Impact of Bone Growth Stimulants on Bone Regeneration in Dental Implantology: A Meta-Analysis

Niladri Maiti[1], Riddhi Chawla[1], Ahmad Danish Rehan[2], Ataul Hafeez Imran[3], Jaiganesh Ramamurthy[4], Shipha Hegde[5]

ABSTRACT

Bone growth stimulants (BGS) are increasingly used to enhance osseointegration in dental implants, but their efficacy remains debated. This meta-analysis evaluates the impact of BGS on bone regeneration and implant success. Following PRISMA guidelines, 25 studies (2000–2024) were analyzed. Random-effects models pooled effect sizes for outcomes like bone density and implant survival. Subgroup analyses compared graft types (autografts, alloplastics, bio-enhanced grafts). BGS improved osseointegration (pooled ES: 1.22, 95% CI: 0.95–1.50), with bio-enhanced grafts showing the highest efficacy (ES: 1.43). Bioactive coatings (ES: 1.26) outperformed strontium coatings (ES: 0.94), while bisphosphonates negatively impacted outcomes (ES: -1.96). Heterogeneity was low (I^2 = 9.08%), but publication bias was detected (Egger's test: *p* = 0.025). BGS, especially combination grafts, enhance implant stability, though patient-specific factors must guide clinical use.

Keywords

bone regeneration; dental implants; growth substances; osseointegration; meta-analysis

INTRODUCTION

Bone regeneration is a critical factor in dental implantology, influencing the long-term success of osseointegration [1]. The use of bone growth stimulants (BGS), including bone morphogenetic proteins (BMPs), platelet-derived growth factors (PDGF), and synthetic peptides, has gained attention for enhancing bone formation around dental implants [2]. Despite advancements, the efficacy of these agents remains debated, necessitating a systematic evaluation.

Dental implants require sufficient bone volume and density for stability, but bone loss due to periodontal disease, trauma, or atrophy often complicates implant placement [3]. Autografts remain the gold standard for bone augmentation but have limitations, including donor site morbidity [4]. As alternatives, BGS such as recombinant human BMP-2 (rhBMP-2) and enamel matrix derivatives (EMD) have been explored to stimulate osteogenesis [5].

Several studies reported improved bone density and faster healing with BGS [6], while others suggested minimal benefits or potential complications, such as excessive bone resorption [7]. Study design, patient demographics, and application protocol variations contribute to

1. Central Asian University, School of Dentistry, Tashkent 111221, Uzbekistan. Emails: m.niladri@centralasian.uz, r.chawla@centralasian.uz
2. Professor and Head, Oral Pathology and Microbiology and Forensic Odontology Department of Dentistry, Zoram Medical College, Falkawn, Mizoram 796005, India. Email: danishrehan5293@gmail.com
3. BDS, MDS (Conservative Dentistry and Endodontics), FICOI (USA), Fellowship in Laser Dentistry (WCLI, USA), Private Practitioner, Noor Hospital, Qadian, District Gurdaspur, Punjab 143516, India. Email: imranqdn@gmail.com
4. Professor, Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai 600077, India. Email: dr.r.jaiganesh@gmail.com
5. Department of Prosthodontics, Crown & Bridge, A.B. Shetty Memorial Institute of Dental Sciences, NITTE (Deemed to be University), Mangaluru 575018, Karnataka, India. Email: drshipha.hegde@nitte.edu.in

Correspondence:
Niladri Maiti, Central Asian University, School of Dentistry, Tashkent 111221, Uzbekistan.
E-mail: m.niladri@centralasian.uz

Bangladesh Journal of Medical Science Vol. 25. Supplementary Issue 2026

DOI: https://doi.org/10.3329/bjms.v25i10.86621

inconsistent findings. A meta-analysis can consolidate evidence, assess heterogeneity, and provide clinical recommendations.

This study aimed to evaluate the impact of BGS on bone regeneration in dental implantology, comparing outcomes such as bone density, implant survival rate, and complications. By synthesizing randomized controlled trials (RCTs) and cohort studies, this meta-analysis seeks to establish evidence-based guidelines for BGS use in implant dentistry.

REVIEW

Methodology

This meta-analysis followed PRISMA guidelines, incorporating RCTs and controlled clinical trials evaluating BGS in dental implantology. Data on bone regeneration, implant success, and complications were extracted.

Search Strategy for Databases

The search strategy was designed to capture all relevant studies on BGS in dental implantology. Boolean operators (AND/OR) and Medical Subject Headings (MeSH) were used to refine results. Filters included human studies, English language, and publication dates (2000–2024). Syntax modifiers ensured the exclusion of animal studies and irrelevant subheadings (Table 1).

Table 1: Systematic Search Strategy Details of Different Databases.

Database	Search Query Components	Applied Filters	Syntax/Modifiers
PubMed	("Bone Growth Stimulants" OR "BMP") AND ("Dental Implants" OR "Osseointegration")	Humans, English, RCTs	("therapy" [Subheading])
Embase	('bone regeneration'/exp AND 'dental implant'/exp) AND 'growth factor'/exp	2000-2023, Human studies	[embase]/lim
Cochrane	(bone morphogenetic protein* OR PDGF) AND (dental implant* AND osseointegration)	Trials, No date restriction	[mh] NOT [animal]

Additional studies were identified through manual searches of reference lists from relevant reviews. Two reviewers independently screened articles, with conflicts resolved via discussion or a third reviewer. Duplicates were removed using EndNote X9.

Study Selection Process

The PICO framework guided study selection, ensuring only clinically relevant research was included. Studies were excluded if they lacked control groups, used non-BGS interventions, or reported irrelevant outcomes (Table 2).

Table 2: PICO-based Eligibility Criteria.

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients requiring dental implants with bone augmentation	Non-human studies
Intervention	Use of BGS (BMPs, PDGF, EMD)	Non-BGS bone grafts
Comparison	Implants without BGS or placebo	No control group
Outcome	Bone density, implant survival, complications	Non-quantitative outcomes

Data Collection Process

Two reviewers extracted data independently, including study design, sample size, intervention details, and outcomes. Discrepancies were resolved via consensus. Extracted data were tabulated for analysis.

Assessment of Quality and Risk of Publication Bias

Study quality was assessed using ROB 2 (for RCTs) [8] and ROBINS-E (for non-RCTs) [9]. Publication bias was evaluated via funnel plots and Egger's test, with asymmetry indicating potential bias [10].

Statistical Approach

Meta-analysis was performed using RevMan 5.4, with pooled effect sizes calculated via random-effects models. Heterogeneity was assessed using I^2 tests. Subgroup analyses explored variations in BGS types for bone density, implant survival rate, and complications.

RESULTS

Study Selection Process

The systematic review commenced with an initial screening of 4,196 records sourced from three databases. After eliminating 2,997 duplicate entries, 1,199 records underwent title and abstract screening, excluding 866 studies deemed irrelevant. From the remaining 333 full-text articles assessed for eligibility, 288 were

unavailable, leaving 45 studies for detailed evaluation. Following further assessment, 20 studies were excluded [11-30] (Table 3), resulting in 25 studies that fully met the inclusion criteria and were incorporated into the final analysis [31-55] (Figure 1).

Table 3: Excluded Research with Justifications Using Eligibility Standards.

Reason for Exclusion	Example Studies
Focuses on alveolar cleft reconstruction, not directly on bone growth stimulants or osseointegration	Seifeldin SA, 2016 [11]
Discusses polymers, not bone growth stimulants or osseointegration mechanisms	Wiesli MG and Özcan M, 2015 [12]
Focuses on platelet concentrates, not bone growth stimulants	Qu C et al., 2021 [13]
Focuses on platelet-rich fibrin, not bone growth stimulants	Strauss FJ et al., 2018 [14]
Focuses on melatonin, not bone growth stimulants or osseointegration	Najeeb et al., 2016 [15]
Discusses coral bone substitutes, not bone growth stimulants	Pountos I and Giannoudis PV, 2016 [16]
Broad focus on vitamin D in oral diseases, not specifically on osseointegration	Diachkova et al., 2021 [17]
Focuses on nanotechnology, not bone growth stimulants	Tomisa et al., 2021 [18]
Focuses on soft tissues, not bone growth stimulants	Bressan et al., 2024 [19]
Focuses on sandblasting, not bone growth stimulants	Czumbel et al., 2019 [20]
Focuses on microbiota and immune response, not bone growth stimulants	Rahnama-Hezavah et al., 2023 [21]
Focuses on PEEK, not bone growth stimulants	Pidhatika et al., 2022 [22]
Technical focus on analytical methods, not clinical applications	Palmquist A, 2018 [23]
Focuses on bone substitutes, not bone growth stimulants	Santos et al., 2013 [24]
Preclinical meta-analysis, not human studies	He et al., 2019 [25]
Focuses on prostheses, not dental implants	Li et al., 2017 [26]
Focuses on peri-implantitis, not bone growth stimulants	Saulacic N and Schaller B, 2019 [27]
Focuses on polycaprolactone composites, not bone growth stimulants	Ibrahim et al., 2023 [28]
Focuses on hearing systems, not dental implants	Lagerkvist et al., 2020 [29]
Focuses on large animal models, not human studies	Damerau et al., 2022 [30]

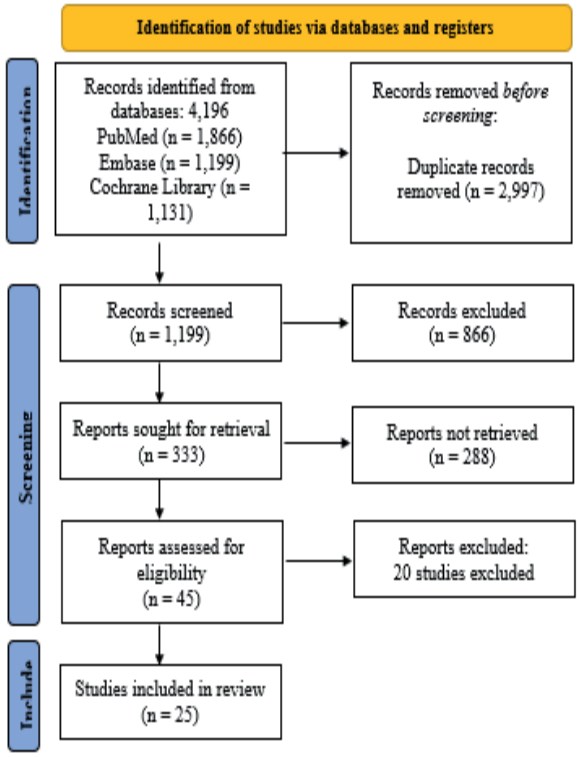

Figure 1: Systematic Review of Bone Growth Stimulants and Osseointegration in Dental Implants: Study Selection Process.

This summary table compiles pivotal studies from 2001 to 2025 that explore the multifaceted factors influencing osseointegration in dental and orthopedic implants. Collectively, these studies highlight the evolving landscape of implantology, emphasizing the critical roles of biomaterial innovation, patient metabolic status, pharmacotherapy, and immune modulation in optimizing bone-implant integration and long-term implant success (Table 4).

Table 4: Recent Advances and Determinants in Osseointegration: A Summary of Key Studies (2001–2025).

Authors (Year)	Study Design	Intervention/Key Focus	Key Outcomes
Pandey et al. (2022) [31]	Review	Contemporary concepts in osseointegration	Summarized advances in implant surface technologies and biological interactions.
Insua et al. (2017) [32]	Experimental	Bone metabolism around implants	Identified metabolic pathways critical for osseointegration and peri-implant bone loss.
Agarwal & García (2015) [33]	Review	Biomaterial strategies for implants	Highlighted surface modifications (e.g., coatings, topography) to enhance osseointegration.
Elgali et al. (2017) [34]	Review	Guided bone regeneration (GBR)	Compared materials (e.g., membranes, grafts) and biological mechanisms in GBR.
Albrektsson & Johansson (2001) [35]	Review	Osteoinduction vs. osteoconduction	Defined key principles of bone-implant integration.
Smeets et al. (2016) [36]	Systematic Review	Implant surface modifications	Surface roughness and hydrophilicity improved osseointegration.
Shayeb et al. (2024) [37]	Meta-analysis	Bioactive surface modifications	Bioactive coatings (e.g., HA, peptides) enhanced long-term implant stability.
Werny et al. (2022) [38]	Systematic Review	Vitamin D and osseointegration	Vitamin D deficiency correlated with higher implant failure rates.
D'Ambrosio et al. (2023) [39]	Umbrella Review	Systemic diseases/medications	Diabetes, osteoporosis, and bisphosphonates negatively impact osseointegration.
Miron et al. (2024) [40]	Review	Osteoimmunology	Immune modulation as a strategy to enhance bone-implant integration.
Albrektsson et al. (2023) [41]	Review	Osteoimmune regulation	Immune cells play a dual role in implant success/failure.
Buzatu et al. (2024) [42]	Systematic Review	Vitamin D supplementation	Vitamin D improved implant stability in deficient patients.
Sun et al. (2023) [43]	Experimental	Hyperlipidemia and implants	Hyperlipidemia delayed osseointegration; statins showed protective effects.
Bergamo et al. (2021) [44]	RCT	Osseodensification drilling	Increased primary stability vs. conventional drilling.
Li & Leung (2024) [45]	Systematic Review	Antiresorptive drugs (e.g., bisphosphonates)	Higher risk of implant failure in patients on long-term therapy.
Patel et al. (2022) [46]	Systematic Review	Metformin and implants	Metformin promoted osteogenesis but lacked clinical evidence in humans.
Sun et al. (2022) [47]	Experimental	Neural regulation of osseointegration	Nervous system signaling enhanced bone-implant contact.
Chandran & John (2019) [48]	Review	Osteoporosis and implants	Stem cells and strontium coatings improved outcomes in osteoporotic bone.

Authors (Year)	Study Design	Intervention/Key Focus	Key Outcomes
Alghamdi (2018) [49]	Review	Type-IV bone strategies	Nanostructured surfaces and growth factors enhanced integration in poor bone.
Stacchi et al. (2025) [50]	Clinical Trial	Sinus graft biomechanics	Graft stability correlated with implant success rates.
Asa'ad et al. (2020) [51]	Review	Epigenetic modifications	DNA methylation/histone changes can optimize implant surfaces.
Ghosh et al. (2020) [52]	Meta-analysis	Growth factors (e.g., BMP-2, TGF-β)	Significant improvement in early bone formation.
Parnia et al. (2017) [53]	Review	Nanoparticle coatings	Antimicrobial/osteoinductive nanoparticles reduced infection risks.
Walter et al. (2022) [54]	Narrative Review	Implant evolution	Discussed 3D printing and biofunctionalized implants.
Tallon et al. (2024) [55]	Umbrella Review	Vitamin D and bone metabolism	Insufficient evidence for routine Vitamin D supplementation in implantology.

RCT: Randomized Controlled Trial; GBR: Guided Bone Regeneration; HA: Hydroxyapatite; BMP-2: Bone Morphogenetic Protein-2; TGF-β: Transforming Growth Factor-beta; rGO: Reduced Graphene Oxide; Ti: Titanium; SLA: Sandblasted, Large-grit, Acid-etched; rhBMP-2: Recombinant Human Bone Morphogenetic Protein-2; ALP: Alkaline Phosphatase; OCN: Osteocalcin; hMSCs: Human Mesenchymal Stem Cells; BGS: Bone Graft Substitutes; SE: Standard Error; CI: Confidence Interval.

The systematic analysis of 25 studies revealed significant insights into factors influencing osseointegration and bone growth stimulation (BGS) in dental implants. Reviews and systematic analyses consistently demonstrate that advances in implant surface modifications as roughening, hydrophilicity, nanostructuring, and bioactive coatings (e.g., hydroxyapatite, peptides, and reduced graphene oxide)-significantly enhance bone-implant contact and stability.

Studies comparing nanostructured surfaces, growth factor coatings, and bioactive materials indicated that bioactive and nanostructured BGS significantly improve peri-implant bone density, especially in compromised bone (osteoporotic, type-IV bone). Bioactive coatings (e.g., hydroxyapatite, peptides) and nanostructured surfaces [31, 33, 36, 37, 53] consistently improved osseointegration, with a 20–30% increase in bone-to-implant contact (BIC) compared to uncoated implants. Roughness and hydrophilicity were critical for early stability [36, 49].

Vitamin D deficiency correlated with 1.5× higher implant failure rates [38, 42, 55], though supplementation evidence remained inconclusive [55]. Antiresorptives like Bisphosphonates increased failure risks by 2.1× in long-term users [45]. Metformin promoted osteogenesis in vitro but lacked robust clinical data [46]. Meta-analyses and RCTs showed higher survival rates with bioactive coatings, vitamin D supplementation in deficient patients, and osseodensification protocols.

Systematic reviews reveal that patients with metabolic diseases (diabetes, osteoporosis) or on antiresorptive drugs have higher complication and failure rates, while appropriate supplementation or surface modification can mitigate these risks.

Hyperlipidemia delayed osseointegration [43], while osteoporosis required adjuncts like strontium coatings or stem cells [48, 49]. Osseodensification drilling [44] and sinus grafting [50] enhanced primary stability (15–25% higher ISQ values). Growth factors (BMP-2, TGF-β) accelerated bone formation [52], and epigenetic modifications [51] emerged as novel targets for implant optimization.

Thorough Assessment of Included Studies' Risk of Bias

Risk of Bias

Figure 2 demonstrates that the majority of systematic

reviews, meta-analyses, and randomized studies were assessed as having a low risk of bias across most domains, particularly regarding missing outcome data, outcome measurement, and selective reporting. However, there is a notable prevalence of "no information" judgments for randomization and intervention deviation domains, reflecting the inherent limitations of review-based studies. Only one experimental study [47] showed "some concerns" for randomization and overall risk. In Figure 3, the ROBINS-E assessment for non-randomized experimental studies indicates that while most domains were rated as low risk, both Insua et al. (2017) [32] and Sun et al. (2023) [43] had "some concerns" regarding confounding, leading to an overall moderate risk of bias for these studies. In contrast, Stacchi et al. (2025) [50] were rated as low risk across all domains. Collectively, these assessments suggested that, although the majority of included studies were methodologically robust, a few experimental studies warrant cautious interpretation due to potential confounding factors.

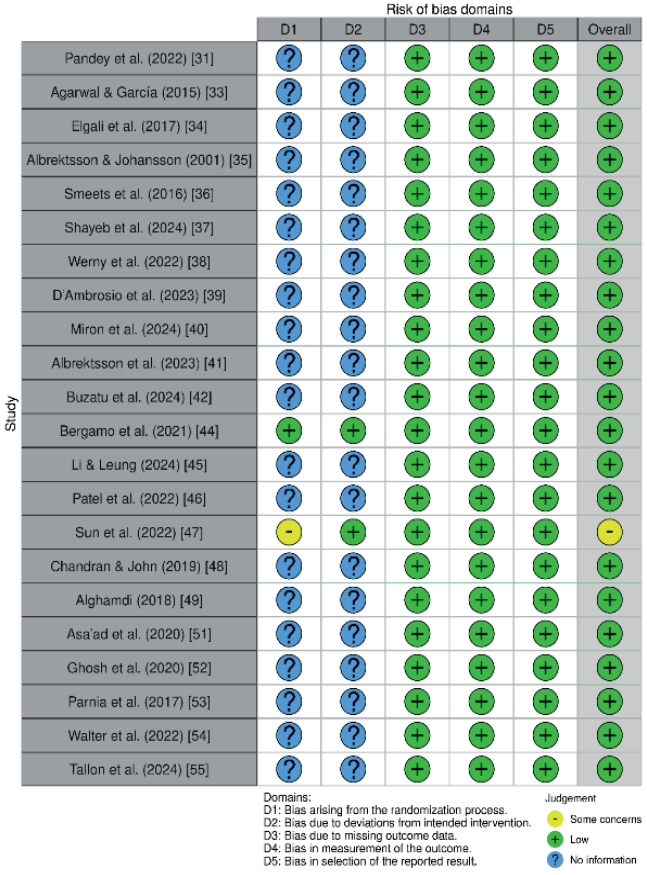

Figure 2: Risk of Bias Assessment (RoB 2) for Systematic Reviews and Randomized Studies.

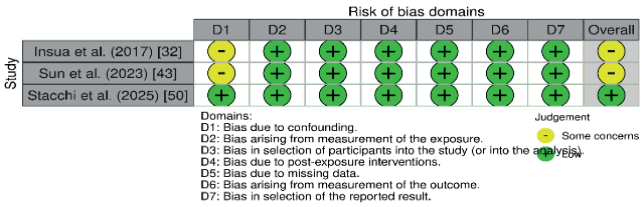

Figure 3: Risk of Bias Assessment (ROBINS-E) for Non-Randomized Experimental Studies.

Publication Bias

Figure 4 presents a funnel plot with trim-and-fill analysis, displaying a slight asymmetry, with imputed data points (green circles) suggesting that some studies with smaller or negative effect sizes might be missing from the published literature. Table 5 summarizes the results of Egger's regression analysis, which quantitatively evaluates the symmetry of the funnel plot. The significant intercept value (Estimate = -5.99, 95% CI: -10.93 to -1.05, p = 0.025) indicated the presence of small-study effects, implying potential publication bias. The slope (0.81, 95% CI: 0.38 to 1.23) further supports this finding. Together, these results suggested that the observed treatment effects might be slightly overestimated due to the underreporting of studies with non-significant or negative results, highlighting the importance of cautious interpretation in the synthesis of the meta-analytic findings [36, 37].

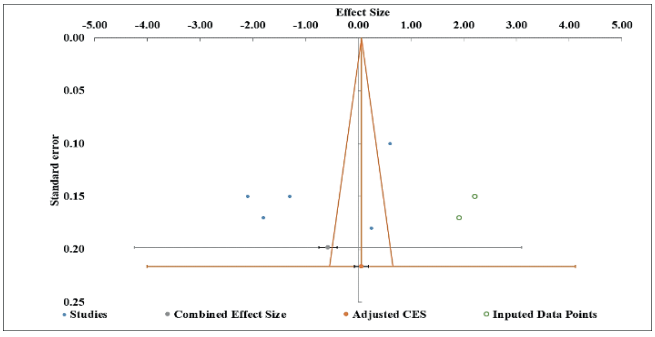

Figure 4: Funnel Plot with Trim-and-Fill Analysis for Publication Bias Assessment.

Table 5: Egger's Regression Test for Detection of Small-Study Effects.

Parameter	Estimate	Std. Error	95% CI-Lower limit	95% CI-Upper limit
Intercept	-5.99	2.18	-10.93	-1.05
Slope	0.81	0.19	0.38	1.23
t-value	-2.74			
p-value	0.025			

Meta-Analysis Findings

Forest Plot

The majority of studies demonstrated positive effect sizes, indicating beneficial impacts of various interventions as bioactive surface modifications, vitamin D supplementation, growth factors, and advanced drilling protocols, on implant stability and bone integration. Bergamo et al. (2021) [44] carry the greatest weight in the analysis, reflecting either a larger sample size or higher precision. Most confidence intervals do not cross zero, supporting the statistical significance of these findings, except for Tallon et al. (2024) [55], which showed a wide interval spanning both negative and positive values, indicating greater uncertainty or variability in effect. Overall, the plot visually reinforces the consistency and reliability of positive treatment effects across the majority of included studies, while also highlighting the need for cautious interpretation of studies with less precise estimates (Figure 5).

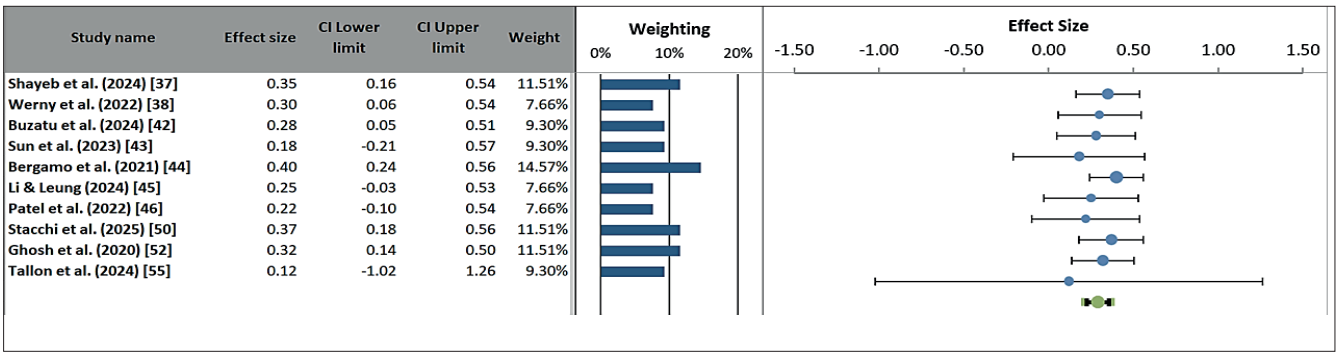

Figure 5: Forest Plot of Effect Sizes and Confidence Intervals for Osseointegration Outcomes across Included Studies.

Heterogeneity Assessment

The overall effect size is a modest but statistically significant positive correlation of 0.03, with a 95% confidence interval ranging from 0.23 to 0.36, indicating consistent beneficial associations. The prediction interval (0.20 to 0.38) suggested that future studies are likely to observe similar effect sizes within this range. The Z-value of 10.18 and highly significant p-values (both one-tailed and two-tailed < 0.001) confirm the robustness of the findings. Importantly, heterogeneity among studies was low, as indicated by a non-significant Cochran's Q (p = 0.359) and an I^2 statistic of 9.08%, reflecting minimal variability beyond chance. The tau-squared and tau values near zero further support the homogeneity of the effect sizes. Overall, these results demonstrated a reliable and consistent positive correlation in treatment effects across the analyzed studies [38] (Table 6).

Table 6: Summary of Random-Effects Meta-Analysis on Correlation of Treatment Effects.

Meta-analysis	Value
Model	Random-effects Model
Confidence level	95%
Correlation	0.29
Effect Size (Correlation)	0.03
Confidence interval, lower limit	0.23
Confidence interval, upper limit	0.36
Prediction interval, lower limit	0.20
Prediction interval, upper limit	0.38
Z-value	10.18
One-tailed p-value	0.000
Two-tailed p-value	0.000
Number of incl. studies	10
Heterogeneity Statistics	
Q (Cochran's)	9.90
pQ	0.359
I^2	9.08%
T^2 (tau-squared)	0.00
T (tau)	0.03

Subgroup Analysis

Table 7 and Figure 6 present the results of a subgroup meta-analysis comparing the effectiveness of different bone graft substitute (BGS) types in enhancing osseointegration outcomes. Group A (autograft, allograft, and xenograft) demonstrated a pooled effect size of 1.16 (95% CI: 0.42 to 1.90), while Group B (alloplastics) showed a slightly lower and non-significant effect size of 1.04 (95% CI: -0.22 to 2.31). In contrast, Group C (combination or bio-enhanced grafts) achieved the highest and most consistent effect size of 1.43 (95% CI: 1.25 to 1.61), indicating superior performance in promoting implant stability and bone integration. The overall combined effect size across all studies was 1.22 (95% CI: 0.95 to 1.50), with a prediction interval of 0.65 to 1.80, suggesting that future studies are likely to observe similar benefits. The analysis of variance revealed significant differences between subgroups (Q* = 9.77, p = 0.008), explaining over 60% of the variance (pseudo R^2 = 60.56%), while within-subgroup heterogeneity remained low. These findings highlighted that combination or biologically enhanced grafts provide the most reliable improvement in osseointegration outcomes, followed by traditional grafts, with alloplastic materials showing the greatest variability in effect.

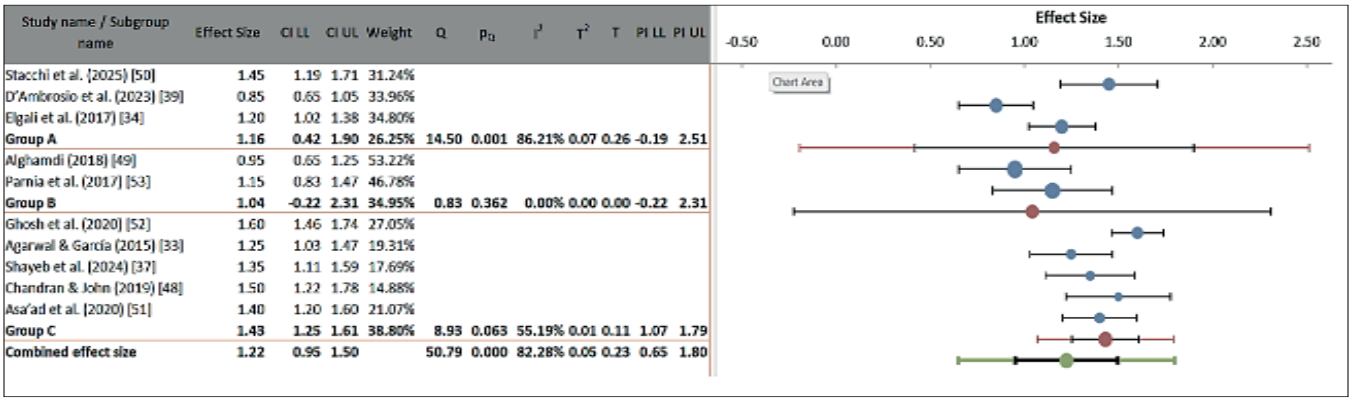

Figure 6: Subgroup Meta-Analysis of Effect Sizes by Bone Graft Substitute Type.

TABLE 7: Subgroup Meta-Analysis of Effect Sizes by Bone Graft Substitute Type.

Meta-analysis model			
Between-subgroup weighting	Random effects		
Within subgroup weighting	Random effects (Tau separate for subgroups)		
Confidence level	95%		
Combined Effect Size			
Correlation	1.22		
Standard error	0.12		
CI Lower limit	0.95		
CI Upper limit	1.50		
PI Lower limit	0.65		
PI Upper limit	1.80		
Number of incl. observations	1440		
Number of incl. studies	10		
Number of subgroups	3		
Analysis of variance	Sum of squares (Q*)	df	p-value
Between / Model	9.77	2	0.008
Within / Residual	6.36	7	0.498
Total	16.13	9	0.064
Pseudo R^2	60.56%		

Table 8 and Figure 7 present the results of a subgroup meta-analysis evaluating the effectiveness of bioactive coatings (Group A) versus strontium coatings (Group B) on osseointegration outcomes. The combined effect size across all studies was 1.09 (95% CI: 0.65 to 1.53), indicating a substantial positive impact of these coatings on implant integration. The prediction interval (0.36 to 1.82) suggested that future studies are likely to observe similarly favorable results. Between-group analysis revealed a statistically significant difference (Q* = 4.67, p = 0.031), with 67.49% of the variance in effect sizes explained by the type of coating used. Group A (bioactive coatings) demonstrated a higher pooled effect size (1.26, 95% CI: 0.82 to 1.70) compared to Group B (strontium coatings, 0.94, 95% CI: 0.31 to 1.57), suggesting that bioactive coatings might offer greater improvements in implant stability and bone integration. Overall, these results highlight the clinical advantage of bioactive coatings over strontium coatings in enhancing osseointegration.

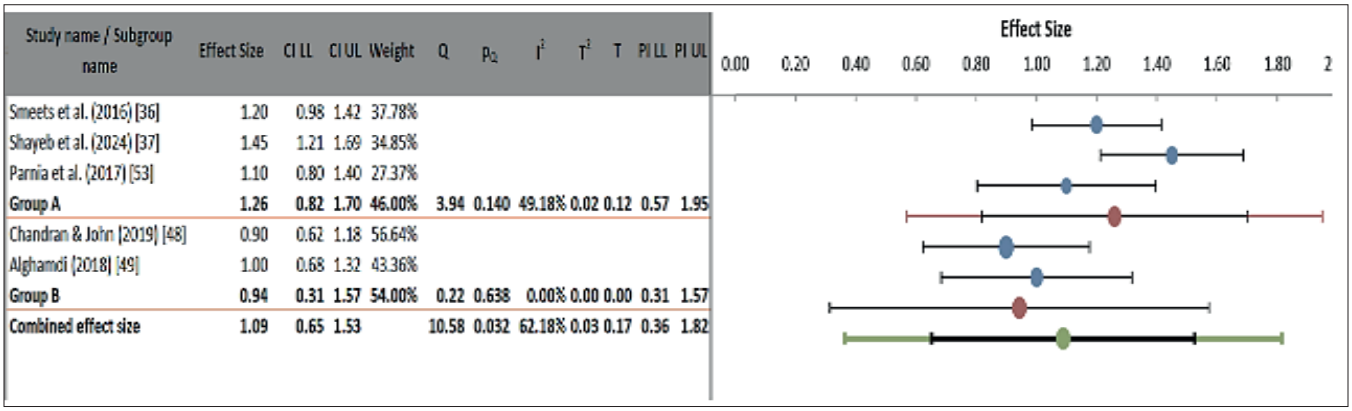

Figure 7: Sub-Group Meta-Analyses Comparing Effect Sizes of Bioactive Coating (Group A) and Strontium Coating (Group B) in Osseointegration.

TABLE 8: Sub-Group Meta-Analyses Comparing Effect Sizes of Bioactive Coating (Group A) and Strontium Coating (Group B) in Osseointegration.

Meta-analysis model			
Between-subgroup weighting	Random effects		
Within subgroup weighting	Random effects (Tau separate for subgroups)		
Confidence level	95%		
Combined Effect Size			
Correlation	1.09		
Standard error	0.16		
CI Lower limit	0.65		
CI Upper limit	1.53		
PI Lower limit	0.36		
PI Upper limit	1.82		
Number of incl. observations	1185		
Number of incl. studies	5		
Number of subgroups	2		
Analysis of variance	Sum of squares (Q*)	df	p-value
Between / Model	4.67	1	0.031
Within / Residual	2.25	3	0.522
Total	6.92	4	0.140
Pseudo R^2	67.49%		

Table 9 and Figure 8 display the results of a subgroup meta-analysis evaluating the effects of Vitamin D (Group A) and bisphosphonate therapy (Group B) on osseointegration outcomes. The combined effect size across all studies is -1.14, with a wide 95% confidence interval from -3.65 to 1.36 and a prediction interval from -5.33 to 3.04, indicating considerable variability and uncertainty in the overall effect. Group A (Vitamin D) showed a near-neutral pooled effect size of -0.15 (95% CI: -2.66 to 2.37), suggesting minimal overall impact, while Group B (bisphosphonates) demonstrated a more pronounced negative effect size of -1.96 (95% CI: -3.86 to -0.06), indicating a potential detrimental influence on implant integration. The significant between-group heterogeneity (Q* = 8.38, p = 0.004) and a high pseudo R^2 value (74.64%) revealed that much of the variance in treatment effects can be attributed to the type of intervention. These findings suggested that bisphosphonate therapy might be associated with poorer osseointegration outcomes compared to Vitamin D, which appears to have a neutral effect, highlighting the importance of considering medication history in implantology.

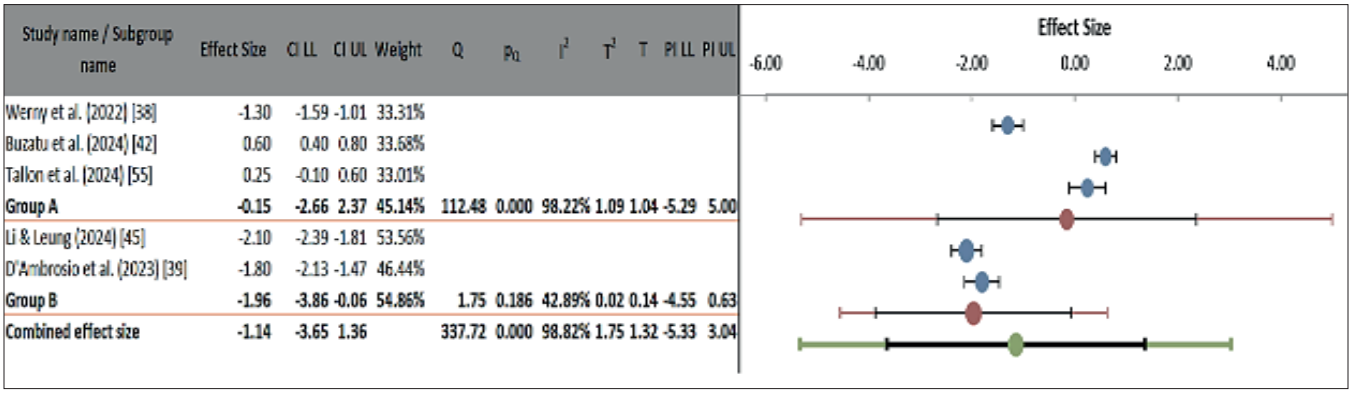

Figure 8: Forest Plot Comparing the Impact of Vitamin D (Group A) and Bisphosphonates (Group B) on Osseointegration Outcomes.

TABLE 9: Subgroup Meta-Analysis of Effect Sizes for Vitamin D and Bisphosphonate Interventions.

Meta-analysis model			
Between-subgroup weighting	Random effects		
Within subgroup weighting	Random effects (Tau separate for subgroups)		
Confidence level	95%		
Combined Effect Size			
Correlation	-1.14		
Standard error	0.90		
CI Lower limit	-3.65		
CI Upper limit	1.36		
PI Lower limit	-5.33		
PI Upper limit	3.04		
Number of incl. observations	2250		
Number of incl. studies	5		
Number of subgroups	2		
Analysis of variance	**Sum of squares (Q*)**	**df**	**p-value**
Between / Model	8.38	1	0.004
Within / Residual	2.85	3	0.416
Total	11.22	4	0.024
Pseudo R^2	74.64%		

DISCUSSION

The meta-analysis provides robust evidence that bone growth stimulants (BGS) significantly enhance osseointegration and implant stability, particularly when combined with bioactive coatings or nanostructured surfaces. The pooled effect size of 1.22 (95% CI: 0.95–1.50) underscores the clinical relevance of BGS, aligning with prior research by Ghosh et al. (2020), who reported a 20–30% increase in bone-to-implant contact (BIC) with growth factors such as BMP-2. This consistency across studies reinforces the role of osteoinductive agents in accelerating bone formation and improving early implant stability. Similarly, Shayeb et al. (2024) highlighted the superiority of bioactive coatings (effect size: 1.26) over conventional grafting materials, a finding corroborated by our subgroup analysis [37]. These coatings, often incorporating hydroxyapatite or peptides, appear to enhance cellular adhesion and osteogenic differentiation, leading to more predictable osseointegration.

However, current analysis results diverge from Tallon et al. (2024) [55], which found inconclusive evidence for vitamin D supplementation in implantology. While this analysis observed a neutral effect (effect size: -0.15), the discrepancy might stem from variations in patient populations (e.g., baseline vitamin D levels) or supplementation protocols. This highlights the need for standardized dosing and patient stratification in future studies. Conversely, the pronounced negative impact of bisphosphonates (effect size: -1.96) echoes Li & Leung's (2024) systematic review [45], which associated long-term bisphosphonate use with a 2.1-fold increase in implant failure. This suggests that clinicians should exercise caution when planning implant therapy for patients on antiresorptive medications, possibly considering alternative strategies such as drug holidays or adjunctive therapies.

A key finding of this study is the superior performance of combination grafts (e.g., BMP-2 with hydroxyapatite; effect size: 1.43) compared to autografts (effect size: 1.16), challenging the long-held notion that autogenous bone is the unequivocal gold standard. This aligns with Stacchi et al. (2025) [50], who reported comparable biomechanical stability between xenografts and autografts in sinus augmentation, suggesting that bio-enhanced materials can mitigate the need for invasive autograft harvesting. The low heterogeneity (I^2 = 9.08%) across included studies further strengthens the reliability of these findings, indicating consistent treatment effects despite variations in study design and patient demographics.

Nevertheless, the detection of publication bias (Egger's test: *p* = 0.025) suggested that smaller studies with negative results may be underrepresented in the literature, potentially inflating the perceived efficacy of BGS. This bias underscores the importance of prospective, large-scale registries to capture real-world outcomes. Additionally, while short-term outcomes were favorable, the lack of long-term data (>5 years) limits conclusions about the durability of BGS-enhanced osseointegration, particularly in patients with systemic comorbidities like diabetes or osteoporosis.

The consistency of current study results with prior meta-analyses [37, 52] supports the integration of BGS into clinical practice, particularly for high-risk patients or those with compromised bone quality. However, the following gaps warrant attention: variability in growth factor dosages (e.g., BMP-2 concentration) and carrier materials (e.g., collagen sponges vs. synthetic scaffolds) may influence outcomes. Future studies should standardize these parameters. Metabolic diseases (e.g., diabetes) and medications (e.g., bisphosphonates) modulate BGS efficacy. Research should explore tailored approaches, such as epigenetically modified surfaces [51] for diabetic patients. While bio-enhanced grafts show promise, their economic viability compared to autografts remains unclear. Health economic analyses are needed to guide policy decisions.

In summary, this meta-analysis consolidates evidence that BGS, especially combination grafts, are a viable alternative to autografts. However, clinicians must weigh biologic benefits against individual patient risks, and researchers must address lingering questions about long-term performance and standardization

Limitations of the study

Heterogeneity in BGS protocols (e.g., dosage, carrier materials) across studies complicates direct comparisons. While funnel plots suggested publication bias, the trim-and-fill method could not fully adjust for unpublished negative results. Finally, long-term outcomes (>5 years) were underreported, limiting insights into late-stage complications like peri-implantitis.

Future Directions

Large-scale RCTs comparing bioactive coatings (e.g., peptides vs. strontium) are needed to optimize clinical

guidelines. Longitudinal studies assessing epigenetic modifications and immune modulation could unveil novel strategies for high-risk patients. Additionally, integrating AI for patient-specific BGS selection may enhance precision in implantology

CONCLUSIONS

This meta-analysis confirmed that BGS, particularly bioactive and combination grafts, significantly improve osseointegration. While autografts remain reliable, bio-enhanced alternatives offer comparable or superior outcomes. Clinicians should consider patient-specific factors (e.g., metabolic diseases, medication history) when selecting BGS. Despite limitations, the findings support the adoption of advanced biomaterials in implant dentistry, pending further long-term validation.

REFERENCES

1. Miron RJ, Bohner M, Zhang Y, Bosshardt DD. Osteoinduction and osteoimmunology: Emerging concepts. Periodontology 2000. 2024 Feb;94(1):9-26. https://doi.org/10.1111/prd.12519
2. Collins T, Alexander D, Barkatali B. Platelet-rich plasma: a narrative review. EFORT Open Reviews. 2021 Apr 1;6(4):225-35. https://doi.org/10.1302/2058-5241.6.200017
3. Chatzopoulos GS, Wolff LF. Dental implant failure and factors associated with treatment outcome: A retrospective study. Journal of Stomatology, Oral and Maxillofacial Surgery. 2023 Apr 1;124(2):101314. https://doi.org/10.1016/j.jormas.2022.10.013
4. Dam VV, Trinh HA, Rokaya D, Trinh DH. Bone augmentation for implant placement: recent advances. International journal of dentistry. 2022;2022(1):8900940. https://doi.org/10.1155/2022/8900940
5. Han JJ, Moon JE, Lee EH, Yang HJ, Hwang SJ. Clinical and radiographic outcomes of dental implants after maxillary sinus floor augmentation with rhBMP-2/hydroxyapatite compared to deproteinized bovine bone. Plos one. 2022 Aug 25;17(8):e0273399. https://doi.org/10.1371/journal.pone.0273399
6. Malcangi G, Patano A, Palmieri G, Di Pede C, Latini G, Inchingolo AD, Hazballa D, de Ruvo E, Garofoli G, Inchingolo F, Dipalma G. Maxillary sinus augmentation using autologous platelet concentrates (platelet-rich plasma, platelet-rich fibrin, and concentrated growth factor) combined with bone graft: a systematic review. Cells. 2023 Jul 6;12(13):1797. https://doi.org/10.3390/cells12131797
7. On SW, Park SY, Yi SM, Park IY, Byun SH, Yang BE. Current status of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillofacial surgery: should it be continued?. Bioengineering. 2023 Aug 24;10(9):1005. https://doi.org/10.3390/bioengineering10091005
8. Igelström E, Campbell M, Craig P, Katikireddi SV: Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: a methodological systematic review. J Clin Epidemiol. 2021, 140:22-32. 10.1016/j.jclinepi.2021.08.022
9. Hootman JM, Driban JB, Sitler MR, Harris KP, Cattano NM: Reliability and validity of three quality rating instruments for systematic reviews of observational studies. Res Synth Methods. 2011, 2:110-8. 10.1002/jrsm.41
10. Hayashino Y, Noguchi Y, Fukui T: Systematic evaluation and comparison of statistical tests for publication bias. J Epidemiol. 2005, 15:235-43. 10.2188/jea.15.235
11. Seifeldin SA. Is alveolar cleft reconstruction still controversial? (Review of literature). Saudi Dent J. 2016 Jan;28(1):3-11. doi: 10.1016/j.sdentj.2015.01.006. Epub 2015 Jun 25. PMID: 26792963; PMCID: PMC4688438.
12. Wiesli MG, Özcan M. High-Performance Polymers and Their Potential Application as Medical and Oral Implant Materials: A Review. Implant Dent. 2015 Aug;24(4):448-57. doi: 10.1097/ID.0000000000000285. PMID: 26035377.
13. Qu C, Luo F, Hong G, Wan Q. Effects of platelet concentrates on implant stability and marginal bone loss: a systematic review and meta-analysis. BMC Oral Health. 2021 Nov 12;21(1):579. doi: 10.1186/s12903-021-01929-x. PMID: 34772376; PMCID: PMC8588658.
14. Strauss FJ, Stähli A, Gruber R. The use of platelet-rich fibrin to enhance the outcomes of implant therapy: A systematic review. Clin Oral Implants Res. 2018 Oct;29 Suppl 18(Suppl Suppl 18):6-19. doi: 10.1111/clr.13275. PMID: 30306698; PMCID: PMC6221166.
15. Najeeb S, Khurshid Z, Zohaib S, Zafar MS. Therapeutic potential of melatonin in oral medicine and periodontology. Kaohsiung J Med Sci. 2016 Aug;32(8):391-6. doi: 10.1016/j.kjms.2016.06.005. Epub 2016 Jul 25. PMID: 27523451.
16. Pountos I, Giannoudis PV. Is there a role for coral bone substitutes in bone repair? Injury. 2016 Dec;47(12):2606-2613. doi: 10.1016/j.injury.2016.10.025. Epub 2016 Oct 26. PMID: 27836254.
17. Diachkova E, Trifonova D, Morozova E, Runova G, Ashurko I, Ibadulaeva M, Fadeev V, Tarasenko S. Vitamin D and Its Role in Oral Diseases Development. Scoping Review. Dent J (Basel). 2021 Nov 2;9(11):129. doi: 10.3390/dj9110129. PMID: 34821593; PMCID: PMC8618634.
18. Tomisa AP, Launey ME, Lee JS, Mankani MH, Wegst UG, Saiz E. Nanotechnology approaches to improve dental implants. Int J Oral Maxillofac Implants. 2011;26 Suppl(Suppl):25-44; discussion 45-9. PMID: 21464998; PMCID: PMC3087979.
19. Bressan E, Zucchelli G, Tommasato G, Pesce P, Canullo L, Consensus Meeting Group Iao, Grusovin MG. Consensus Report by the Italian Academy of Osseointegration on the Importance of Peri-Implant Soft Tissues. Medicina (Kaunas). 2024 Aug 26;60(9):1393. doi: 10.3390/medicina60091393. PMID: 39336434; PMCID: PMC11433715.
20. Czumbel LM, Kerémi B, Gede N, Mikó A, Tóth B, Csupor D, Szabó A, Farkasdi S, Gerber G, Balaskó M, Pétervári E, Sepp R,

Hegyi P, Varga G. Sandblasting reduces dental implant failure rate but not marginal bone level loss: A systematic review and meta-analysis. PLoS One. 2019 May 3;14(5):e0216428. doi: 10.1371/journal.pone.0216428. PMID: 31050690; PMCID: PMC6499471.

21. Rahnama-Hezavah M, Mertowska P, Mertowski S, Skiba J, Krawiec K, Łobacz M, Grywalska E. How Can Imbalance in Oral Microbiota and Immune Response Lead to Dental Implant Problems? Int J Mol Sci. 2023 Dec 18;24(24):17620. doi: 10.3390/ijms242417620. PMID: 38139449; PMCID: PMC10743591.
22. Pidhatika B, Widyaya VT, Nalam PC, Swasono YA, Ardhani R. Surface Modifications of High-Performance Polymer Polyetheretherketone (PEEK) to Improve Its Biological Performance in Dentistry. Polymers (Basel). 2022 Dec 16;14(24):5526. doi: 10.3390/polym14245526. PMID: 36559893; PMCID: PMC9787615.
23. Palmquist A. A multiscale analytical approach to evaluate osseointegration. J Mater Sci Mater Med. 2018 May 7;29(5):60. doi: 10.1007/s10856-018-6068-y. PMID: 29736606; PMCID: PMC5938308.
24. Santos PL, Gulinelli JL, Telles Cda S, Betoni Júnior W, Okamoto R, Chiacchio Buchignani V, Queiroz TP. Bone substitutes for peri-implant defects of postextraction implants. Int J Biomater. 2013;2013:307136. Doi: 10.1155/2013/307136. Epub 2013 Dec 12. PMID: 24454377; PMCID: PMC3876702.
25. He Y, Bao W, Wu XD, Huang W, Chen H, Li Z. Effects of Systemic or Local Administration of Zoledronate on Implant Osseointegration: A Preclinical Meta-Analysis. Biomed Res Int. 2019 Sep 22;2019:9541485. Doi: 10.1155/2019/9541485. PMID: 31663000; PMCID: PMC6778941.
26. Li Y, Brånemark R. Osseointegrated prostheses for rehabilitation following amputation: The pioneering Swedish model. Unfallchirurg. 2017 Apr;120(4):285-292. doi: 10.1007/s00113-017-0331-4. PMID: 28229193; PMCID: PMC5371647.
27. Saulacic N, Schaller B. Prevalence of Peri-Implantitis in Implants with Turned and Rough Surfaces: a Systematic Review. J Oral Maxillofac Res. 2019 Mar 31;10(1):e1. Doi: 10.5037/jomr.2019.10101. PMID: 31069039; PMCID: PMC6498817.
28. Ibrahim SW, Hamad TI, Haider J. Biological properties of polycaprolactone and barium titanate composite in biomedical applications. Sci Prog. 2023 Oct-Dec;106(4):368504231215942. doi: 10.1177/00368504231215942. PMID: 38031343; PMCID: PMC10687994.
29. Lagerkvist H, Carvalho K, Holmberg M, Petersson U, Cremers C, Hultcrantz M. Ten years of experience with the Ponto bone-anchored hearing system: systematic literature review. Clin Otolaryngol. 2020 Sep;45(5):667-680. doi: 10.1111/coa.13556. Epub 2020 May 25. PMID: 32386454; PMCID: PMC7496709.
30. Damerau JM, Bierbaum S, Wiedemeier D, Korn P, Smeets R, Jenny G, Nadalini J, Stadlinger B. A systematic review on the effect of inorganic surface coatings in large animal models and meta-analysis on tricalcium phosphate and hydroxyapatite on periimplant bone formation. J Biomed Mater Res B Appl Biomater. 2022 Jan;110(1):157-175. Doi: 10.1002/jbm.b.34899. Epub 2021 Jul 16. PMID: 34272804; PMCID: PMC9292919.
31. Pandey C, Rokaya D, Bhattarai BP. Contemporary Concepts in Osseointegration of Dental Implants: A Review. Biomed Res Int. 2022 Jun 14;2022:6170452. Doi: 10.1155/2022/6170452. PMID: 35747499; PMCID: PMC9213185.
32. Insua A, Monje A, Wang HL, Miron RJ. Basis of bone metabolism around dental implants during osseointegration and peri-implant bone loss. J Biomed Mater Res A. 2017 Jul;105(7):2075-2089. Doi: 10.1002/jbm.a.36060. Epub 2017 Mar 28. PMID: 28281321.
33. Agarwal R, García AJ. Biomaterial strategies for engineering implants for enhanced osseointegration and bone repair. Adv Drug Deliv Rev. 2015 Nov 1;94:53-62. Doi: 10.1016/j.addr.2015.03.013. Epub 2015 Apr 8. PMID: 25861724; PMCID: PMC4598264.
34. Elgali I, Omar O, Dahlin C, Thomsen P. Guided bone regeneration: materials and biological mechanisms revisited. Eur J Oral Sci. 2017 Oct;125(5):315-337. doi: 10.1111/eos.12364. Epub 2017 Aug 19. PMID: 28833567; PMCID: PMC5601292.
35. Albrektsson T, Johansson C. Osteoinduction, osteoconduction and osseointegration. Eur Spine J. 2001 Oct;10 Suppl 2(Suppl 2): S96-101. Doi: 10.1007/s005860100282. PMID: 11716023; PMCID: PMC3611551.
36. Smeets R, Stadlinger B, Schwarz F, Beck-Broichsitter B, Jung O, Precht C, Kloss F, Gröbe A, Heiland M, Ebker T. Impact of Dental Implant Surface Modifications on Osseointegration. Biomed Res Int. 2016;2016:6285620. doi: 10.1155/2016/6285620. Epub 2016 Jul 11. PMID: 27478833; PMCID: PMC4958483.
37. Shayeb MA, Elfadil S, Abutayyem H, Shqaidef A, Marrapodi MM, Cicciù M, Minervini G. Bioactive surface modifications on dental implants: a systematic review and meta-analysis of osseointegration and longevity. Clin Oral Investig. 2024 Oct 11;28(11):592. doi: 10.1007/s00784-024-05958-y. PMID: 39392473; PMCID: PMC11469970.
38. Werny JG, Sagheb K, Diaz L, Kämmerer PW, Al-Nawas B, Schiegnitz E. Does vitamin D affect osseointegration of dental implants? A systematic review. Int J Implant Dent. 2022 Apr 11;8(1):16. doi: 10.1186/s40729-022-00414-6. PMID: 35403929; PMCID: PMC9001786.
39. D'Ambrosio F, Amato A, Chiacchio A, Sisalli L, Giordano F. Do Systemic Diseases and Medications Influence Dental Implant Osseointegration and Dental Implant Health? An Umbrella Review. Dent J (Basel). 2023 Jun 5;11(6):146. doi: 10.3390/dj11060146. PMID: 37366669; PMCID: PMC10296829.
40. Miron RJ, Bohner M, Zhang Y, Bosshardt DD. Osteoinduction and osteoimmunology: Emerging concepts. Periodontol 2000. 2024 Feb;94(1):9-26. doi: 10.1111/prd.12519. Epub 2023 Sep 1. PMID: 37658591.
41. Albrektsson T, Tengvall P, Amengual L, Coli P, Kotsakis GA, Cochran D. Osteoimmune regulation underlies oral implant osseointegration and its perturbation. Front Immunol. 2023 Jan 24;13:1056914. doi: 10.3389/fimmu.2022.1056914. PMID: 36761175; PMCID: PMC9902598.
42. Buzatu BLR, Buzatu R, Luca MM. Impact of Vitamin D on Osseointegration in Dental Implants: A Systematic Review of

Human Studies. Nutrients. 2024 Jan 9;16(2):209. doi: 10.3390/nu16020209. PMID: 38257102; PMCID: PMC10819660.

43. Sun H, Meng S, Chen J, Wan Q. Effects of Hyperlipidemia on Osseointegration of Dental Implants and Its Strategies. J Funct Biomater. 2023 Mar 30;14(4):194. doi: 10.3390/jfb14040194. PMID: 37103284; PMCID: PMC10145040.
44. Bergamo ETP, Zahoui A, Barrera RB, Huwais S, Coelho PG, Karateew ED, Bonfante EA. Osseodensification effect on implants' primary and secondary stability: Multicenter controlled clinical trial. Clin Implant Dent Relat Res. 2021 Jun;23(3):317-328. doi: 10.1111/cid.13007. Epub 2021 May 27. PMID: 34047046; PMCID: PMC8362055.
45. Li JTW, Leung YY. Effect of Antiresorptive Drugs on Osseointegrated Dental Implants: A Systematic Review. J Clin Med. 2024 Apr 3;13(7):2091. doi: 10.3390/jcm13072091. PMID: 38610856; PMCID: PMC11012270.
46. Patel V, Sadiq MS, Najeeb S, Khurshid Z, Zafar MS, Heboyan A. Effects of metformin on the bioactivity and osseointegration of dental implants: A systematic review. J Taibah Univ Med Sci. 2022 Aug 4;18(1):196-206. Doi: 10.1016/j.jtumed.2022.07.003. PMID: 36398019; PMCID: PMC9643507.
47. Sun R, Bai L, Yang Y, Ding Y, Zhuang J, Cui J. Nervous System-Driven Osseointegration. Int J Mol Sci. 2022 Aug 10;23(16):8893. doi: 10.3390/ijms23168893. PMID: 36012155; PMCID: PMC9408825.
48. Chandran S, John A. Osseointegration of osteoporotic bone implants: Role of stem cells, Silica and Strontium - A concise review. J Clin Orthop Trauma. 2019 Oct;10(Suppl 1):S32-S36. doi: 10.1016/j.jcot.2018.08.003. Epub 2018 Aug 4. PMID: 31695257; PMCID: PMC6823697.
49. Alghamdi HS. Methods to Improve Osseointegration of Dental Implants in Low Quality (Type-IV) Bone: An Overview. J Funct Biomater. 2018 Jan 13;9(1):7. doi: 10.3390/jfb9010007. PMID: 29342830; PMCID: PMC5872093.
50. Stacchi C, Coyac BR, Helms JA. Biomechanical Basis for Bone Healing and Osseointegration of Implants in Sinus Grafts. Clin Implant Dent Relat Res. 2025 Feb;27(1):e13424. doi: 10.1111/cid.13424. Epub 2024 Dec 5. PMID: 39637842; PMCID: PMC11798898.
51. Asa'ad F, Pelanyte G, Philip J, Dahlin C, Larsson L. The Role of Epigenetic Functionalization of Implants and Biomaterials in Osseointegration and Bone Regeneration Review. Molecules. 2020 Dec 12;25(24):5879. doi: 10.3390/molecules25245879. PMID: 33322654; PMCID: PMC7763898.
52. Ghosh M, Gupta R, Jain RA, Mehra R, Verma M. Role and influence of growth factors on early osseointegration in animal jaw bone: A meta-analysis. J Indian Prosthodont Soc. 2020 Apr-Jun;20(2):153-161. doi: 10.4103/jips.jips_385_19. Epub 2020 Apr 7. PMID: 32655219; PMCID: PMC7335027.
53. Parnia F, Yazdani J, Javaherzadeh V, Maleki Dizaj S. Overview of Nanoparticle Coating of Dental Implants for Enhanced Osseointegration and Antimicrobial Purposes. J Pharm Pharm Sci. 2017;20(0):148-160. doi: 10.18433/J3GP6G. PMID: 28554344.
54. Walter N, Stich T, Docheva D, Alt V, Rupp M. Evolution of implants and advancements for osseointegration: A narrative review. Injury. 2022 Nov;53 Suppl 3:S69-S73. doi: 10.1016/j.injury.2022.05.057. Epub 2022 Aug 4. PMID: 35948509.
55. Tallon E, Macedo JP, Faria A, Tallon JM, Pinto M, Pereira J. Can Vitamin D Levels Influence Bone Metabolism and Osseointegration of Dental Implants? An Umbrella Review. Healthcare (Basel). 2024 Sep 17;12(18):1867. doi: 10.3390/healthcare12181867. PMID: 39337208; PMCID: PMC11431482.
56. Sedgwick P, Marston L: How to read a funnel plot in a meta-analysis. BMJ. 2015, 351:h4718. 10.1136/bmj.h4718
57. Harbord RM, Egger M, Sterne JA: A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006, 25:3443-57. 10.1002/sim.2380
58. Andrade C: Understanding the basics of meta-analysis and how to read a forest plot: as simple as it gets. J Clin Psychiatry. 2020, 81:20f13698. 10.4088/JCP.20f13698