), 39 (57%)	6*	Biphasic CPC and CSC	ABG (Anterior Iliac Crest)	B, C, D, G, H

Bucholz et al's[31] patient population was younger and, along with Russell et al,[32] proportionally less female, although these differences were not substantial.
*Where mean duration of follow-up was not reported, the maximum per-protocol follow-up was reported instead.
A, postoperative articular depression; ABG, autologous bone graft; B, articular depression at long-term follow-up; BG, bioactive glass granules; C, mechanical alignment at long-term follow-up; CPC, calcium phosphate cement; CSC, calcium sulphate cement; D, frequency of surgical site infection at tibial defect site; E, frequency of secondary surgical interventions; F, defect site pain at long-term follow-up; G, perioperative blood loss; H, duration of surgery; HA, hydroxyapatite; N/A, not available; PTG, porous titanium granules.

(ABG), typically from the anterior iliac spine, has been preferred given its proposed structural and osteogenic properties.[14]

However, this intervention is not without significant complication profiles, both at the recipient fracture site and the site of bone graft harvest.[17,18] Additional donor site morbidity is associated with an 8.6% risk of major complications, including infection and reoperation.[18] Furthermore, following anterior iliac spine graft harvesting, approximately 40% of patients will still suffer from pain six-months postoperatively.[19]

Subsequently, interest in synthetic bone graft substitutes has increased over recent decades, underpinned by translational research into advanced, bioengineered, biomaterials.[20] Animal studies have demonstrated the biomechanical superiority of calcium phosphate cements relative to cancellous ABG in maintaining the reduction of depression following intra-articular tibial plateau defects.[21] Cadaveric studies corroborate this biomechanical advantage, demonstrating improved stiffness and decreased displacement in synthetic bone grafts.[22] Despite the perceived advantages of an improved mechanobiological environment and no donor site morbidity, to date there is limited high-quality clinical evidence to warrant the perceived additional costs of synthetic grafts.

This meta-analysis aims to assimilate the relevant high-quality randomized controlled trials (RCTs) to ascertain whether ABGs demonstrate clinical superiority to synthetic bone grafts in the management of tibial plateau fractures.

Methods

Protocol and registration. This systematic review and meta-analysis was undertaken in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[23] guidance and the Cochrane Handbook for Systematic Reviews of Interventions.[24] The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database on 7 September 2021 (accessible under CRD42021270073). Ethical approval and informed consent were not required for this research.

Eligibility criteria. Eligibility criteria were considered with respect to the population, intervention, comparator, outcome and study design (PICOS) framework.[24] We interrogated reported populations of tibia plateau fractures patients, to compare the use of synthetic bone substitutes with the standard of care ABG in RCTs.[16,17] Our primary outcome was postoperative articular depression. Secondary outcomes included mechanical alignment, satisfaction with reduction, return to functionality, perioperative blood loss, duration of surgery, defect site pain at long-term follow-up and frequencies of defect site infections and secondary surgical interventions.

In vitro or cadaveric experiments, and observational and non-randomized clinical studies were ineligible, ensuring the highest applicability to clinical practice. Studies investigating tibial plateau fractures in patients under 16 years old, benign or malignant bone tumours, or fracture nonunion were also excluded, as were studies exploring chondral defect repair.

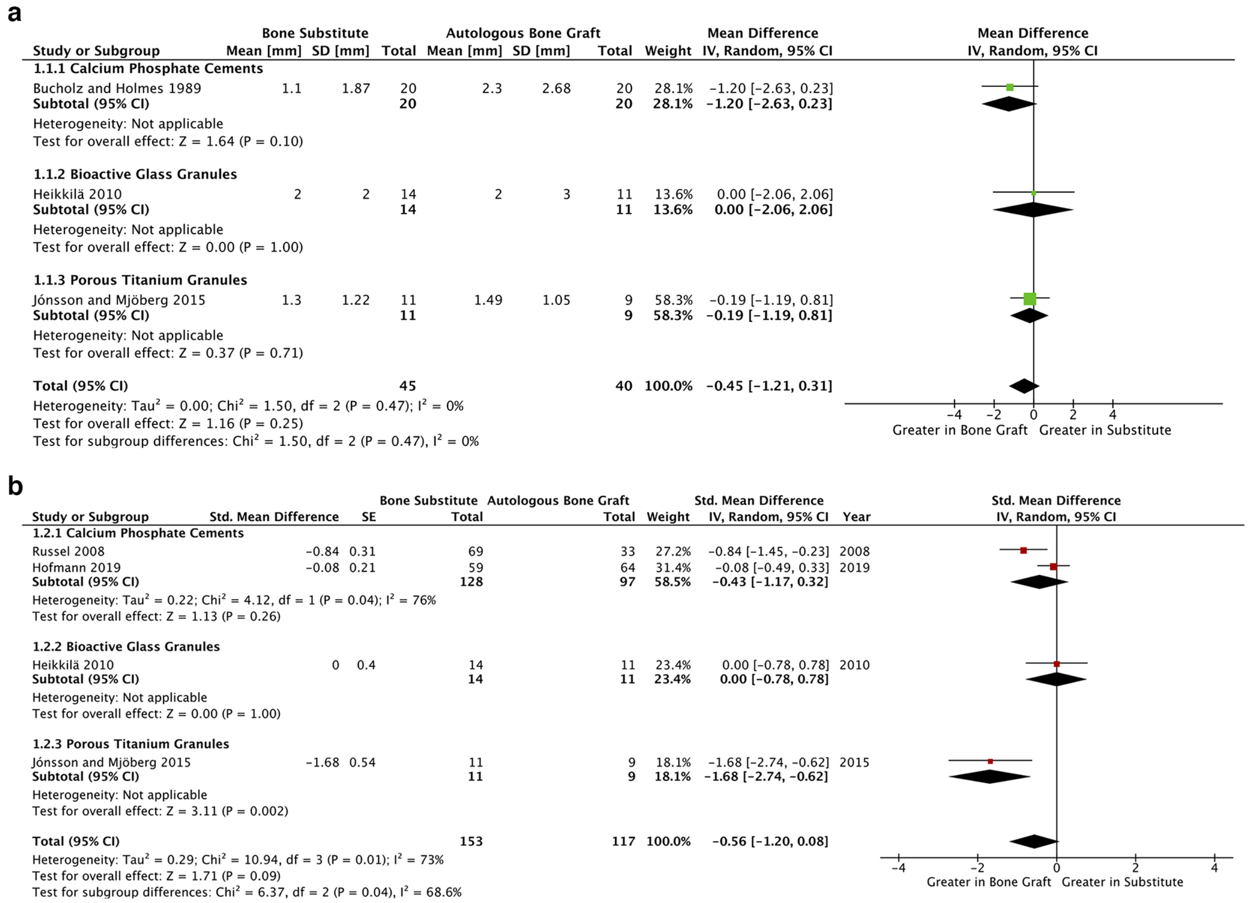

Fig. 2

a) Forest plot of postoperative articular depression outcome data. This figure presents a forest plot of articular reduction at postoperative follow-up, using data from three studies.[31,33,35] b) Forest plot of long-term articular depression outcome data. This figure presents a forest plot of articular reduction at long-term follow-up (≥ six months postoperatively). This panel includes data from four studies.[32,33,35,36] CI, confidence interval; IV, inverse variance; SD, standard deviation; SE, standard error.

We searched databases from their inception to 28 July 2021. When indicated, we requested manuscripts from non-English language publications and unpublished literature. These were only excluded if the corresponding authors did not respond.

Information sources and search strategy. Our search strategy (Supplementary Table i) was executed on the "MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations 1946 to July 28th, 2021", "EMBASE 1980 to 2021 Week 30", and "Cochrane Central Register of Controlled Trials" databases. This was augmented by a further Boolean search: "Tibia Plateau Fracture AND (Bone Substitute OR Bone Graft)" on the National Institute of Health Clinical Trials Registry and the Bone and Joint Database. Manual reference list screening was performed on all relevant reviews and included articles.

Study selection and risk of bias assessment. After deduplication, 3,078 records were screened by at least two reviewers (GC and MK). Disagreements between reviewers were resolved by the senior author (DS). Cohen's kappa was calculated to assess inter-rater reliability between reviewers.[25]

Risk of bias was assessed using the contemporaneous Cochrane Risk of Bias 2 (ROB2) tool.[26] The overall risk of bias was assessed for each set of outcome data included in our synthesis and was ascribed, according to its worst domain, as either low-risk, some concerns, or high-risk. High-risk outcome data were excluded from our synthesis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the certainty of each assimilated outcome.[27]

Data collection process, data items, and effect measures. Data relating to the primary and secondary outcomes was extracted from each article under the observation of at least one other author. Where necessary, any further or missing outcome data was requested from corresponding authors. We sought further descriptive population-level values for study treatment groups (e.g. sample size, mean patient age, and proportion of female sex) and to capture possible ascertainment biases and indicate sources of heterogeneity.

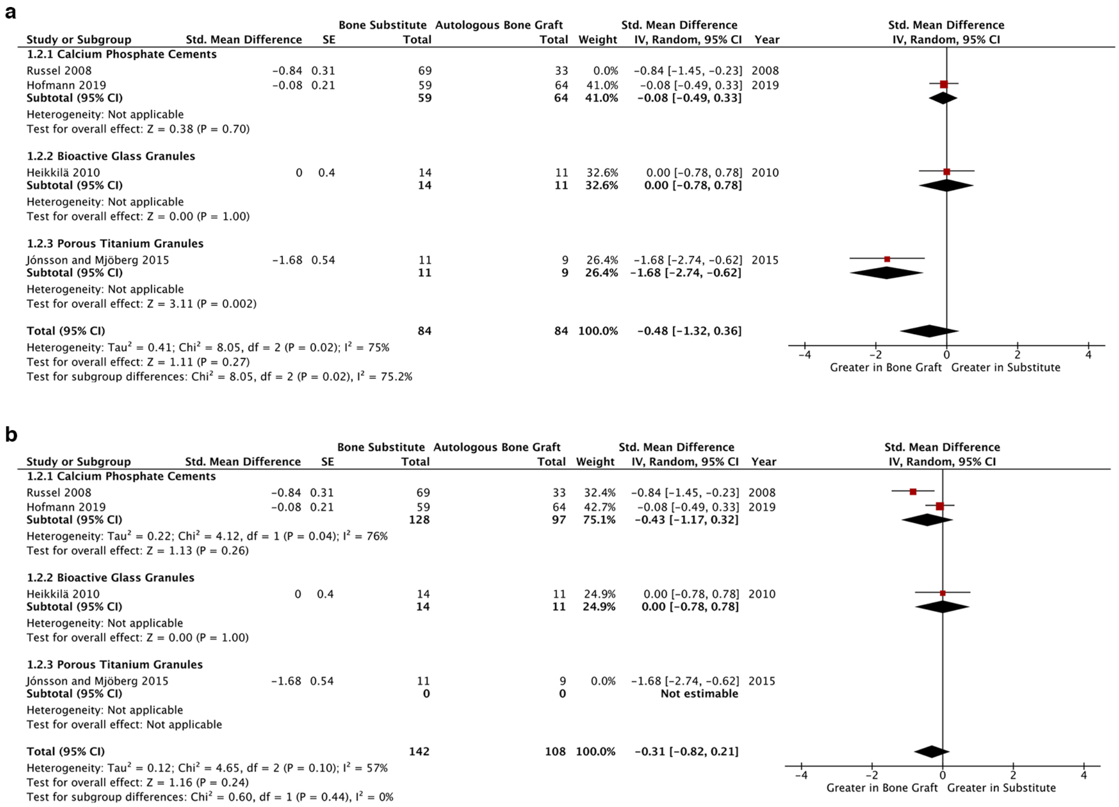

Fig. 3

a) Sensitivity analysis of Figure 2b exploring the impact of Russell et al's[32,33,35,36] reported effect sizes in contributing heterogeneity within the long-term articular reduction outcome. b) Sensitivity analysis of Figure 2b exploring the impact of Jónsson and Mjöberg's[32,33,35,36] reported effect sizes in contributing heterogeneity within the long-term articular reduction outcome.CI, confidence interval; IV, inverse variance; SE, standard error.

We defined the immediate postoperative period as any time within the contiguous two weeks and long-term follow-up, as the last reported measurements, taken at least six months postoperatively.

Continuous outcomes were directly compared by mean difference and 95% confidence intervals (CIs). Similarly, discontinuous outcomes were compared by calculating odds ratio (OR) and 95%CIs.

Where outcomes were reported as continuous or discontinuous measurements between studies, we contacted the authors for continuous outcome data. If necessary, standard mean differences (SMD) and corresponding standard error (SE) of discontinuous outcome data were calculated from ORs and 95% CIs using Chinn's method.[28] This approach is recommended by the Cochrane Handbook for Systematic Review of Intervention and summarized in Supplementary Methods 1.[28] Where necessary, standard deviation (SD) was imputed from sample range value using Wan et al's[29] adaptive method, outlined in Supplementary Methods 2.

Statistical analysis. Pairwise meta-analyses were performed using an inverse-variance, random effects model. The corresponding forest plots were generated using Review Manager v. 5.4 (The Cochrane Collaboration, UK).[30]

Heterogeneity was assessed according to the I^2 statistic. Post-hoc sensitivity analysis was indicated in assimilations of three or more studies, where heterogeneity was, at least, moderate ($I^2 > 30\%$).[24]

A prespecified subgroup was assembled from synthetic, calcium phosphate cement (CPC), substitutes. Post-hoc, we identified bioactive glass granule and porous titanium granule subgroups. Subgroup analyses were also conducted in Review Manager 5.4 using the X^2 function.[30]

Results

Following de-duplication, 3,078 records were identified. After screening and manuscript assessment, six studies were initially identified in our review (Figure 1).[31-36] Inter-rater reliability indicated substantial agreement (Cohen's k = 0.72).[26] Additional information on almost-eligible studies is presented in Supplementary Results 1.

The selected RCTs represent 353 fractures across 352 patients from 1989 to 2019.[31] One study was set in the USA, one in both Canada and the USA, and four across Northern or Central Europe (Table I). Study populations and treatment arms were directly comparable.[31-36]

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI	Year
2.1.1 Calcium Phosphate Cements					
Russel 2008	−0.55	0.79	5.3%	−0.55 [−2.10, 1.00]	2008
Hofmann 2019	−0.24	0.21	75.0%	−0.24 [−0.65, 0.17]	2019
Subtotal (95% CI)			**80.3%**	**−0.26 [−0.66, 0.14]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.70); $I^2 = 0\%$					
Test for overall effect: Z = 1.28 (P = 0.20)					
2.1.2 Bioactive Glass Granules					
Heikkilä 2010	−0.28	0.41	19.7%	−0.28 [−1.08, 0.52]	2010
Subtotal (95% CI)			**19.7%**	**−0.28 [−1.08, 0.52]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.68 (P = 0.49)					
Total (95% CI)			**100.0%**	**−0.26 [−0.62, 0.09]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0\%$					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$					

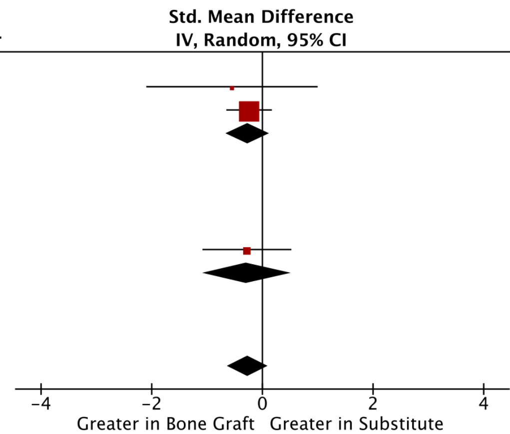

Fig. 4

Forest plot of mechanical alignment outcome data, comparing the tibiofemoral angle of injured/uninjured lower limbs from patients in three studies.[32,33,35] CI, confidence interval; IV, inverse variance; SE, standard error.

Study-specific sources of bias and reporting biases. Following risk of bias assessments (Supplementary Table ii), we excluded Pernaa et al[34] from our meta-analysis. This paper presented mean 11-year follow-up data of Heikkilä et al.[33] However, it included a substantive loss of subjects to follow-up (approximately 50%), which exacerbated attrition bias.[33,34] Thus, our study selection process identified five studies (comprising 338 fractures) suitable for meta-analysis (Figure 1).

Following patient randomization according to the date of presentation, the unblinded nature of Bucholz et al[31] represents clear loss of allocation concealment, introducing concerns around ascertainment biases.[26] Despite this, the baseline characteristics of both groups were highly comparable, indicating researchers' equipoise and limiting the magnitude of these concerns.

Both Hofmann et al[36] and Russell et al[32] reported partial or complete missing data in approximately 15% of patients randomized. These were primarily attributed to loss to follow-up. Given the challenges associated with maintaining patient engagement in large surgical trials, we did not feel these indicated a particular risk of bias.[26,32,36] The small number of studies precluded assessment of publication bias with Egger's test.[24] The certainty of each synthesized outcome, as determined by the GRADE framework, is presented in Supplementary Table iii.[27]

Articular depression and mechanical alignment. All RCTs included in our synthesis reported on articular reduction, which was measured with anteroposterior radiographs.[31-33,35,36] An absence of statistically improved reduction was observed by three studies at immediate postoperative follow-up, with pooled analysis observing a non-significantly smaller malreduction with the use of synthetic grafts (mean difference -0.45 mm, p = 0.25, 95% CI -1.21 to 0.31, $I^2 = 0\%$, Figure 2a).[31,33,35] Bucholz et al[31] was the only study included in this outcome analysis without a low overall risk of bias. Here, some concerns were attributed to the ascertainment of treatment groups and uncertainty as to whether radiological outcome data collection was blinded.[26]

When comparing synthetic grafting to ABG, a statistically non-significant improvement in articular reduction was observed in long-term (> six months) follow-up analysis of four studies, each with low overall risks of bias (SMD -0.56, p = 0.09, 95% CI -1.20 to 0.08, $I^2 = 73\%$, Figure 2b).[32,34-36] Sensitivity analyses (Figures 3a and 3b) implicate both Russell et al[32] and Jónsson and Mjöberg's[35] reported effect-sizes in the heterogeneity of this outcome.

Pernaa et al[34] reported mean postoperative articular depression of 1.4 mm (0 to 2) in the bioactive glass and 1.6 mm (0 to 5) in the ABG groups, respectively. Similarly, at final follow-up (mean 11 years; 10 to 14), articular depression was 1.4 mm (0 to 2) and 1.4 mm (0 to 4) in the bioactive glass and ABG groups; indicating, despite its high risk of bias, extended long-term efficacy of bioactive glass void filler.[26,33,34]

Mechanical alignment at long-term follow-up was compared radiologically in three studies, demonstrating insignificant differences in alignment when compared to the other leg using weightbearing, anteroposterior radiographs (SMD -0.26, p = 0.15, 95% CI -0.62 to 0.09, $I^2 = 0\%$, Figure 4).[32,33,36] This finding correlates with Pernaa et al,[34] which reported no significant mean contralateral (affected/unaffected knee) differences in the tibiofemoral angle in the bioactive glass and ABG groups. All studies assimilated in this outcome had a low overall risk of bias. Overall certainty in the quality of these three outcomes was high, according to our GRADE analysis (Supplementary Table iii).[27]

Anticipated adverse events. Defect site pain at long-term follow-up was extracted from three studies.[31,33,35] Two of these studies had had high overall risks of bias,

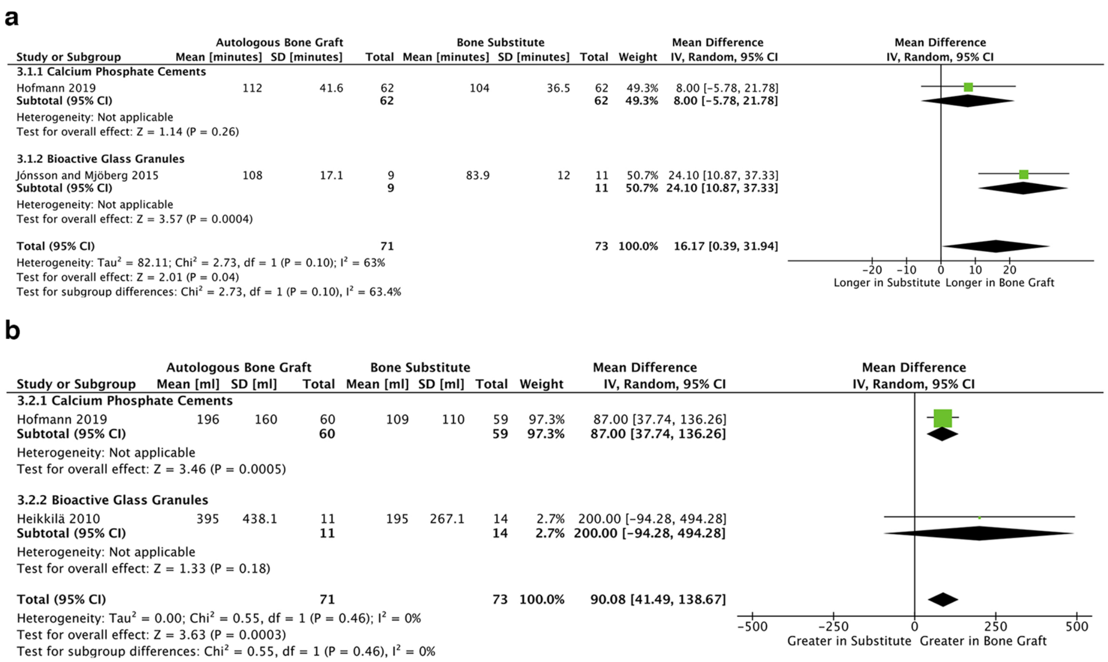

Fig. 5

a) Forest plot of reported duration of surgical procedures (from incision to suture time) within two studies.[35,36] b) Forest plot of reported perioperative blood loss (collected during surgery) from two studies.[33,36] CI, confidence interval; IV, inverse variance; SD, standard deviation.

so were excluded from the synthesis. Pernaa et al[34] (bioactive glass: mean 0.4; ABG: mean 1.0, using a ten-point visual analogue scale) reported little difference. Bucholz et al[31] was also excluded from this outcome synthesis as there was no reported methodology for measuring defect site pain at long-term follow-up, introducing high risk of information biases. However, this study too reported little difference when comparing synthetic and ABG interventions (OR 0.78, p = 0.72, 95% CI 0.19 to 3.13).

Jónsson and Mjöberg[35] identified a non-significant signal for reduced long-term defect site pain between synthetic substitutes and ABG (OR 0.34, p = 0.27, 95% CI 0.05 to 2.26). Overall certainty in this outcome was moderate (Supplementary Table iii), following the relative imprecision in the context of the demonstrable patient impact, and additional concerns of information biases arose following unblinded data collection; however, these concerns were limited by an acceptable, standardized methodology.[26,27,35]

Small but statistically significant reductions in duration of surgery and blood loss were observed. Assimilation of two studies identified this reduction in surgery duration (mean difference 16.17 minutes, p = 0.04, 95% CI 0.39 to 31.94, I^2 = 63%, Figure 5a).[35,36] Similarly two different studies identified the reduction in blood loss (mean difference 90.08 ml, p < 0.001, 95% CI 41.49 to 138.67, I^2 = 0%, Figure 5b).[33,36] All studies synthesized for these two outcomes showed low risk of bias in their respective outcomes.[26] Overall certainty in the quality of both these outcomes was high, according to our GRADE analysis (Supplementary Table iii).[27]

Unanticipated adverse events. A synthesis of four studies accumulated data on 294 fractures, giving an overall surgical site infection rate of 2.7% (8/294) (Figure 6a).[31-33,36] Pooled analysis revealed no difference between substitutes and ABG (OR 0.72, p = 0.58, 95% CI 0.18 to 2.94, I^2 = 0%). In Pernaa et al,[34] one patient in the ABG group developed a mild wound infection but none did from the bioactive glass group (OR 0.63, p = 0.79, 95% CI 0.02 to 18.37), showing no significant difference from the consensus of analyzed literature.

Three studies (representing 174 fractures) comprehensively reported secondary surgical interventions throughout their follow-up period (Table I), which are summarized in Supplementary Table iv.[31,32,36] These showed a combined occurrence rate of 4.3% (7/164) and a statistically non-significant signal towards increased frequency in patients receiving ABG, relative to the synthetic bone substitute group (OR 0.66, p = 0.53, 95% CI 0.13 to 3.34, I^2 = 0%, Figure 6b). Noticeably, Russell et al[32] reported no secondary surgical interventions in both treatment groups, and thus this studies effect size could not be estimated or assimilated.

In both outcomes, the concerns around population ascertainment in Bucholz et al[31] were the only potential risks of bias identified.[32,33,35,36] Following outcome imprecision, in the context of demonstrable patient impact, overall certainty in the quality of both frequency of surgical site infection and secondary surgical

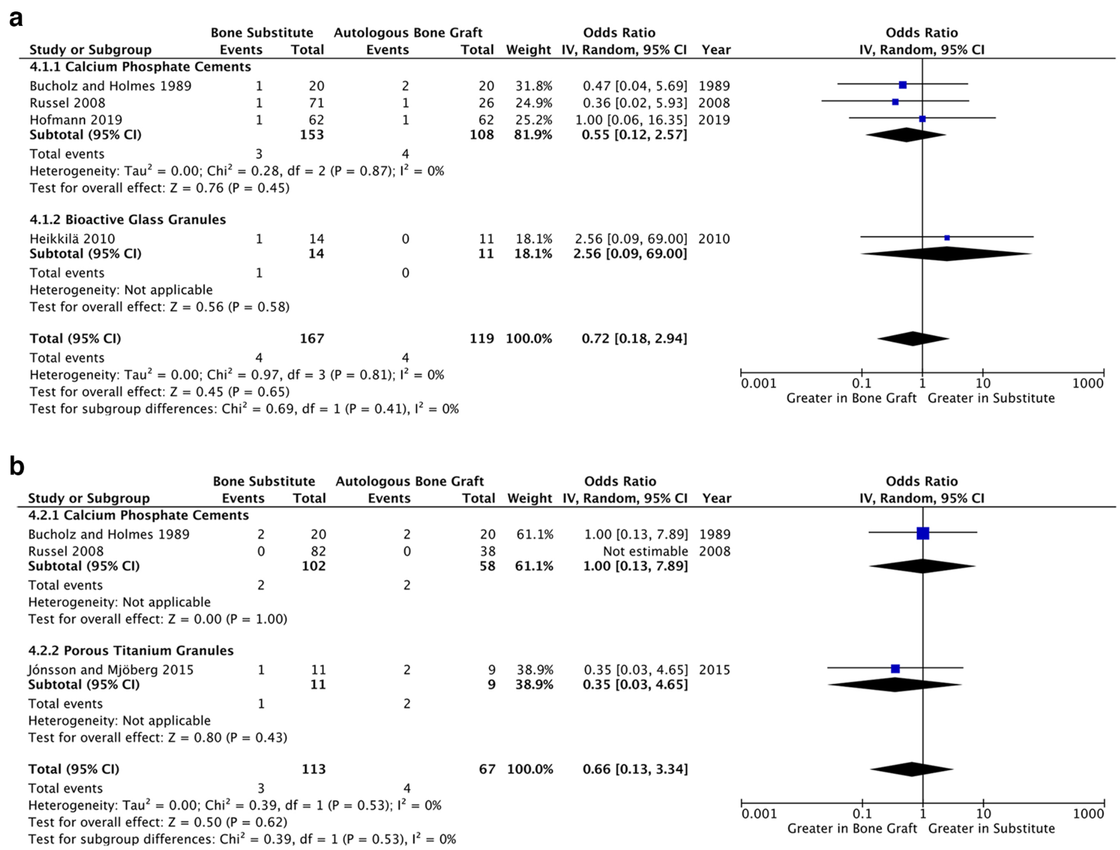

Fig. 6

a) Forest plot of reported surgical site infections in four study cohorts.[31-33,36] b) Forest plot of unanticipated secondary surgical interventions in three study cohorts.[31,32,35] CI, confidence interval; IV, inverse variance.

interventions outcomes was moderate, according to our GRADE analysis (Supplementary Table iii).[27]

Limb functionality. Heterogeneity arising from several measures of limb functionality precluded comparisons of this domain. Bucholz et al[31] reported total return to employment in both ABG and synthetic study arms (20/20, n = 20). Russell et al[32] identified no statistical differences in either knee flexion and extension at both six- and 12-month follow-up. Heikkilä et al[33] and Pernaa et al[34] present patient reported satisfactions at long-term follow-up. We elected not to synthesize these measures, given the overlapping patient groups and high attrition in Pernaa et al.[34] Furthermore, both patient populations were unblinded, introducing possible information biases. Both studies reported no significant differences in “Excellent” results (Heikkilä et al[33] OR 0.90, p = 0.90, 95% CI 0.18 to 4.41; Pernaa et al[34] OR 7.00 p = 0.26, 95% CI 0.24 to 206.80) between ABG and synthetic grafts.

Jónsson and Mjöberg[35] found no significant difference in Lysholm knee score at 12 months between ABG and synthetic grafts (mean difference 2.920, p = 0.65, 95% CI -10.2465 to 16.0874). Finally, Hofmann et al[36] graphically presented quality of life and functionality using the 12-item short form survey (SF-12) mental and physical component summaries, respectively. Although these data could not be extracted, no clinically or statistically significant difference between synthetic and ABG treatments were observed.[36]

Discussion

While it is widely accepted that open reduction and internal fixation of complex tibial plateau fractures is the gold standard for management, it is often assumed that the presence of a metaphyseal void mandates immediate surgical intervention with void filler.[6,11,15–18,32,37,38] However, biomechanical studies do not replicate the evolving scenario seen with fracture healing, and there remain no quality in vivo experiments that replicate the biomechanics of a bipedal plateau void.[39]

Historically, ABG has been considered the preferred defect void filler, given its proposed satisfaction of ideal biological, mechanical, and economic criteria for bone grafts.[14–16,31,40–43] However, harvesting ABGs imparts additional morbidity.[17–19,44] Structural concerns surround the relatively low density of cancellous iliac bone, exacerbating resorption in acute injury and impairing the maintenance of reduction.[45] Furthermore, a recent systematic review concluded that, despite ongoing research, there is currently insufficient evidence to elucidate the utility of biologically active bone grafts in fracture healing.[46]

Indeed, consensus indicates that synthetic bone grafts may provide a viable alternative void filler in the setting of tibial plateau fractures.[31–37,40,47–49]

This meta-analysis represents the most contemporary synthesis of high-quality (Oxford Centre for Evidence-Based Medicine, OCEBM, Level 1), randomized-controlled literature comparing synthetic and autologous bone grafts for tibial plateau fractures, and supersedes a previous systematic review containing lower-level literature.[40,50] The primary outcomes of this analysis indicate non-significant signals towards increased accuracy of initial surgical reduction and the preservation of articular reduction at the long-term (> six months) follow-up period, when comparing synthetic and autologous grafts. This is consistent with the limited mechanical characteristics of ABGs, relative to synthetic grafts in preclinical literature.[51,52]

The substantial heterogeneity ($I^2 = 73\%$) in long-term articular reduction was driven by two factors. Firstly, a large magnitude of effect attributed to titanium granules perhaps indicates resilience towards early resorption.[35] Secondly, despite both being pragmatic, comparable RCTs, Russell et al[32] and Hofmann et al[36] reported inconsistent estimates of the effect of CPC compared to ABG on long-term articular reduction. However, Russell et al[32] followed patients 12 months postoperatively, while Hofmann et al's[36] final follow-up was six months postoperatively. Consequently, this potentially masks the true effect size in our observed findings.

Small but significant improvements in duration of surgery and blood loss were observed in synthetic bone grafts, relative to ABGs, when measured. The magnitude of these (16.17 minutes and 90.08 ml) are consistent with graft harvesting in previous literature.[17–19,45,53] The heterogeneity identified in duration of surgery may arise from differences in study setting, including procedural familiarity and local incidences between the single-centre in Jónsson and Mjöberg,[35] and the multicentre Hofmann et al.[36] Alternatively, it may indicate greater simplicity in the application of titanium granules relative to biphasic calcium phosphate and sulphate cements.[35,36] Regardless, these findings have implications for contemporary practice, representing marginal but statistically significant gains in perioperative morbidity and, in this context, demonstrating the non-inferiority of synthetic grafting. Blood loss is a key surgical morbidity, and reduced duration of surgery impacts provision of both orthopaedic and anaesthetic services, especially given widespread increased systemic pressures around the COVID-19 pandemic, the additional morbidity associated with prolonged anaesthesia, and environmental concerns surrounding inhaled anaesthetics.[54–57]

Three studies reported on mechanical alignment, which may be predictive of impaired long-term functionality and subsequent development of osteoarthritis, at follow-up, and concluded there was no difference in alignment between synthetic and autologous bone grafts.[32,33,35,47,58] Functional outcome data in our evidence base was limited and showed no preference for synthetic or autologous bone grafts. There were non-significant differences in measured adverse event outcomes – specifically pain – frequency of surgical site infection, or in adverse events that required secondary surgery, which favoured synthetic rather than autologous grafts. Subsequently, we could not observe statistical divergence in the adverse event profiles of the graft types we explored; however, delayed synthetic graft resorption might be reasonably expected in synthetic bone graft subtypes.[20,59]

Despite its importance to patients and prominence in epidemiological literature, there was limited high-quality reporting of long-term defect site pain.[1-5,31,34,35] Measures of patient-reported functional outcomes and quality of life, which are at the core of contemporary orthopaedic research, were highly heterogenous in our evidence base and thus limited assimilation.[60] Furthermore, there is a noticeable lack of outcome data beyond 12 months and cost-benefit analyses, limiting comparison of these treatments in these contexts. These shortcomings indicate the need for a further, large-scale, pragmatic RCT in this setting to consolidate these limitations in the literature. In the setting of advancing synthetic graft materials and the adverse effects of autologous grafting, researchers may also seek to compare osteosynthesis using synthetic grafts versus fixation alone.[17-20,59,61,62] In this case, it will be important for the pragmatic design of this trial to optimize the selection of .

It should not be concluded that synthetic void fillers are superior to ABGs. Instead, we suggest that the biological attributes of ABG provide little measurable benefit to tibial plateau fracture patients. There are several key limitations to our study. As with many RCTs, there is often an unseen selection bias which can be compounded by meta-analysis.[61] In this case, patients are more likely to be included in trials who have larger defect voids and more complex fracture patterns. Consequently, while these results are not likely generalizable to the wider setting of tibial plateau fractures (where bone grafting is less frequently indicated), this self-selection may act to limit variation in fracture patterns within study populations, thus maintaining the internal validity of this review.[3]

Furthermore, surgeons with a certain preference or familiarity with a particular graft may introduce performance biases.[63] Additionally, postoperative variation arises between geographical and temporal variance in rehabilitation pathways, and the psychosocial and economic factors determining patient engagement within these pathways introduce heterogeneity when comparing long-term outcomes. However, sampled study population samples were drawn from more economically developed countries.[31-36] While limiting the applicability of study findings to patients in less economically developed countries, this contributes to homogeneity when comparing studies in this synthesis. Furthermore, all but one study was actively recruiting patients between 1999 and 2009, this temporal distribution again supporting internal validity.[31-36]

Although sampling databases from inception, and thus including Bucholz et al,[31] may have introduced some historical practice variation, this study explored hydroxyapatite as a synthetic bone graft, which is still used contemporaneously.[64,65] Finally, a wide variety of graft options have been included in this review, possibly introducing heterogeneity to the synthetic treatment group. These factors, in combination with our small number of assimilated studies, may limit the power of our analysis and increase exposure to publication bias. However, pragmatically, this synthesis still presents the highest quality (OCEBM, Level 1) evidence in this setting.[50,63]

In conclusion, this meta-analysis challenges the longheld paradigm that the gold standard for void management in tibial plateau fractures is ABG.[14-16] Our findings indicate that if a surgeon selects a synthetic bone graft to supplement fixation of a tibial plateau fracture, they can expect an equivalent accuracy of initial reduction and maintenance of long-term reduction, alongside minor reductions in operating time and blood loss. Subsequently, in this setting, surgeons should select void fillers while considering patient morbidity and operating time in surgical care provision. However, future research is needed to elucidate the optimal method in the surgical management of bone voids in tibial plateau fractures.

Take home message

- This analysis challenges the accepted paradigm that autologous bone grafting provides the gold standard of care, relative to synthetic bone grafts, in the management of complex tibial plateau fractures.
- Small but statistically significant reductions in mean perioperative blood loss and mean operating time were associated with synthetic bone grafting, while maintenance of reduction, pain, functionality, and adverse event profiles were statistically similar between treatment groups.
- In the management of complex tibial plateau fractures, surgeons should select void-filler based on wider considerations such as patient multimorbidity and systemic factors.

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Supplementary material

The supplementary material contains additional information on our statistical methodology and outlines the literature search undertaken. It also summarises the excluded studies, the risk of bias evaluations (ROB2) of included studies and the certainty of evidence (GRADE) evaluation for synthesised outcomes. Finally, the complete list of adverse events from our literature sample is presented.

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