Vol. 7, No. 6, June 2026
E-ISSN:2723 – 6692 P-ISSN:2723– 6595
http://jiss.publikasiindonesia.id/

The Future of Non-Union Repair: Synthetic Bone Grafts as Biomaterial-Based Solutions for Human Fracture Healing

I Putu Oka Pramudya[1]*, Komang Adi Praja Semara Putra[2]
Universitas Hang Tuah Surabaya, Indonesia[1]
Universitas Mataram NTB, Indonesia[2]
Email: okapramu123@gmail.com[1]*, semaraputra9@gmail.com[2]

Keywords:
Biocompatible Materials; Bone Substitutes; Calcium Phosphates; Fracture Healing; Fractures.

Abstract

Fracture non-union remains a complex orthopedic problem that often requires both mechanical stability and biological augmentation. Synthetic bone grafts have emerged as biomaterial-based alternatives or adjuncts to autologous grafting because they are widely available, avoid donor-site morbidity, and can be engineered for Oste conduction, controlled resorption, and local drug delivery. This systematic literature review and proportional meta-analysis evaluated the types and clinical impact of synthetic bone grafts used in human fracture non-union and post-traumatic bone defect repair.

A systematic search of PubMed, Scopus, and Google Scholar was performed for English-language studies published from 2021 to 2026. Eligible studies included human clinical reports using hydroxyapatite, beta-tricalcium phosphate, biphasic calcium phosphate, calcium sulfate, bioactive glass, injectable bone cement, antibiotic-loaded grafts, or composite/3D-printed scaffolds. The primary outcome was union or consolidation proportion, with secondary outcomes including time to union, infection control, complications, reoperation, and functional recovery. From 6,665 records, 21 studies met the eligibility criteria. Synthetic grafts generally demonstrated favorable outcomes, with most studies reporting union rates above 75% and several achieving complete union. The pooled union efficacy from 15 quantitative observations was 90.4% (95% CI: 84.2–96.7%). However, heterogeneity was high (I^2 = 76.5%), reflecting variation in graft material, defect size, infection status, fixation strategy, and adjunct use. Synthetic bone grafts are promising osteoconductive scaffolds for fracture non-union repair, particularly as graft extenders, antimicrobial carriers, or patient-specific constructs. Nevertheless, their limited intrinsic osteogenic and Oste inductive capacity means they are best used with stable fixation and appropriate biological or antimicrobial augmentation.

INTRODUCTION

Fracture non-union remains one of the most challenging complications in orthopaedic trauma, reflecting a failure of the biological and mechanical processes required for normal bone healing. Although most fractures heal uneventfully, non-union still occurs in a clinically meaningful proportion of patients. The overall probability of non-union has been reported at approximately 1.9% per fracture, with rates increasing up to 9% in specific fracture types and

age groups, particularly tibial and clavicular fractures (Chmali et al., 2022; Jiang et al., 2022). Broader epidemiological data suggest an overall non-union rate of approximately 4.9–5%, with the highest rates observed in the scaphoid (15.5%), tibia and fibula (14.0%), and femur (13.9%) (Zargarbashi et al., 2021; Zhou et al., 2025). In long-bone fractures, reported non-union rates generally range from 5% to 10%, although estimates vary according to fracture location, injury severity, and patient characteristics (Ehrnthaller et al., 2024; Li et al., 2023; Rios et al., 2024; Smolinská et al., 2023).

The burden of non-union is particularly evident in long-bone fractures, open injuries, segmental bone defects, infection-related cases, and fractures associated with poor soft-tissue coverage or inadequate mechanical stability. The tibia is consistently recognized as one of the most vulnerable bones because of its subcutaneous location, limited soft-tissue envelope, and precarious blood supply (Morcovescu et al., 2024; Nicholson et al., 2021; Sidiropoulos et al., 2023). A systematic review and meta-analysis involving more than 41,000 patients with tibial fractures reported a pooled non-union prevalence of 6.8%, with higher risks associated with open fractures, high-energy mechanisms, infection, smoking, diabetes, and other patient comorbidities (Nicholson et al., 2021; Sidiropoulos et al., 2023). Open tibial fractures carry an even greater risk, with non-union rates reported at 14.1%, while fractures requiring soft-tissue reconstruction may demonstrate rates of approximately 10–22% (Burke et al., 2023; Castillo et al., 2023). Clinically, non-union is associated with persistent pain, impaired mobility, prolonged rehabilitation, repeated surgical procedures, delayed return to work, and reduced quality of life. Its economic burden is also substantial, with non-union reported to approximately double direct healthcare costs and reduce health-related quality of life to levels comparable with stroke (Alam et al., 2023; Flores et al., 2024; Roberts et al., 2021).

Effective treatment of fracture non-union therefore requires correction of both mechanical and biological deficiencies. Stable fixation and infection control remain fundamental, particularly in cases involving instability, open injury, or infected non-union (Marmor et al., 2021; Nicholson et al., 2021). However, biological augmentation is often required to restore the local healing environment, especially in atrophic non-unions, segmental defects, and biologically compromised fracture sites (Lu et al., 2025; Marmor et al., 2021; Mehta, 2025). Autologous bone graft has long been considered the gold standard for enhancing fracture repair because it provides osteogenic cells, Oste inductive growth factors, and an osteoconductive scaffold (Campanacci et al., 2021; Engel, 2025; Rodham et al., 2023). Nevertheless, its use is limited by donor-site morbidity, restricted graft volume, increased operative time, blood loss, and postoperative pain (Chua et al., 2024; Schmidt, 2021; Tokeshi et al., 2023). These limitations have encouraged the development of synthetic bone graft substitutes as biomaterial-based alternatives or adjuncts in non-union management.

The urgency of this research is underscored by the substantial clinical and economic burden of fracture non-union, the limitations of current treatment options, and the growing interest in biomaterial-based solutions that can overcome the shortcomings of autologous bone grafting. As the global population ages and the incidence of traumatic injuries and orthopaedic surgeries continues to rise, the need for effective, safe, and widely available bone graft substitutes has become increasingly pressing. Furthermore, the rising prevalence of antimicrobial resistance complicates the management of infected non-unions, highlighting the need for biomaterials that can deliver local antimicrobial therapy while supporting bone

regeneration. The novelty of this research lies in its systematic evaluation of the types and clinical impact of synthetic bone grafts in human fracture non-union, employing both qualitative synthesis and quantitative meta-analysis to provide a comprehensive overview of current evidence.

Commonly used synthetic bone grafts include hydroxyapatite, beta-tricalcium phosphate, biphasic calcium phosphate, calcium sulfate, bioactive glass, injectable bone cements, and composite biomaterials (Georgeanu et al., 2023; Mayfield et al., 2022; Valtanen et al., 2021). These materials are primarily designed to provide an osteoconductive scaffold for bone ingrowth, although some may also offer controlled resorption, local antibiotic delivery, structural support, or antimicrobial potential (Gallo et al., 2025; Georgeanu et al., 2023; Mayfield et al., 2022; Razii et al., 2023). In fracture non-union, synthetic grafts may help fill bone defects, preserve space for regeneration, support fixation, reduce dependence on autograft harvesting, and improve the local environment for union. However, their clinical effectiveness may vary according to graft composition, defect size, vascularity, infection status, fracture stability, and whether they are used alone or combined with autograft, bone marrow aspirate concentrate, antibiotics, or growth factors (Marmor et al., 2021; Nauth et al., 2023; Rodríguez-Merchán, 2022; Wier et al., 2025). Therefore, this systematic literature review aims to identify the types of synthetic bone grafts used in the treatment of fracture non-union in humans and to evaluate their clinical impact on union rate, time to union, functional recovery, infection control, complications, and reoperation.

METHOD

Study Design and Review Protocol

This study was conducted as a systematic literature review and proportional meta-analysis to evaluate synthetic bone grafts as biomaterial-based solutions for human fracture non-union and post-traumatic bone defect repair. The review focused on hydroxyapatite, beta-tricalcium phosphate, biphasic calcium phosphate, calcium sulfate, bioactive glass, injectable bone cement, antibiotic-loaded grafts, and composite or 3D-printed scaffolds. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The research question was developed using the PICO framework:

1. Population (P): Human patients with fracture non-union, delayed union, infected non-union, or post-traumatic bone defects.
2. Intervention (I): Synthetic bone grafts or biomaterial-based substitutes, including HA, β-TCP, BCP, calcium sulfate, bioactive glass, injectable bone cement, antibiotic-loaded grafts, and composite scaffolds.
3. Comparison (C): Autologous bone graft, allograft, standard surgical care, fixation alone, or no comparator in single-arm studies.
4. Outcome (O): Bone union or consolidation as the primary outcome, with secondary outcomes including time to union, infection eradication, functional recovery, complications, reoperation, and graft failure.

Eligibility Criteria

Studies were included if they reported clinical use of synthetic bone grafts in human fracture non-union, delayed union, infected non-union, or post-traumatic bone defects. Studies

with mixed grafting techniques were included only when the synthetic graft component was clearly described.

Table 1 Inclusion and Exclusion Criteria

Aspect	Inclusion Criteria	Exclusion Criteria
Study type	Original clinical studies, cohort studies, retrospective or prospective studies, case series, pilot studies, and case reports	Reviews, editorials, commentaries, letters, conference abstracts, and non-original articles
Population	Human fracture non-union, delayed union, infected non-union, post-traumatic bone defect, or segmental defect	Animal, in vitro, cadaveric, laboratory-only, or non-fracture-related studies
Intervention	Synthetic bone grafts, HA, β-TCP, BCP, calcium sulfate, bioactive glass, injectable cement, antibiotic-loaded grafts, or 3D-printed scaffolds	Autograft-only, allograft-only, xenograft-only, or biological therapy without synthetic scaffold
Comparator	Autologous graft, allograft, standard surgery, fixation alone, or no comparator	No clinically relevant comparator or unclear treatment approach
Outcomes	Union, consolidation, time to union, infection control, function, complications, reoperation, or graft failure	No relevant clinical outcome
Year	2021–2026	Published before 2021
Language	English	Non-English publications

Literature Search Strategy

A systematic search was conducted using PubMed, Scopus, and Google Scholar. Search terms included combinations of: “fracture nonunion”, “fracture non-union”, “delayed union”, “infected non-union”, “segmental bone defect”, “synthetic bone graft”, and “bone graft substitute”. The search was limited to English-language articles published from 2021 to 2026. After duplicate removal, titles and abstracts were screened, followed by full-text assessment using the eligibility criteria. Reference lists of eligible studies were also reviewed manually.

Data Extraction and Synthesis

Data were extracted using a standardized form. Extracted variables included author, year, study design, sample size, fracture site, type of non-union or bone defect, infection status, synthetic graft material, adjunctive treatment, fixation method, union outcome, time to union, infection eradication, complications, reoperation, and key findings.

Findings were synthesized narratively according to graft material, clinical indication, union outcome, infection control, and complications. A proportional meta-analysis was performed using union or consolidation proportion as the primary quantitative outcome. Union efficacy was calculated as:

$$\text{Union efficacy} = \frac{\text{union cases}}{\text{total cases}} \times 100\%$$

For studies with 100% union or zero failure events, continuity correction was applied:

$$\text{Corrected effect size} = \frac{\text{union cases} + 0.5}{\text{total cases} + 1}$$

The corrected effect size and standard error were used for meta-analytic estimation, while the raw union percentage was reported descriptively. Studies without extractable total cases and union events were included only in the qualitative synthesis. This method follows the article

focus on synthetic graft types and their clinical impact on union, infection control, complications, and reoperation in human fracture non-union.

RESULTS AND DISCUSSIONS

The systematic literature search identified a total of 6,665 records from three electronic databases: Scopus (n = 178), PubMed (n = 51), and Google Scholar (n = 6,436). During the identification stage, 6,200 records were excluded because they were duplicates (n = 1,558), not published within the predefined period of 2021–2026 (n = 3,614), not open access (n = 131), non-original research (n = 471), or abstract-only records (n = 426).

After this initial process, 465 records were screened by title and abstract. Of these, 293 records were excluded because they were not related to fracture non-union. A total of 172 full-text articles were then assessed for eligibility.

Following full-text assessment, 151 articles were excluded because they were in vivo/in vitro studies (n = 51), animal studies (n = 48), or model-based studies (n = 52). Finally, 21 studies met the eligibility criteria and were included in the final systematic review. These studies provided clinical evidence on the use of synthetic bone grafts and biomaterial-based scaffolds in human fracture non-union and post-traumatic bone defect repair, particularly regarding bone union, consolidation, infection control, functional recovery, complications, and reoperation. The study selection process is shown in Figure 1.

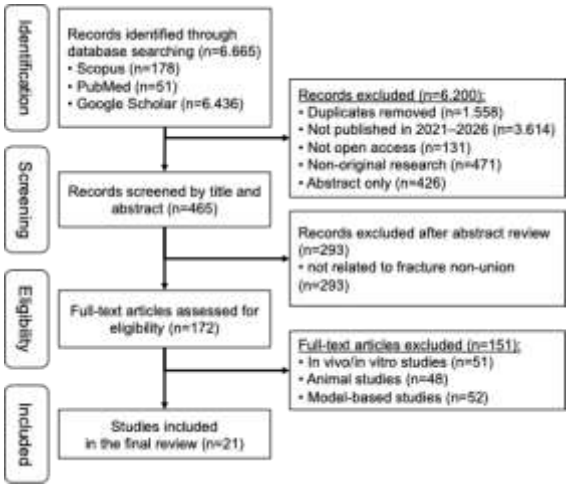

Figure 1 PRISMA Flow Diagram

Key Findings

Synthetic bone grafts generally showed favourable clinical outcomes in human fracture non-union and post-traumatic bone defect reconstruction, although results varied by graft type, defect size, infection status, and surgical technique. High union or consolidation rates were reported in several studies. Gerich et al. (2025) found that NVD003, combining adipose-derived stem cells with synthetic HA/TCP, achieved union in 89% (8/9) of adult lower-limb non-unions, with mean healing at 6 months. Kalantar et al. (2024) reported union in 5/5 distal femoral defect cases using synthetic graft mixed with autologous iliac graft, with mean union time of 159 days. Choi et al. (2024) and Caterini et al. (2016) reported 100% union using HA-based grafts combined with rhBMP-2 or rhBMP-7 and autologous bone, while Yang et al. (2022) found 100% healing within 3 months using a fully resorbable HA/calcium sulfate substitute.

In infected non-union and chronic bone infection, synthetic grafts also appeared useful as antimicrobial or antibiotic-carrying scaffolds. Van Vugt et al. (2021) reported 100% clinical consolidation and 100% infection eradication using S53P4 bioactive glass with BMAC in infected tibial non-unions. Yücel et al. (2025) found that silver ion-doped HAP–TCP achieved infection eradication and bone union in 91.7% (11/12) of patients within 3–6 months. Steinhausen et al. (2021) showed that S53P4 bioactive glass achieved complete healing in 77%, comparable to autologous graft at 78%, with faster full weight bearing, 5.9 vs 10.7 months. Aljawadi et al. (2022) also reported 98% fracture union with Cerament-G, including 86.3% primary union and 11.7% delayed union.

Composite and 3D-printed scaffolds showed promising but inconsistent outcomes, especially in large segmental defects. Laubach et al. (2022) reported successful reconstruction of large long-bone defects using patient-specific PCL/β-TCP or mPCL-TCP scaffolds combined with autologous graft, with fusion in 3/4 cases within 9 months in one cohort. However, Lodewijks et al. (2025) reported limited efficacy of PCL/TCP scaffolds in very large post-traumatic defects, with median defect size of 10.5 cm and failure in 50% (5/10) due to mechanical failure or persistent infection. Findeisen et al. (2025) also showed more modest results in large femoral and tibial defects, with consolidation reaching 64.3% within 2 years.

Several smaller studies and case reports supported the potential role of synthetic grafts as adjuncts rather than standalone substitutes. Siregar et al. (2021) reported complete union and good function in a 10 cm femoral defect where synthetic graft was used as an adjunct. Khanfar (2021) reported complete consolidation of talar neck non-union using BCP granules, while Thilak et al. (2024) showed long-term remodelling of an HA–bioactive glass composite into living lamellar bone after 14 years. Overall, the included studies suggest that synthetic bone grafts can support bone union, defect filling, infection control, and functional recovery, but their success is strongly influenced by biological augmentation, stable fixation, adequate vascularity, and defect complexity.

The included studies showed generally high union efficacy after synthetic bone graft or scaffold-based treatment. Most studies reported union rates above 75%, with several achieving 100% union. The highest corrected effect sizes were observed in studies with complete union, while the lowest efficacy was reported by (Lodewijks et al., 2025), with 50.0% union and an effect size of 0.50. Overall, the data suggest that synthetic bone grafts and biomaterial scaffolds may support bone union, although outcomes vary across defect size, infection status, scaffold type, and surgical technique.

Table 2. Pooled Union Efficacy Data

Name, Year	Total Cases	Union Cases	Failure Cases	Efficacy (%)	Effect Size	Effect Size Standard Error
Aljawadi et al., 2022	51	50	1	98.04	0.98	0.02
Steinhausen et al., 2021	51	39	12	76.47	0.77	0.06
Sambri et al., 2023	93	72	21	77.42	0.77	0.04
Gengatharan et al., 2024	35	35	0	100.00	0.99	0.02
Elnokeety et al., 2022	20	20	0	100.00	0.98	0.03
Giannoudis et al., 2025	14	14	0	100.00	0.97	0.05
Yang et al., 2022	14	14	0	100.00	0.97	0.05

Name, Year	Total Cases	Union Cases	Failure Cases	Efficacy (%)	Effect Size	Effect Size Standard Error
Yücel et al., 2025	12	11	1	91.67	0.92	0.08
Lodewijks et al., 2025	10	5	5	50.00	0.50	0.16
Gerich et al., 2025 (1)	9	8	1	88.89	0.89	0.11
Gerich et al., 2025 (2)	4	4	0	100.00	0.90	0.13
Laubach et al., 2022	4	4	0	100.00	0.90	0.13
Thilak et al., 2024	1	1	0	100.00	0.75	0.31
Ryu et al., 2021	1	1	0	100.00	0.75	0.31
Khanfar et al., 2021	1	1	0	100.00	0.75	0.31

Table 3. Article Data Extraction

Author, Year	Aim	Sample Size	Method	Key Findings
Gerich et al., 2025	Early clinical use of NVD003 for non-union and CPT.	13 patients	Phase 1b/2a prospective clinical study	NVD003, combining adipose-derived stem cells with synthetic HA/TCP, achieved union in 89% (8/9) adult lower-limb non-unions; mean healing was 6 months. All 4 CPT patients achieved lasting union without adverse events.
Kalantar et al., 2024	Modified Masquelet technique for distal femoral defects.	5 patients	Retrospective case series	Synthetic graft mixed with autologous iliac graft in a 3:1 ratio led to union in 5/5 patients, with mean union time of 159 days.
Laubach et al., 2022	Clinical translation of scaffold-guided bone regeneration.	4 cases	Clinical trial / case series	Patient-specific 3D-printed PCL/β-TCP scaffolds with autologous RIA graft achieved successful reconstruction of large long-bone defects; exact union rate was not reported.
Van Vugt et al., 2021	BMAC and S53P4 BAG for infected tibial non-unions.	5 patients	Retrospective case series	S53P4 bioactive glass with BMAC achieved 100% clinical consolidation and 100% infection eradicationin infected tibial non-unions with mean defect size of 4.6 cm.
(Rizvi et al., 2024)	Ilizarov technique for infected non-union and bone defects.	24 patients	Prospective observational study	Bone grafting, including alloplast/synthetic options, supported healing in defects averaging 5.67 cm; outcomes were 58.33% outstanding and 29.17% good.
(Siregar et al., 2021)	Femoral shaft defect reconstruction using fibular graft.	2 patients	Case series	Synthetic graft was used as an adjunct in a 10 cm femoral defect, achieving complete union, bridging callus, and good function at 80 weeks.
Choi et al., 2024	rhBMP-2, autologous bone, and HA	24 patients	Prospective case series	rhBMP-2 with autologous bone and HA granulesachieved 100% union

Author, Year	Aim	Sample Size	Method	Key Findings
	for long-bone nonunion.			at 12 months, with no adverse effects or BMP-2 antibody formation.
Caterini et al., 2016	Treatment of recalcitrant atrophic humeral non-union.	12 patients	Retrospective study	rhBMP-7, HA pellets, and autologous bone graftachieved 100% union, with mean healing time of 7.3 months and functional recovery.
Yang et al., 2022	Fully resorbable Ca/P/S-based synthetic substitute.	14 cases	Retrospective study	Ezechbone®/CBS-400 made of HA and calcium sulfate achieved 100% success, with all cases healed within 3 months.
Yücel et al., 2025	Silver-doped calcium phosphate graft for chronic bone infection.	12 patients	Retrospective cohort study	Silver ion-doped HAP–TCP achieved infection eradication and bone union in 91.7% (11/12) patients within 3–6 months.
Chloros et al., 2022	Masquelet technique for tibial nonunions and defects.	17 patients	Retrospective study	RIA autograft enhanced with Vitoss or BonAliveachieved 88.2% union (15/17) at a mean of 8 months.
Laubach et al., 2022	3D-printed scaffolds for large lower-extremity defects.	4 patients	Prospective pilot study	3D-printed mPCL-TCP scaffolds with autologous graft achieved fusion in 3/4 cases within 9 months; the BMP-2 case achieved bony fusion and hardware removal.
Findeisen et al., 2025	Diamond concept for large femoral and tibial defects.	70 patients	Retrospective descriptive analysis	Large nonunions with mean defect size of 6.77 cm were treated using Masquelet technique with Vitoss/TCP or Bioglass; consolidation reached 64.3% within 2 years.
Laubach M et al., 2022	Scaffold-guided regeneration for posttraumatic long-bone defects.	4 patients	Case study	3D-printed mPCL-TCP scaffolds showed bony ingrowth through pores >2 mm. One 10 cm tibial defect achieved comprehensive regeneration and full weight bearing at 23 months.
Lodewijks et al., 2025	PCL/TCP scaffolds with IMT for large posttraumatic defects.	10 patients	Retrospective cohort study	PCL/TCP scaffolds with autologous bone and BMAC showed limited efficacy in median 10.5 cm defects; failure occurred in 50% (5/10), requiring revision for mechanical failure or infection.
Herath et al., 2024	Patient-specific scaffold design for complex defects.	3 patients	Case study / technical validation	Custom 3D-printed mPCL-TCP scaffolds were used for femur and humerus defects; one included BMP-eluting collagen sponge. Numerical union rate was not reported.
Aljawadi et al., 2022	Cerament-G for fracture voids and local	51 patients	Retrospective data analysis	Cerament-G achieved 98% fracture union: 86.3%primary union, 11.7% delayed union, and 1.9% non-union. Trabecular void

Author, Year	Aim	Sample Size	Method	Key Findings
	antibiotic delivery.			healing >50% occurred in 90.5%; mean long-bone healing was 11 months.
Steinhausen et al., 2021	S53P4 BAG versus autologous graft in infected non-unions.	83 patients	Retrospective comparative study	S53P4 bioactive glass achieved complete healing in 77%, comparable to autologous graft (78%), with faster full weight bearing: 5.9 vs 10.7 months.
Sambri et al., 2023	PerOssal beads for chronic osteomyelitis defects.	93 patients	Retrospective multicenter cohort study	PerOssal composed of 51.5% HA and 48.5% calcium sulfate achieved complete defect filling in 37.9% and partial filling in 41.4% at 12 months; no pathological fractures occurred.
Thilak et al., 2024	HA ceramic matrix for critical-size cortical defect.	1 patient	Case report	Synthetic HA–bioactive glass composite with fibular autograft showed durable regeneration; at 14 years, the matrix became living lamellar bone and iso-dense with normal bone.
Ryu et al., 2021	Patient-specific crib cage for mandibular non-union/mal-union.	1 patient	Case report	A 3D-printed titanium crib cage with cellular allograft achieved bony healing, normal function, and no pain or infection at 7 months.
Giannoudis et al., 2025	b.Bone scaffold for iliac crest defect reconstruction.	15 participants	Prospective first-in-human trial	b.Bone HA scaffold loaded with Mg^{2+}/Sr^{2+} achieved complete radiological healing in 12/14 participants (85.7%) by 365 days, with 0% non-union and 0% implant failure.
Gengatharan, 2024	Synthetic substitutes versus autograft in distal radius fixation.	450 patients	Retrospective analysis	Calcium phosphate-based synthetic substitutes showed outcomes comparable to autograft, with 100% fracture union and average union time of 2 months.
Elnokeety et al., 2022	HTO with ACL reconstruction using synthetic graft.	20 patients	Prospective study	TUTOBONE® synthetic cancellous graft provided stable fixation and successful healing, with better mechanical support than β-TCP; exact union rate was not specified.
Khanfar, 2021	Synthetic graft for talar neck non-union.	1 patient	Case report	A 10-month talar neck non-union treated with BCP Bicalphos granules achieved complete consolidation in 1/1 patient (100%), full motion, and return to sports.

Meta-Analytic Findings on Union Efficacy of Synthetic Bone Grafts

The meta-analytic test (Table 4) showed a significant pooled effect, $t(14) = 31.01$, $p < 0.001$, indicating that synthetic bone grafts were associated with a statistically significant union

or consolidation effect across the included studies. However, the heterogeneity test was also significant, Qe(14) = 46.65, $p < 0.001$, showing that the treatment effects varied substantially between studies. This suggests that the clinical efficacy of synthetic bone grafts is not uniform and may be influenced by graft type, defect size, infection status, anatomical location, fixation stability, and adjunctive biological treatments.

The pooled effect estimate (Table 5) was 0.904, meaning that the overall union efficacy was approximately 90.4%. The 95% confidence interval was 0.842–0.967, indicating a consistently favorable pooled union rate. However, the 95% prediction interval was 0.714–1.095, suggesting that future studies may report wider variation in outcomes. The upper value exceeding 1.0 should be interpreted as a statistical artifact of the model scale, not as a biological union rate above 100%. The heterogeneity was high, with $I^2 = 76.545\%$, supported by $\tau^2 = 0.007$ and $H^2 = 4.263$, confirming meaningful between-study variability.

The model included 15 observations (Table 6). The fit indices showed acceptable model estimation, with the maximum likelihood model producing Log Likelihood = 9.368, AIC = −14.74, BIC = −13.32, and AICc = −13.74. The REML model showed Log Likelihood = 8.148, AIC = −12.30, BIC = −11.02, and AICc = −11.20. These values support the statistical adequacy of the model, although interpretation should still consider the high heterogeneity among included studies.

Table 4. Meta-Analytic Tests

	Test	p
Heterogeneity	Q_e (14) = 46.65	< .001
Pooled effect	T (14) = 31.01	< .001

Table 5. Meta-Analytic Estimates

		95% CI		95% PI	
	Estimate	**Lower**	**Upper**	**Lower**	**Upper**
Pooled effect	0.904	0.842	0.967	0.714	1.095
τ	0.084	0.039	0.167		
τ^2	0.007	0.002	0.028		
I^2	76.545	41.011	92.796		
H^2	4.263	1.695	13.881		

Table 5. Fit Measures

	Observations	Log Lik.	Deviance	AIC	BIC	AICc
ML	15	9.368	28.72	-14.74	-13.32	-13.74
REML	15	8.148	-16.30	-12.30	-11.02	-11.20

The forest plot (Figure 2) showed that most studies had high effect sizes, generally ranging from 0.75 to 0.99, with several studies approaching complete union. Studies such as Aljawadi et al. (2022), Gengatharan et al. (2024), Yang et al. (2022), Elnokeety et al. (2022), and Giannoudis et al. (2025) contributed strongly to the favourable pooled effect. The lowest effect was observed in Lodewijks et al. (2025), with an effect size of 0.50, reflecting poorer outcomes in large segmental defects. Smaller studies and case reports had wider confidence intervals, indicating lower precision despite positive union outcomes.

The funnel plot (Figure 3) showed a generally cantered distribution of studies around the pooled effect, but some asymmetry was present. This pattern may reflect small-study effects, clinical heterogeneity, or differences in study precision rather than definite publication bias. The presence of studies with larger standard errors, especially small case reports, indicates that the pooled estimate should be interpreted cautiously. Overall, the funnel plot supports a generally favourable treatment effect, but the evidence remains heterogeneous.

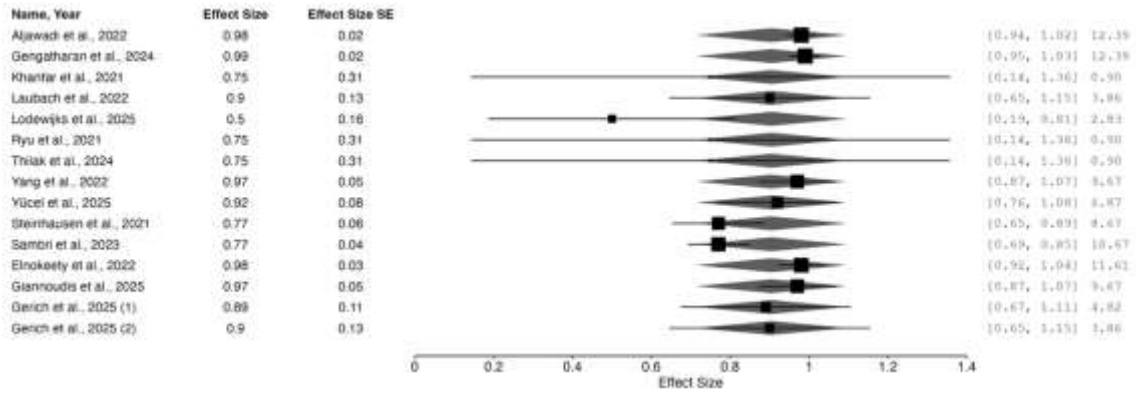

Figure 2 Forest Plot

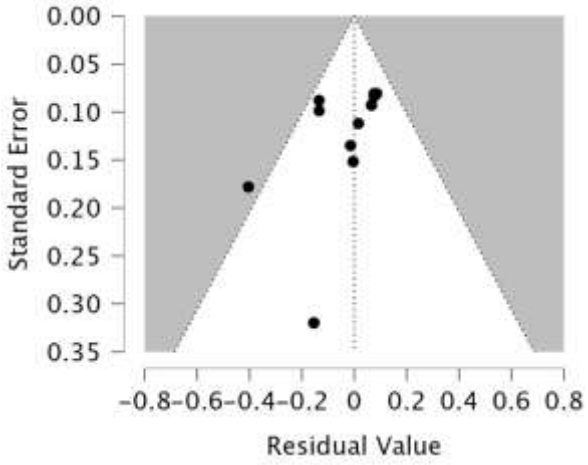

Figure 3 Residual Funnel Plot

Types of Synthetic Bone Grafts Used in Non-Union Fracture Repair

Several synthetic bone graft materials have been reported in human fracture non-union and bone defect reconstruction studies. These materials include hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), biphasic calcium phosphate (BCP), calcium sulfate (CS), bioactive glass (BAG), injectable bone cement, and composite biomaterials. Their primary role is to provide an osteoconductive scaffold that supports bone ingrowth, rather than to fully replicate the biological function of autologous bone grafts.

Hydroxyapatite is a highly biocompatible calcium phosphate ceramic characterized by slow resorption kinetics and long-term structural stability (Thilak et al., 2024). Because it does not dissolve rapidly, HA is particularly useful when prolonged scaffold support is required. It is also commonly incorporated into composite materials, such as PerOssal beads, which combine nanocrystalline HA with calcium sulfate (Sambri et al., 2023). In contrast, β-TCP

exhibits greater resorbability and is designed to degrade more rapidly than HA while being progressively replaced by host bone (Laubach et al., 2022). It is frequently employed in 3D-printed composite scaffolds, including medical-grade polycaprolactone–tricalcium phosphate (mPCL-TCP) constructs (Lodewijks et al., 2025).

Biphasic calcium phosphate (BCP) combines HA and β-TCP to balance scaffold persistence with controlled biodegradability. One example is the *b.Bone* scaffold, produced through biomorphic transformation to replicate cortical bone microarchitecture using HA, β-TCP, and substituted ions such as Mg^{2+} and Sr^{2+} (Giannoudis et al., 2025). Calcium sulfate is highly bioabsorbable and cost-effective; however, its rapid dissolution limits its reliability as a long-term osteoconductive scaffold when used in isolation (Aljawadi et al., 2022). Consequently, calcium sulfate is frequently combined with HA or other calcium-based ceramics as seen in Cerament-G and PerOssal to maintain an osteoconductive framework after the calcium sulfate phase has been resorbed (Sambri et al., 2023).

Bioactive glass, particularly the S53P4 formulation, represents another clinically important synthetic graft material. It is composed of SiO_2, Na_2O, CaO, and P_2O_5, and upon implantation releases ionic dissolution products that elevate local pH and osmotic pressure while forming a silica-rich surface layer that subsequently converts into a hydroxyapatite-like mineral phase (Steinhausen et al., 2021). These properties make bioactive glass valuable not only as an osteoconductive substrate but also as a potential antimicrobial biomaterial in the management of infected bone defects. Injectable bone cement, such as Cerament-G, can be delivered as a paste or powder that sets *in situ*. Cerament-G contains 40% HA within a 60% calcium sulfate matrix and functions as both a bone void filler and a local antibiotic carrier (Aljawadi et al., 2022).

Composite biomaterials are increasingly utilized because they integrate the mechanical and biological strengths of different material classes. A key example is mPCL-TCP, which combines the elasticity of a biodegradable polymer with the osteoconductivity of TCP ceramic (Herath et al., 2024; Laubach et al., 2022; Lodewijks et al., 2025). These scaffolds can be additively manufactured into patient-specific geometries, making them suitable for the reconstruction of irregular and large post-traumatic bone defects. Scaffold porosity is a clinically important design parameter: mPCL-TCP scaffolds may exhibit approximately 70% porosity with pore diameters of 2–3 mm (Lodewijks et al., 2025), while *b.Bone* scaffolds contain approximately 300 μm channels that replicate cortical bone architecture and stiffness (Giannoudis et al., 2025).

The key material characteristics of synthetic bone grafts include osteoconductivity, porosity, resorption behavior, mechanical support, and carrier capability. Their three-dimensional (3D) architecture permits host osteoblasts, mesenchymal stem cells (MSCs), and capillaries to migrate across the fracture gap (Laubach et al., 2022; Yang et al., 2022). High porosity and interconnected pore networks support vascularization and cellular ingrowth. However, the resorption profile must be matched to the pace of new bone formation; calcium sulfate may resorb too rapidly, whereas composites incorporating HA, bioactive glass, or polycaprolactone (PCL) provide more sustained mechanical and biological support (Lodewijks et al., 2025; Sambri et al., 2023). Although these grafts typically require supplementary metallic fixation to bear physiological loads, they can assist in elevating depressed intra-articular

fragments, filling metaphyseal comminution zones, and bridging bicortical defects (Gengatharan et al., 2024; Laubach et al., 2022).

An additional clinically important advantage is the capacity of synthetic scaffolds to function as local drug delivery carriers. They can deliver antibiotics such as gentamicin or vancomycin, or antimicrobial silver ions, directly into infected non-union sites while minimizing systemic toxicity (Aljawadi et al., 2022; Yücel et al., 2025). Their porous architecture can also accommodate biological adjuncts such as bone marrow aspirate concentrate (BMAC) or recombinant human bone morphogenetic protein-2 (rhBMP-2), thereby enhancing the osteobiological environment at the defect site (Laubach et al., 2022; Van Vugt et al., 2021).

Despite these advantages, synthetic bone grafts should be understood primarily as osteoconductive scaffolds rather than complete biological substitutes for autologous bone grafts (Gengatharan et al., 2024). Autologous bone remains the gold standard in non-union repair because it simultaneously provides osteoconduction, osteoinduction, and osteogenesis (Gerich et al., 2025). Synthetic grafts lack living osteogenic cells and intrinsic osteoinductive growth factors; consequently, they are most appropriately used as graft extenders or supplementary scaffolds rather than standalone treatments (Gengatharan et al., 2024; Gerich et al., 2025; Lodewijks et al., 2025). For critical-sized bone defects, supplementation with BMAC, MSCs, reamer–irrigator–aspirator (RIA)-harvested autograft, or recombinant BMPs is generally required to achieve reliable bone regeneration (Gerich et al., 2025; Laubach et al., 2022; Van Vugt et al., 2021).

Clinical Efficacy of Synthetic Bone Grafts in Fracture Non-Union

Synthetic bone grafts demonstrate promising clinical efficacy in fracture non-union management, primarily by providing osteoconductive support while eliminating the donor-site morbidity associated with autologous graft harvesting (Steinhausen et al., 2021). Reported union rates are generally high across the literature. Cerament-G achieved a 98% fracture union rate in traumatic bone voids (Aljawadi et al., 2022), while NVD003 an adipose-derived stem cell graft substitute reached an 89% union rate with no reported refractures (Gerich et al., 2025). In distal radius non-unions treated with synthetic substitutes and locking plate fixation, union was achieved in 100% of cases, with no patients requiring re-grafting (Gengatharan et al., 2024).

Time to union varies according to defect complexity and anatomical location. Distal radius non-unions achieved radiological union at a mean of 2 months (Gengatharan et al., 2024), whereas tibial and femoral diaphyseal defects managed using a modified Masquelet technique with synthetic spacer mesh united after a mean of 159 days (Kalantar et al., 2024). In more severe long-bone defects, union required approximately 8 months (Chloros et al., 2022). These findings suggest that smaller metaphyseal defects tend to heal more rapidly, while large diaphyseal segmental defects require longer biological and mechanical recovery periods.

Clinical improvement is also reflected in patient-reported pain and functional outcomes. Patients receiving NVD003 reported complete resolution of pain as early as 1.5 months postoperatively (Gerich et al., 2025). Successful reconstruction of complex long-bone defects enabled patients to regain full, pain-free weight-bearing without the need for assistive devices (Laubach et al., 2022). In arthroscopic knee reconstruction augmented with synthetic grafts,

100% of patients rated their knee function as normal or nearly normal and successfully returned to high-level sporting activity (Ashraf et al., 2022).

Despite these favorable outcomes, complications remain clinically significant, particularly in massive or infected defects. A study of 3D-printed PCL/TCP scaffolds reported complications in 50% of patients, including persistent infection and fixation failure necessitating revision surgery due to incomplete bone ingrowth (Lodewijks et al., 2025). Conversely, S53P4 bioactive glass demonstrated a lower reoperation rate and fewer secondary defect-filling procedures compared with autograft (Steinhausen et al., 2021), indicating that clinical outcomes are strongly dependent on the choice of graft material, adequacy of infection control, and mechanical fixation stability.

Given that most synthetic grafts function primarily as osteoconductive scaffolds and lack intrinsic osteogenic cells or potent osteoinductive activity, they are rarely used as standalone treatments (Gerich et al., 2025). They are therefore commonly combined with RIA autograft (Laubach et al., 2022), BMAC (Van Vugt et al., 2021), adipose-derived MSCs (Gerich et al., 2025), or osteoinductive growth factors such as rhBMP-2 and Peptide-15 (Laubach et al., 2022; Lodewijks et al., 2025). In septic non-union, synthetic scaffolds may also be loaded with local antimicrobial agents, including gentamicin-impregnated Cerament-G, vancomycin-eluting Cerament-V, silver-ion–doped grafts, or S53P4 bioactive glass (Aljawadi et al., 2022; Steinhausen et al., 2021; Yücel et al., 2025). The available data did not yield strong evidence supporting the use of platelet-rich plasma (PRP) as a biological adjunct in this context.

Clinical efficacy also differs by anatomical site. In the tibia and femur, synthetic scaffolds augmented with BMAC or RIA autograft have been employed for large segmental defects, enabling eventual full weight-bearing (Laubach et al., 2022), while S53P4 bioactive glass has demonstrated benefit in infected tibial non-unions (Van Vugt et al., 2021). In the humerus, silver-ion–doped synthetic grafts supported infection eradication and bone healing in chronic osteomyelitis complicated by non-union (Yücel et al., 2025). In the distal radius and scaphoid, calcium phosphate grafts provided adequate structural support with outcomes comparable to those of autologous grafts (Gengatharan et al., 2024; Yang et al., 2022). Synthetic grafts have also been reported in the management of talar neck non-union (Khanfar et al., 2021) and mandibular continuity defects (Ryu et al., 2021).

Treatment success in non-union repair is contingent upon the fulfillment of the "diamond concept": stable mechanical fixation, an osteoconductive matrix, osteoinductive growth factors, osteogenic cells, and adequate vascularity (Chloros et al., 2022; Gerich et al., 2025). Key limiting factors include inadequate fixation stability, defect size exceeding 5 cm (Laubach et al., 2022), compromised vascularity or soft-tissue envelope requiring flap coverage (Chloros et al., 2022; Sambri et al., 2023), septic non-union necessitating radical debridement (Chloros et al., 2022), multidrug-resistant infection (Steinhausen et al., 2021), and patient-related risk factors such as age greater than 60 years, active smoking, elevated body mass index (BMI), diabetes mellitus, and osteoporosis (Chloros et al., 2022; Findeisen et al., 2025).

Clinical Considerations, Limitations, and Future Perspectives

Synthetic bone grafts offer several important clinical advantages in fracture non-union management. Their primary benefit is unlimited availability, which eliminates the need for harvesting large volumes of autologous bone from the iliac crest (Gerich et al., 2025). This

avoids donor-site morbidity, including chronic pain, hematoma formation, vascular injury, and pelvic instability (Gerich et al., 2025; Ryu et al., 2021). Synthetic grafts also provide a more controlled and reproducible composition, circumventing the biological variability inherent to autografts and the potential disease transmission risks associated with allografts (Steinhausen et al., 2021; Yang et al., 2022). Furthermore, advances in 3D printing and additive manufacturing now enable patient-specific scaffold fabrication for large, geometrically complex, post-traumatic bone defects (Herath et al., 2024; Laubach et al., 2022).

Nevertheless, synthetic bone grafts are associated with important limitations. Most currently available materials function primarily as osteoconductive scaffolds, with limited osteoinductive capacity due to the absence of living osteogenic cells and native growth factors (Gerich et al., 2025; Ryu et al., 2021). Their resorption behavior remains inconsistent across material classes. Certain calcium sulfate formulations may dissolve too rapidly, while 3D-printed PCL/TCP scaffolds may remain incompletely resorbed even after three years, occasionally resulting in fibrous tissue formation rather than mature lamellar bone (Lodewijks et al., 2025; Yang et al., 2022). These limitations may contribute to inconsistent outcomes, including revision or failure rates of up to 50% in large segmental defect cohorts (Lodewijks et al., 2025). Accordingly, synthetic grafts frequently require augmentation with biological adjuncts such as BMAC, RIA autograft, or rhBMP-2 to achieve reliable bone regeneration (Laubach et al., 2022; Lodewijks et al., 2025).

The available evidence base is also highly heterogeneous, precluding the identification of a single gold-standard synthetic graft material for fracture non-union repair (Lodewijks et al., 2025; Van Vugt et al., 2021). Published studies evaluate a diverse range of materials including PCL/TCP, S53P4 bioactive glass, and calcium sulfate-based cements across multiple anatomical sites such as the femur, tibia, humerus, and radius (Aljawadi et al., 2022; Lodewijks et al., 2025; Steinhausen et al., 2021). Clinical contexts also vary considerably, with some studies incorporating septic non-unions and others focusing exclusively on aseptic bone defects. Surgical strategies range from single-stage grafting to two-stage Masquelet reconstruction (Chloros et al., 2022; Van Vugt et al., 2021). Outcome measures are similarly inconsistent, encompassing radiological union, fusion scores, infection eradication rates, reoperation rates, and time to full weight-bearing (Lodewijks et al., 2025; Van Vugt et al., 2021).

Future development in this field should focus on advanced composite biomaterials, antibiotic-eluting grafts, bioactive scaffolds, and personalized bone regeneration strategies. Scaffold architecture may be optimized through porous structural designs such as Voronoi tessellations or triply periodic minimal surfaces (TPMS) to simultaneously enhance mechanical strength and promote vascular ingrowth (Herath et al., 2024). For infected non-unions, antibiotic-loaded constructs including Cerament-G, Cerament-V, and silver-ion–doped grafts may facilitate eradication of multidrug-resistant biofilms through sustained local antimicrobial release, without the systemic toxicity associated with intravenous antibiotic therapy (Aljawadi et al., 2022; Yücel et al., 2025). Growth factor delivery systems incorporating rhBMP-2 or BMAC may further augment local osteogenesis at the defect site (Laubach et al., 2022; Van Vugt et al., 2021). Ultimately, the field is progressing toward fully personalized biomaterial-based reconstruction, integrating virtual surgical planning, 3D printing, and autologous stem-cell engineering including adipose-derived cellular implants such as NVD003 to match each

patient's anatomical defect geometry and intrinsic biological healing capacity (Gerich et al., 2025; Herath et al., 2024; Ryu et al., 2021).

CONCLUSION

Synthetic bone grafts are promising biomaterial-based options for fracture non-union repair, particularly because they are widely available, avoid donor-site morbidity, and can be engineered as porous, osteoconductive scaffolds. Clinical outcomes are generally favorable, with reported union rates of 89–100% and healing times ranging from 2 months to 8 months, although success depends strongly on fixation stability, defect size, vascularity, infection control, and patient-related risk factors. However, because most synthetic grafts lack intrinsic osteogenic and osteoinductive properties, they are best used as graft extenders or carriers combined with biological or antimicrobial adjuncts rather than as complete substitutes for autologous bone grafts.

REFERENCE

Alam, M., Shirazi, A., & Alaradi, H. (2023). Association of Fracture Location and Pattern With Nonunion or Malunion in Tibia Fractures Managed With Intramedullary Nailing: A Retrospective Study. *Cureus*. https://doi.org/10.7759/cureus.49156

Burke, C. E., Mundy, L. R., Gupta, J., Wong, A., Enobun, B., O'Hara, N. N., Bangura, A., O'Connor, K., Jauregui, J. J., Miller, N. F., O'Toole, R. V, & Pensy, R. A. (2023). Secondary Bony Defects After Soft Tissue Reconstruction in Limb-Threatening Lower Extremity Injuries: Does the Approach to Flap Elevation Matter? *Journal of Reconstructive Microsurgery*, *40*(01), 059–069. https://doi.org/10.1055/s-0043-1768219

Campanacci, D. A., Scalici, G., & Scorianz, M. (2021). Regenerative Medicine in Orthopaedic Surgery. *International Journal of Bone Fragility*, *1*(3), 107–113. https://doi.org/10.57582/ijbf.210103.107

Castillo, I. A., Heiner, J. A., Meremikwu, R. I., Kellam, J. F., & Warner, S. J. (2023). Where Are We in 2022? A Summary of 11,000 Open Tibia Fractures Over 4 Decades. *Journal of Orthopaedic Trauma*, *37*(8), e326–e334. https://doi.org/10.1097/bot.0000000000002602

Chmali, K., ElIdrissi, M., Abid, H., ElIbrahimi, A., Berraho, M., & Elmrini, A. (2022). Aseptic Nonunion of the Tibia Treated by Plating and Bone Grafting: Retrospective Study About 40 Cases. *Journal of Orthopaedic Surgery and Research*, *17*(1). https://doi.org/10.1186/s13018-022-03216-z

Chua, S. K. K., Wong, W.-S.-Y., Koh, D. T. S., Sultana, R., Soong, J., Lee, K. H., & Razak, H. R. B. A. (2024). Faster Bone Gap Union in Medial Opening Wedge High Tibial Osteotomy With 3d-Printed Synthetic Bioresorbable Polycaprolactone and Tricalcium Phosphate Osteotomy Gap Fillers Compared to Allogeneic Osteotomy Gap Fillers: A Retrospective Matched-Pair Cohort Study. *Cartilage*, *16*(1), 24–35. https://doi.org/10.1177/19476035241246609

Ehrnthaller, C., Hoxhaj, K., Manz, K., Zhang, Y., Fürmetz, J., Böcker, W., & Linhart, C. (2024). Preventing Atrophic Long-Bone Nonunion: Retrospective Analysis at a Level I Trauma Center. *Journal of Clinical Medicine*, *13*(7), 2071. https://doi.org/10.3390/jcm13072071

Engel, E. E. (2025). Updates on Bone Grafts and Substitutes. *Revista Brasileira De Ortopedia*, *60*(06), 001–009. https://doi.org/10.1055/s-0045-1814114

Flores, M. J., Brown, K., O'Marr, J. M., Adejuyigbe, B., Rodarte, P., Gomez-Alvarado, F., Nwachuku, K., Urva, M., & Shearer, D. (2024). The Economic Impact of Infection and/or Nonunion on Long-Bone Shaft Fractures: A Systematic Review. *Ota International the Open Access Journal of Orthopaedic Trauma*, *7*(3). https://doi.org/10.1097/oi9.0000000000000337

Gallo, M. C., Elias, A., Reynolds, J. M., Ball, J. R., & Lieberman, J. R. (2025). Regional Gene Therapy for Bone Tissue Engineering: A Current Concepts Review. *Bioengineering*, *12*(2), 120. https://doi.org/10.3390/bioengineering12020120

Georgeanu, V. A., Gîngu, O., Antoniac, I., & Manolea, H. O. (2023). Current Options and Future Perspectives on Bone Graft and Biomaterials Substitutes for Bone Repair, From Clinical Needs to Advanced Biomaterials Research. *Applied Sciences*, *13*(14), 8471. https://doi.org/10.3390/app13148471

Jiang, Y., Wang, X., Huang, W., Zhu, Y., Zhang, K., & Feng, D. (2022). A Novel Bone Graft Technique Combined With Plating for Aseptic Recalcitrant Long Bone Nonunion. *BMC Musculoskeletal Disorders*, *23*(1). https://doi.org/10.1186/s12891-022-05830-8

Li, Z., Liu, J., Li, C., Wu, M., Li, Y., Cui, Y., Xiong, W., Yang, F., & Liu, B. (2023). Advances in the Application of Bone Transport Techniques in the Treatment of Bone Nonunion and Bone Defects. *Orthopaedic Surgery*, *15*(12), 3046–3054. https://doi.org/10.1111/os.13936

Lodewijks, A. J. L., Warin, M. M. R., Van Der Broeck, L. C. A., Fois, M. G., Lopez-Iglesias, C., Blokhuis, T. J., Van Griensven, M., & Poeze, M. (2025). Long-term follow-up of patients with large segmental bone defects treated with 3D-printed polycaprolactone/tricalcium phosphate scaffolds. *European Journal of Trauma and Emergency Surgery*, *51*(1), 326.

Lu, G., Huo, Z., & Chen, E. (2025). Clinical Outcomes of Tibial Nonunion Treatment Through the Combination of PRP, Autogenous Iliac Bone Grafting, and Augmentation Plating. *Frontiers in Surgery*, *12*. https://doi.org/10.3389/fsurg.2025.1573679

Marmor, M., Matz, J., McClellan, R. T., Medam, R., & Miclau, T. (2021). Use of Osteobiologics for Fracture Management: The When, What, and How. *Injury*, *52*, S35–S43. https://doi.org/10.1016/j.injury.2021.01.030

Mayfield, C. K., Ayad, M., Lechtholz-Zey, E., Chen, Y., & Lieberman, J. R. (2022). 3d-Printing for Critical Sized Bone Defects: Current Concepts and Future Directions. *Bioengineering*, *9*(11), 680. https://doi.org/10.3390/bioengineering9110680

Mehta, D. (2025). Technology Behind Augmenting Fracture Healing. *Bulletin of the Hospital for Joint Diseases*, *83*(1), 56–62. https://doi.org/10.1097/bh9.0000000000000010

Morcovescu, A., Pop, H., Mihai, M. M., Constantinescu, A., Branaru, M. G., Paraschiv, R., Vlad, R. M., & Bica, F. (2024). Non-Vascularized Fibular Autograft and Locking Plate: A Solution to the Resistant Nonunion of a Tibial Metaphyseal Fracture. *Cureus*. https://doi.org/10.7759/cureus.58831

Nauth, A., Crist, B. D., Morshed, S., Watson, J. T., & Pape, H. (2023). Management of Aseptic Nonunions and Severe Bone Defects: Let Us Get This Thing Healed! *Ota International the Open Access Journal of Orthopaedic Trauma*, *6*(3S). https://doi.org/10.1097/oi9.0000000000000258

Nicholson, J. A., Makaram, N. S., Simpson, H., & Keating, J. F. (2021). Fracture Nonunion in Long Bones: A Literature Review of Risk Factors and Surgical Management. *Injury*, *52*, S3–S11. https://doi.org/10.1016/j.injury.2020.11.029

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., & Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, *372*.

Razii, N., Docherty, L. M., Halai, M., Mahendra, A., & Gupta, S. (2023). Injectable Synthetic Beta-Tricalcium Phosphate/Calcium Sulfate (GeneX) for the Management of Contained Defects Following Curettage of Benign Bone Tumours. *Current Oncology*, *30*(4), 3697–3707. https://doi.org/10.3390/curroncol30040281

Rios, J. J., Juan, C., Shelton, J. M., Paria, N., Oxendine, I., Wassell, M., Kidane, Y. H., Cornelia, R., Jeffery, E., Podeszwa, D. A., Conway, S. J., Wise, C. A., & Tower, R. J. (2024). Spatial Transcriptomics Implicates Impaired BMP Signaling in NF1 Fracture Pseudarthrosis in Murine and Patient Tissues. *Jci Insight*, *9*(16). https://doi.org/10.1172/jci.insight.176802

Rizvi, S. M. M. H., Hui, L., & Tao, S. (2024). *Clinical Efficacy of the Ilizarov Technique in the Treatment of Infected Non Union And Bone Defects Results of at least 2 Years of Follow-up.*

Roberts, H. J., Donnelley, C. A., Haonga, B. T., Kramer, E., Eliezer, E., Morshed, S., & Shearer, D. (2021). Intramedullary Nailing Versus External Fixation for Open Tibia Fractures in Tanzania: A Cost Analysis. *Ota International the Open Access Journal of Orthopaedic Trauma*, *4*(3), e146. https://doi.org/10.1097/oi9.0000000000000146

Rodham, P., Giannoudis, V. P., Kanakaris, N. K., & Giannoudis, P. V. (2023). Biological Aspects to Enhance Fracture Healing. *Efort Open Reviews*, *8*(5), 264–282. https://doi.org/10.1530/eor-23-0047

Rodríguez-Merchán, E. C. (2022). Bone Healing Materials in the Treatment of Recalcitrant Nonunions and Bone Defects. *International Journal of Molecular Sciences*, *23*(6), 3352. https://doi.org/10.3390/ijms23063352

Schmidt, A. H. (2021). Autologous Bone Graft: Is It Still the Gold Standard? *Injury*, *52*, S18–S22. https://doi.org/10.1016/j.injury.2021.01.043

Sidiropoulos, K., Panagopoulos, A., Tsikopoulos, K., Saridis, A., Assimakopoulos, S. F., Kouzelis, A., Vrachnis, I., & Givissis, P. (2023). Septic Tibial Nonunions on Proximal and Distal Metaphysis—A Systematic Narrative Review. *Biomedicines*, *11*(6), 1665. https://doi.org/10.3390/biomedicines11061665

Siregar, H., Gunawan, R., & Fitriadi, D. (2021). A Case Series: Non-vascularized Autologous Fibular Graft in the Treatment of Major Segmental Bone Defect after Post-traumatic at Diaphyseal Femur. *Open Access Macedonian Journal of Medical Sciences*, *9*(C), 175–181.

Smolinská, V., Csöbönyeiová, M., Zamborský, R., & Danišovič, Ľ. (2023). Stem Cells and Their Derivatives: An Implication for the Regeneration of Nonunion Fractures. *Cell Transplantation*, *32*. https://doi.org/10.1177/09636897231183530

Tokeshi, S., Fukawa, T., Itadera, E., Akazawa, T., Fujiyoshi, T., Takaso, M., Nakagawa, K., Yamauchi, T., Osada, N., & Ohtori, S. (2023). Efficacy and Safety of Beta-Tricalcium Phosphate/Polylactic-Co-Glycolic Acid for Implantation of Bone Defects. *Cureus*. https://doi.org/10.7759/cureus.43597

Valtanen, R. S., Yang, Y., Gurtner, G. C., Maloney, W. J., & Lowenberg, D. W. (2021). Synthetic and Bone Tissue Engineering Graft Substitutes: What Is the Future? *Injury*, *52*, S72–S77. https://doi.org/10.1016/j.injury.2020.07.040

Wier, J., Shelby, H., Bergren, S., Patterson, J. T., & Lieberman, J. R. (2025). Modern Approaches and Emerging Biological Therapies to Treat Fracture Nonunion. *Pharmaceutics*, *17*(11), 1457. https://doi.org/10.3390/pharmaceutics17111457

Zargarbashi, R., Bagherpour, A., Keshavarz-Fathi, M., Panjavi, B., & Zarchi, M. B. (2021). Prognosis of Congenital Pseudarthrosis of the Tibia: Effect of Site of Tibial Pseudarthrososis and Fibular Involvement. *Journal of Pediatric Orthopaedics*, *41*(7), 422–427. https://doi.org/10.1097/bpo.0000000000001861

Zhou, X., Liu, Y., Chen, H., Hu, X., Zhu, G., Liu, K., Jiang, Z., Xiao, H., & Mei, H. (2025). Clinical Study of the 'U'-Shaped Staple-Guided Growth Technique in the Treatment of Congenital Anterolateral Bowing of the Tibia in Children. *Journal of Pediatric Orthopaedics B*, *34*(6), 608–615. https://doi.org/10.1097/bpb.0000000000001237