Review

Role and influence of growth factors on early osseointegration in animal jaw bone: A meta-analysis

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Abstract

Aim: Growth factors (GFs) are polypeptides, which are intricately involved in the regulation of bone formation, preservation, and regeneration through gene expression. However, the role of these bioactive agents in osseointegration of dental implants has not been substantially proven. The objective of this systematic review (SR) and meta-analysis was to explore the effect of GFs on early osseointegration of dental implants in animal jaws. An attempt to decipher an adjunctive role of GFs in modulating predictable bone growth in peri-implant areas was done.

Materials and Methods: An electronic and manual search of different databases was performed. Only randomized controlled trials (RCTs) were included and reviewed. The risk of bias (ROB) of the selected studies was assessed using the SR Centre for Laboratory Animal Experimentation (Cochrane) tool. A meta-analysis was also performed to evaluate the different study characteristics quantitatively.

Statistical Analysis used: The total Weighted mean difference was evaluated using the Rev-Manv5.3 algorithm. Chi-square test and I^2 test were done to assess the heterogeneity between the studies.

Results: Seven RCTs were included in the study. These were associated with a high ROB. The total weighted mean difference (WMD) of the percentage of bone–implant contact was 3.25% (95% confidence interval [CI] = 1.49%–6.03%; $P = 0.001$; $I^2 = 91\%$) between groups with and without exogenous application of GFs. The total WMD of the percentage of newly formed bone area was 4.48% (95% CI = 2.31%–5.90%; $P < 0.00001$, $I^2 = 84\%$). A high level of heterogeneity ($P < 0.001$ for Chi-square test; $I^2 > 50\%$) among comparable studies was observed.

Conclusion: The ancillary application of external GFs exhibited evidence of early osseointegration, resulting in more predictable and faster results. However, a careful discernment of conclusions drawn from this SR is a must before conducting any human trials.

Keywords: Dental implants, early osseointegration, growth factors

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INTRODUCTION

Dental implant has been acknowledged as one of the most successful and evidence-based treatment modalities for partial and complete edentulism.[1] Osseointegration is a biological phenomenon by which the implant makes a direct structural and functional contact with the living bone without any intervening fibrous tissue.[2,3] Predictable osseointegration is the basic tenet for a successful implant therapy.[3]

Although implants demonstrate superior functional recovery, they must undergo an intricate chain of events during osseous remodeling at the bone–implant interface. Implant placement elicits a cascade of biological events leading to simultaneous resorption of the surrounding bone and *de novo* bone formation at the bone–implant interface.[4] This healing phase may take up to 6 months or more.[5] A reduction in postoperative healing time can be achieved by accelerated osseointegration.[6] To achieve this objective, the induction of regeneration of adjacent tissues through an external stimulus may be an approach.[7,8]

The advent of tissue engineering has enabled to biologically functionalize the implant surface.[9] Growth factors (GFs) are one such "osteoinductive scaffolds" that are believed to stimulate undifferentiated cells into osteoblasts.[10] They serve as chemoattractants for undifferentiated mesenchymal cells, thereby regulating angiogenesis, chemotaxis, and cellular multiplication.[7] Bone morphogenetic proteins (BMPs), platelet-derived GF (PDGF), vascular endothelial GF, nerve GF, and fibroblast GF (FGF) are some of the GFs that are being extensively studied in this regard.[11-15]

GFs have also been recognized to play a beneficial role in cases of immediate implantation or complex alveolar defects. They provide for an effective tool to enhance the rate of osseointegration of dental implants, especially by increasing the rate of tissue regeneration. Efforts are therefore being made to incorporate such biomimetic proteins on the surface of the implant.[16-19] However, GFs have been associated with a few adverse effects too, such as osteoclast-regulated bone resorption[19] and facial edema.[11] Hence, *in vivo* studies have been primarily preferred in animal models to determine the safety and efficacy of the same.

The primary objective of this systematic review (SR) was to evaluate the role of GFs in the early osseointegration of dental implants in animal jaws. An evaluation of the key parameters of osseointegration such as bone–implant contact (BIC), implant stability quotients, and new bone implant area was performed.[10] An appraisal of the delivery methods[20] and optimal concentration of GFs was also done.

The specific question formulated using the PICOT (P: Population, I: Intervention, C: Comparison, O: Outcome, T: Time, S: Study design) format was "What is the role of GFs (I/C) on early (T) implant osseointegration (O) in animal jaws (P)?"

MATERIALS AND METHODS

The preferred reporting items for SRs and meta-analyses guidelines formed the basis for this review.

Study design

Type of study: Randomized controlled trials (RCTs).

Type of participants: Animals receiving implants placed in their jaws.

Type of intervention: Exogenous application of GFs either on implant surface or at the osteotomy site.

Type of comparison: Implants receiving exogenous GFs versus implants not receiving any exogenous GFs.

Type of outcome: Early implant osseointegration.

Time: Less than or up to 3 months.

Inclusion criteria

1. RCT done on animals
2. The implant surface or the implant osteotomy received an exogenous application of GFs
3. Dental implants placed in the jaws of the animal to stimulate the salivary atmosphere
4. The healing period considered was less than or up to 3 months to include only those studies which signify early osseointegration
5. Control groups were clearly mentioned
6. Evaluation of implant osseointegration was done by local invasive and noninvasive methods such as histologic, histomorphometric, and radio frequency analysis.

Exclusion criteria

1. Articles with full text not available
2. Studies on isolated bone defects and bone augmentation
3. *In vitro* studies, case reports, and literature reviews
4. Studies with the placement of implants in the tibia, femur, or any other location apart from the jaws.

The electronic databases PubMed, Ovid and SCOPUS were searched for relevant titles and abstracts, in English, without time restrictions in July 2019. The keywords/medical subject headings terms used for the search strategies were "growth factors" or "GF" and "osseointegration" or "bone formation" and "dental implant" or "endosseous implants". The list of references of the pertinent articles was scanned manually as an adjunct to the electronic search. Articles written in other languages were considered if their written translations were available in English.

The titles and abstracts of the studies obtained by the search protocol were checked and the irrelevant articles and duplicates were excluded. Full texts of the publications considered suitable based on an appraisal of their abstracts were further read and screened for their eligibility. Two reviewers (M.G and R.J) selected the studies with the pre-decided criteria. Disagreements were resolved by a third reviewer (R.G) [Figure 1].

The following data were recorded from each study: first author, publication year, type of animal, number of animals, implant characteristics, number of implants, type of GF, quantity of GF, mode of application of GF, healing period, BIC percentage, newly formed bone, bone density, and implant stability quotient.

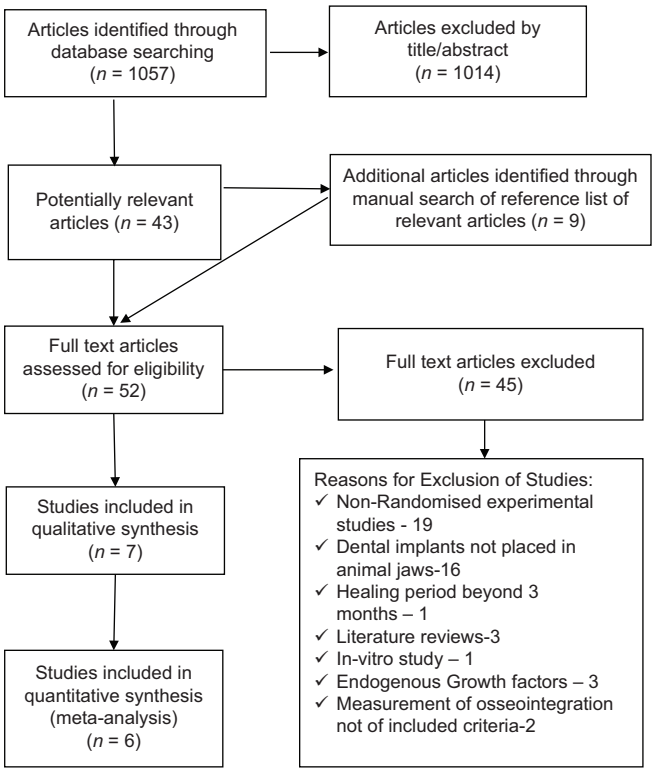


Figure 1: Article selection flowchart based on the inclusion and exclusion criteria

The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk-of-bias (ROB) tool having the Cochrane risk guidelines was used for the evaluation. The following appraisals were done from the selected studies: selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting).The ROB was adjudged as high, low, or moderate on the basis of the above-mentioned domains. A common consensus paved the way for resolving any disagreement.

Meta-analysis could be done only for the percentage of newly formed bone in the regenerated tissue and percentage of BIC. The analysis of adverse effects was not possible because of the lack of systematic reporting. RevMan v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was used to assess the total weighted mean difference (WMD) between the results with and without the use of GF. Each article was individually assessed for its results. The Chi-square test and the I^2 test were used to assess heterogeneity. Normally, in case of low I^2 value, a fixed-effect model is used, and in high I^2 value, random-effect model is adopted. To graphically represent both the results for all the included studies, forest plots were generated. The confidence intervals (CIs) were stated at 95% levels ($a = 0.05$).

RESULTS

The related articles were shortlisted in accordance with the corresponding flowchart [Figure 1]. Once the three electronic search engines were searched for the selection of the articles, 1057 articles were identified through database searching. Potentially relevant articles after reading the titles to abstracts amounted to 43. After manual screening through references of the shortlisted articles, nine more were included. Figure 1 highlights the reasons for excluding 45 of the 52 articles assessed. The rest of the seven studies formed the basis of the present review.

The essentials of these seven studies have been tabulated in Tables 1 and 2. The nature of the GF delivery and implant surgery varied in different studies. The studies by Wang *et al.* and Xu *et al.* had immediate placement of coated implants.[25,26] Three of the remaining studies applied exogenous GF at the osteotomy site.[21,22,27] The remaining two studies involved conventional placement of coated dental implants in animal jaws.[23-25] All studies were conducted among canines (dogs) except Wang *et al.* and Guzalinuer who used rabbits.[26,27]

The measurement of osseointegration was done as per the study by Chang.[10] This included histomorphometric analysis (BIC and bone–implant area formed), histologic methods through staining or computerized evaluation, and radiofrequency analysis. Density of the new bone deposited was measured only in one study.[22] Two of the studies considered the concentrations of the GFs used as a factor affecting the level of osseointegration.[22,24]

The ROB assessed for the shortlisted studies using the SYRCLE tool is tabulated in Table 3. Baseline characteristics were mentioned in all the included studies, thus allowing intra- and interstudy comparisons. A lack of mention of the method of blinding and allocation concealment suggested a high selection and performance bias. It was hard to judge the detection bias, as most of the articles did not mention performance bias and blinding for outcome detection. All the studies were seen to follow the study protocol along with a clear mention of sample loss. This resulted in a low risk of attrition and reporting bias. A high reporting bias was seen in the study by Wikesjö *et al.* because of incomplete BIC results. To summarize, all studies included in the review were found to have a high ROB. Publication bias however could not be assessed using a funnel plot because the number of articles included was <10.

Table 4 gives the meta-analysis of four studies reporting the percentage of BIC in the regenerated tissue using

Table 1: Study characteristics: Materials and Methods

Study characteristics			Material and methods					
Author, date	Animal	Population	Growth factor	Mode of application	Implant characteristic	Number of implant placed	Healing period	Measurement of osseointegration
1. Meraw *et al.*, 2000[21]	Hound dogs (adults)	*n*=5	BMP-2 + PDGF + bFGF + TGF-b	Growth factor cement packed in to 0.75 mm circumferential defect	Smooth machine-polished titanium	30	3 months	Histological examination with a semiautomated computerized technique
2. Wikesjö *et al.*, 2008[22]	Hound Labrador mongrel dogs. (adults)	*n*= 12	rh-BMP-2 at 1.5 ml or rh-BMP-2 at 3.0 ml	Coating of sterile implants in lyophilized rh-BMP-2. Incubation for 30 min followed by air drying for 6 h or overnight	Titanium porous oxide implant with a reference notch 5 mm apical to implant platform	48	8 weeks	Histotechnical examination including flourecent light microscopy, Stevenel's blue and picro fuschin stain
3. Al-Hezaimi *et al.*, 2013[23]	Female beagle dogs	*n*=6	Commercially available rh-PDGF-BB or prototype viscous rh-PDGF-BB	Coating of implants 15 min prior to the insertion	Tapered 3.4 × 8.5, blasted, acid etched, and hydroxyapatite discrete crystal deposited titanium implant	24	3 and 6 weeks	Histological evaluation including RBS and acid fushsin counter stain and light microscopy. Radio frequency analysis using osstell
4. Kim *et al.*, 2015[24]	Beagle dogs (adults)	*n*=4	rh-BMP-2 at 0.1, 0.5 and 1 mg/ml	Coating of implants by immersion in protein solution	7 mm × 3.5 mm titanium implants SLA	24	8 weeks	Implant stability and histomorphometric analysis of flourochrome labelling using laser microscopy
5. Xu *et al.*, 2015[25]	Male Labrador dogs (adults)	*n*=6	rh-PDGF-BB + BMSCs + b-TCP	Growth factor filled constructs packed in the mesial part of immediate sockets	3.75 mm × 10 mm pure titanium implants were installed into the distal area of the bone defect	24	12 weeks	Histologic and histomorphometric analysis using van Gieson's picro fuchsin and observed under light microscopy
6. Wang *et al.*, 2017[26]	New Zealand rabbit (young)	*n*=36 in 3 groups	TGF-b3 + DPSC	DPSC + TGF-b3 + PBS filled in the immediate osteotomy sites	3 ×1 0 mm titanium implants with SLA surface	72	4 and 8 weeks	Alizarin red staining immune-histochemical detection of bone sialoprotein, osteocalcin and Type I collagen and histomorphometric analysis
7. Guzalinur, 2018[27]	New Zealand rabbit (young)	*n*= 18	TGF-b3 + DPSC	DPSC + TGF-b3 + PBS filled in the osteotomy sites	3 mm × 10 mm titanium implants with SLA surface	36	2 weeks	HE staining, immunohistochemical staining and real-time PCR

*BMP-2: Bone morphogenetic protein-2, PDGF: Platelet-derived growth factor, bFGF: b-fibroblast growth factor, TGF-b: Transforming growth factor, rh-PDGF-BB: Recombinant platelet growth factor-BB, BMSCs: Bone marrow stem cells, b-TCP: b-tricalcium phosphate, DPSC: Dentin pulp stem cell, SLA: Sandblasted with large grit and acid etched, rh-BMP-2: Recombinant human - BMP-2, RBS: Random blood sugar, PCR: Polymerase chain reaction, PBS: Phosphate buffer saline, HE: Heamatoxylin-eosin staining

Table 2: Study characteristics: Results and Conclusion

		Results				Conclusion
Author, date	Variables of osseointegration measured	Percentage new bone area formed (% or mm^2)	BIC (%)	Bone density of new bone (%)	Implant stability quotient	
1. Meraw *et al.*, 2000[21]	BIC and amount of bone per area	Growth factor cement=76.8±3.7 Plain cement=67.4±6.2 Control=64±4.2	Growth factor cement=77.4±7.2 Plain cement=59.2±12.6 Control=54.8±12.3	N/A	N/A	Significant effect of GFC on increased bone-to-implant contact and amount of bone per surface area within peri-implant defects
2. Wikesjö *et al.*, 2008[22]	Percent BIC of new bone and resident bone, area of newly formed bone, bone density	0.75 mg/ml=5.0±2.2 1.5 mg/ml=5.6±2.2 3.0 mg/ml=7.4±3.5 Control=0.7±0.3	N/A	0.75 mg/ml=72 1.5 mg/ml=62 3.0 mg/ml=60 Control=40	N/A	rh-BMP-2 coated onto titanium porous oxide implant surfaces induced clinically relevant local bone formation including vertical augmentation of the alveolar ridge and osseointegration. Higher concentrations/doses were associated with untoward effects
3. Al-Hezaimi *et al.*, 2013[23]	Percent BIC	N/A	At 3 weeks, control=58.7±4.1 Commercially=78.0±12.5 Prototype=59.4±17.6%	N/A	N/A	Results of this study showed that the implant surface that is utilized in this study can be a suitable carrier for rh-PDGF-BB. The study provides evidence that use of rh-PDGF-BB surface treatment improved initial bone formation and enhanced early osseointegration
4. Kim *et al.*, 2015[24]	Percent BIC, bone volume percent, implant stability	N/A	Control=0.67±1.15 0.1 mg/ml=10.24±10.99 0.5 mg/ml=24.47±6.63 1.0 mg/ml=18.42±8.65	N/A	Control=60.17±3.25–0.1 mg/ml=64.83±3.19–0.5 mg/ml=71.67±6. –1.0 mg/ml=72.00±2.68	In the open defect area surrounding the SLA implant, coating with 0.5 and 1.0 mg/mL concentrations of rh-BMP-2 was more effective, compared with untreated group, in promoting bone regeneration and osseointegration
5. Xu *et al.*, 2015[25]	Percentage of new bone area and BIC	1. BMSCs/rh-PDGF-BB/β-TCP=48.73±9.48 2. BMSCs/β TCP=35.74±7.18 3. rh-PDGF-BB/β-TCP=32.5±6.09 4.β-TCP alone=19.1±6.63	1. BMSCs/rh-PDGFBB/β-TCP=72.51±10.98 2. BMSCs/β TCP=50.88±6.68 3. rh-PDGF-BB/β-TCP=46.31±9.06 4. β-TCP alone=31.95±6.56	N/A	N/A	Tissue-engineered bone consisting of rh-PDGF-BB/BMSCs/β-TCP significantly promoted new bone formation in defects around implants in canine mandibles in vivo. Furthermore, osseointegration between the tissue-engineered bone and dental implants was enhanced by the use of rh-PDGF-BB/BMSCs/β-TCP construct
6. Wang *et al.*, 2017[26]	Implant bone contact rate, trabecular width and trabecular area percentage	PBS=13.31±1.96 DPSC=27.67±3.19 TGF-b3 + DPSC=51.23±7.26	PBS=36.92±4.53 DPSC=47.16±4.17 TGF-b3 + DPSC=76.28±3.35	N/A	N/A	DPSC has osteogenic differentiation potential; TGF-b3 can promote the osteogenic differentiation of DPSC; TGF-b3 combined with DPSC can effectively promote the osseointegration of implants
7. Guzalinur, 2018[27]	Percentage of new implant-bone area	Experimental=24.6±5.3 Control=11.3±2.8 Blank=7.6±3.8	N/A	N/A	N/A	The bone quality and number of newly formed bone cells were better in the experimental group than the other two.TGF-b3 has the potential to promote transformation of DPSc into osteoblasrs and promote osseointegrationaround the dental implant

*BMP-2: Bone morphogenetic protein-2, PDGF: Platelet-derived growth factor, TGF-b: Transforming growth factor, rh-PDGF-BB: Recombinant platelet growth factor-BB, BMSCs: Bone marrow stem cells, b-TCP: b-tricalcium phosphate, DPSC: Dentin pulp stem cell, PBS: Phosphate buffer solution, N/A: Not available, SLA: Sandblasted with large grit and acid etched, rh-BMP-2: Recombinant human - BMP-2, BIC: Bone-implant contact, GFC : Growth factor Cement, N/A : Not available

histomorphometric measurements.[21,23,25,26] The total WMD of the percentage of BIC was 3.25% (95% CI = 1.49% to 6.03%; $P = 0.001$; $I^2 = 91$ %). These studies revealed a high degree of heterogeneity ($P < 0.00001$ for Chi-square test; $I^2 = 91\%$).

Four studies[21,25-27] reported the percentage of newly formed bone for the second meta-analysis as computed in Table 5. However, studies by Wikesjö *et al.* and Kim *et al.* could not be included as their results were reported in square millimetre and not in percentage, thus precluding their use in the meta-analysis.[22,24] For newly formed bone, the pooled WMD of the percentage of newly formed bone was 4.48% (95% CI = 2.31% to 5.90%; $P < 0.00001$, $I^2 = 84\%$). A high degree of heterogeneity ($P = 0.0003$ for Chi-square test; $I^2 = 84\%$) was found in the included studies.

DISCUSSION

This SR and meta-analysis aimed at evaluating the effect of GFs on early osseointegration of dental implants in animal jaws. Randomized control trial studies were only included as they are associated with a higher level of evidence as compared to nonrandomized experimental studies.[28] Till date, there is a lack of human studies in this research question, highlighting the fact that there needs to be substantial safety evidence to use GFs in the living tissue along with dental implants. Hence, an SR was done to understand the efficacy of use of GFs around dental implants in animals.

The purpose of choosing animal jaws as the site of implant placement was to acknowledge the influence of oral native conditions on the physiology of osseointegration.[29] There

Table 3: Risk of bias of the seven shortlisted studies

	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding for performance bias	Random outcome assessment	Blinding for detection bias	Incomplete outcome data	Selective outcome reporting
Wang T. 2017	+	+	–	–	–	–	–	+	+
Wikesjo UM. 2008	?	+	–	?	–	–	+	+	+
Xu L. 2015	–	+	–	?	–	–	+	+	+
Al-Hezaimi K. 2014	+	+	–	?	–	–	–	+	+
Kim NH. 2015	?	+	–	?	–	–	–	+	+
Meraw SJ. 2000	?	+	–	–	–	–	+	+	+
Guzalinuer A. 2018	+	+	–	–	–	–	–	+	+

+Low risk of bias, -High risk of bias, ?Unclear risk of bias

Table 4: Meta-analysis: Bone-Implant Contact

Study or Subgroup	Experimental			Control			Std.Mean Difference		
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Meraw 2000	77.4	7.2	10	54.8	12.3	10	26.4%	2.15 [1.00, 3.30]	2000
Al-Hezaimi 2013	78	12.5	12	58.7	4.1	12	26.8%	2.00 [0.99, 3.02]	2013
Ling 2015	72.51	10.98	6	31.95	6.56	6	21.9%	4.14 [1.82, 6.46]	2015
Wang 2017	51.23	7.26	24	13.31	1.96	24	24.9%	7.01 [5.44, 8.58]	2017
Total (95% CI)			52			52	100.0%	3.76 [1.49, 6.03]	

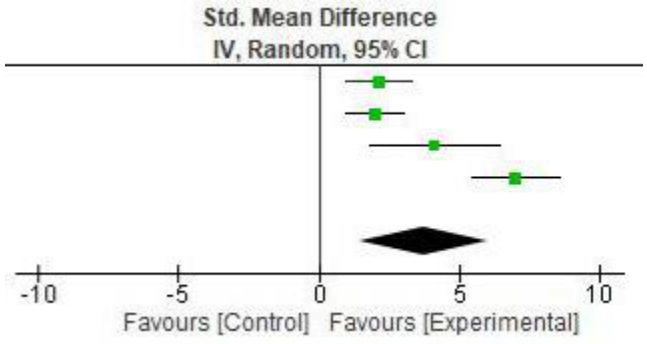
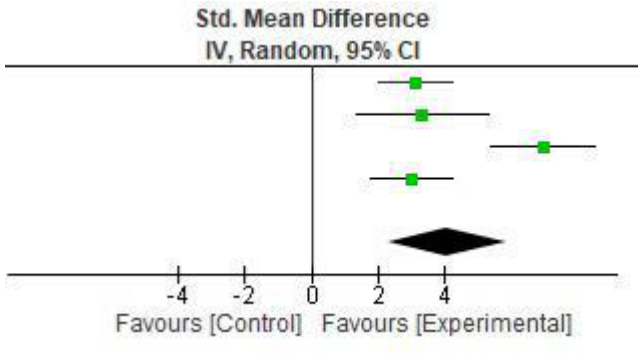


Table 5: Meta-analysis: Newly formed bone area

Study	Experimental			Control			Std.Mean Difference		
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Meraw 2000	76.8	3.7	15	64	4.2	15	27.0%	3.15 [2.03, 4.26]	2000
Ling 2015	48.73	9.48	6	19.1	6.63	6	22.0%	3.34 [1.36, 5.33]	2015
Wang 2017	51.23	7.26	24	13.31	1.96	24	24.5%	7.01 [5.44, 8.58]	2017
Guzalinur 2018	24.6	5.3	12	11.3	2.8	12	26.4%	3.03 [1.80, 4.26]	2018
Total (95% CI)			57			57	100.0%	4.11 [2.31, 5.90]	



were studies that had evaluated the osseointegration for a period >3 months.[30] However, the purpose of this study was to evaluate how effective the biologic mediators are in terms of rate of bone regeneration and amount of new bone formation for a duration of less than or up to 3 months. This was of clinical significance as GFs could be effective tools to increase implant stability in a shorter than the normal time period, especially in cases of immediate implantation, thereby shortening the overall rehabilitation span.[31]

Several GFs were researched on the RCTs included in this review, of which rh-BMP-2 was studied the most extensively. As concluded by Meraw, 2000; Wikesjö, 2008; and Kim, 2015 in their respective RCTs, transforming GF β-3 (Wang, 2017) and PDGF (Xu, 2015) can play a pivotal role in accelerating new bone formation, especially around immediate titanium implants.[25,26]

In the seven studies included in the SR, most of them had used a combination of GFs or a mix of GFs with stem cells. As concluded by Meraw *et al.*, a combination may be better than a single GF as early bone healing involves complex events and interactions.[21] As noted by Kaigler *et al.*, combination products unite tissue-specific matrices with highly concentrated bioactive peptides to amplify tissue regenerative capacity.[12]

The concentration of GFs to be used was another point to be noted. Wikesjö *et al* concluded that an optimum concentration of 1.5 mg/ml of rh-BMP-2 was found to have a higher regenerative bone capacity in contrast to higher concentrations of GF.[22] Kim *et al.* asserted that values up to 1mg/ml of rh-BMP-2 were found to be effective in promoting osseointegration.[24] Less dense bone found with 3 mg/ml of rh-BMP-2[22] could be attributed to more extensive and aggressive bone remodeling and seroma formation observed with higher concentrations.[32]

The mode of local delivery of GFs was also an essential factor influencing their efficacy. According to Lee, a controlled sustained release of GFs was better than rapid bolus release. Therefore, a proper carrier for the GFs on the dental implants is of utmost importance. For this very reason, the study by Wikesjö highlighted the role of titanium porous oxide surface with open pores to be an effective rh-BMP2 carrier. In the study by Meraw *et al.*, the use of a bioabsorbable cement served to deliver a combination of BMP-2, TGF-β, FGF, and PDGF.

Along with the SR, a meta-analysis was conducted to understand the overall effect of exogenous GFs on percentage of BIC and amount of new bone formation. Forest plots, used as an integral tool in meta-analysis, provided a visual assessment of the individual studies and cumulative treatment effect of the studies. As observed in both the forest plots, noticeable between-study variability was noted though each study's treatment effect was on the same side of the line of no effect. In addition, the individual treatment effect did not line up on a vertical axis, indicating a difference in treatment effect magnitude among studies. To make the interpretation absolute, statistical heterogeneity was computed using I^2 values. In the present study, a high level of heterogeneity was observed in the meta-analysis (as depicted by high I^2 value) of new peri-implant bone area formed and BIC. This may be due to a

number of confounding variables – difference in the nature and amount of GFs used, animals experimented, type of surface treatment of dental implants, surgical procedures employed, and different methods of histomorphometric analysis. In case of studies with a high I^2 value (>50%), the bias caused by differences in methodology of included studies was minimized by applying a random-effect model. Likewise, a high heterogeneity advocates a cautious approach toward the results.

All the included studies reported a positive association between the use of GFs and increased rate and amount of osseointegration. This positive association was determined using the "*Z*" statistics (as evident in the meta-analysis). A significant *Z*-test means that the effect size is non-zero, hence making the $P < 0.001$.

However, randomized control studies having greater sample size and longer follow-up are needed to decrease the heterogeneity among studies. Furthermore, a higher level of substantiation, based on the uniform standardized protocols, is necessary to eliminate the possibility of any adverse effects with the use of these bioinductive surface treatments.

CONCLUSION

This SR and meta-analysis were conducted to elucidate the role of ancillary application of exogenous GFs on the rate and amount of osseointegration. The favorable results exhibited by external GFs in conjunction with stem cells and other biomimetic agents can be used to fulfill the need of early osseointegration, thus promoting more predictable and faster results. However, as noted from the meta-analysis, there is a high degree of interstudy variability and statistical heterogeneity. This calls for more evidence-based randomized control trials based on an acceptable standardized protocol for more definitive interpretation.

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Conflicts of interest
There are no conflicts of interest.

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