Journal of
Clinical & Medical Surgery

www.jclinmedsurgery.com

ISSN 2833-5465
Open Access
Volume 4

Research Article

Enhancing Titanium Implants with rhBMP-2 for Improved Osseointegration

Sam Anu[1]; Ahmed Waqar[2]; BARRAK Fadi[1,3]*

[1]School of Medicine and Dentistry, University of Central Lancashire, UK.

[2]School of Mathematics and Physics, College of Health and Science, University of Lincoln, UK.

[3]VSS Academy, London, UK.

***Corresponding Author: Fadi Barrak**
School of Medicine and Dentistry, University of Central Lancashire, UK.
VSS Academy, London, UK.
Email: fnbarrak@uclan.ac.uk

Article Information

Received: Dec 01, 2023
Accepted: Jan 31, 2024
Published: Feb 07, 2024
Archived: www.jclinmedsurgery.com

Abstract

Early dental implant occurs failure due to poor osseointegration between the bone tissue and implant surface. Adding osseoinductive biomaterials such as bone morphogenetic proteins to the surface of the implant improves the quality and osseointegration of osseointegration. They trigger the conversion of mesenchymal stem cells into osteoblast cells producing new bone. This study aimed to assess the effects of adding bone morphogenetic proteins (rhBMP-2) to the implant surfaces on the extend and strength of osseointegration. This review used studies from Dentistry and Oral Sciences Source, Medline on EBSCo host platform, and CINAHL Ultimate Databases. In-vivo studies with randomised controlled trials from 01/01/2013 to 12/31/2023 were included. Seven animal studies on the surface modification of SLA implants with rhBMP-2 on different carriers were selected based on the inclusion criteria with low risk of bias. The bone area, volume, and bone-implant contact in the new bone formed were measured. The strength of osseointegration was measured in two studies as removal torque and implant stability quotient. Statistically significant increase in new bone formation and bone-implant contact was seen in rhBMP-2 immobilized on heparinised implant surface. Three studies showed significant increase in bone formation when rhBMP-2 was added. bone-implant contact showed statistically significant increase in the experimental group in only two studies. There was no significant difference in the bone-implant contact, removal torque and implant stability quotient analysis in five studies. The biofunctionalisation using rhBMP-2 is promising to increase the extent and strength of osseointegration. It influences the outcome measures of osseointegration even though to display statistical significance rhBMP-2 should have sustained release and concentration. Carriers such as Hydroxyapatite (HAp), Heparin and poly (D,L lactide-co-glycolide) (PLGA) microspheres can biofunctionalise implant surfaces with rhBMP-2. Further studies are needed to identify the ideal carriers and doses needed to increase in the bone implant contact and strength of osseointegration.

Keywords: Dental implants; Osseointegration; Biofunctionalisation; Bone Morphogenetic Proteins (BMP); rhBMP-2.

Citation: Anu S, Waqar A, Fadi B. Enhancing Titanium Implants with rhBMP-2 for Improved Osseointegration. J Clin Med Surgery. 2024; 4(1): 1135.

Introduction

According to the UN report on world population ageing in 2020, globally there are 727 million persons aged 60 years and over. This number is expected to increase from the current 9.3% to 16% over the next three decades [1]. The incidence of caries among British adults has reduced but the incidence of severe periodontal disease has increased [2]. These primary causes of tooth removal result in a growing number of patients seeking solutions for full or partial tooth loss. Implant-supported prostheses are attractive due to their biological and functional benefits, offering excellent long-term results to patients [3]. Studies show that dental implants between 100,000-300,000 implants are placed per year [4]. The success rate depends mainly on the way the individual's bone integrates with the implant surface called osseointegration. A retrospective cohort study to investigate causes of failure of implants, classified as early failure and late failure was conducted by Manor et al. The main cause of early failure was found to be the lack of osseointegration at 73.2%. Osseo-integration is the direct contact between living bone tissue and the implant surface by Branemark [5]. The implant's primary stability depends on factors such cortical bone volume, implant size, and surface features. This stability weakens in the first few weeks due to bone changes. To compensate for this, the secondary stability, mainly from the newly formed bone, becomes crucial. This bond on the implant surface is biological, not mechanical [6]. Historically, several modifications to the implant surface properties such as structure, surface roughness, chemistry, surface charge, and wettability have been examined to improve the osseointegration [5]. Recently, microroughening methods such as sandblasting or electrochemical deposition and altering the surface activity through acid etching, anodising, or activation are used to boost osseointegration [7]. Specific growth factors such as Bone Morphogenetic Proteins (BMP) to stimulate the creation of bone tissue have been explored. This phenomenon involves the proliferation and differentiation of the undifferentiated stem cells, osteoprogenitor cells and preosteoblasts into osteoblasts enhancing implant osseointegration. Among the family of BMPs, rhBMP-2 and BMP-7 seem to possess the highest osteoinductive potential [8]. Studies involving local application of rhBMP at fracture sites and bone analysis for BMP expression showed elevated upregulation for 21 days during healing [9]. A review on in vivo studies of BMP coated titanium implant surface measured the bone formation outcome each week up to 3 weeks [10]. Another systematic review on the effects of bioactive drugs such as bisphosphonates, calcium phosphates and BMP by coating the implant surface or using carriers showed significantly improved osseointegration by BMPs and calcium phosphate, but only bone to implant contact was measured [11]. This review aimed to critically appraise the extent and strength of osseointegration achieved by the biofunctionalisation of the implant surface with rhBMP-2 by analysing the outcomes including new Bone Area (BA) or Bone Volume (BV), bone implant contact from histological evaluations and the Removal Torque (RT), the Resonance Frequency Analysis (RFA) or Implant Stability Quotient (ISQ) compared to that achieved by the Sand-blasted, Large grit Acid etched (SLA) titanium implants.

Materials and methods

To explore the research question, a systematic review of published Randomised Controlled Trials (RCT) was the selected research method. In vivo animal randomised controlled trials studies, with or without split mouth design, and assessing follow up outcomes from 3 weeks to 3 months with low risk of bias were included. Studies not included in the earlier reviews and not analysed for more outcomes according to this inclusion criteria were included in this review.

Studies that did not meet the inclusion criteria such as cohort and case control studies and in vitro studies which could not provide the outcome measures such as removal torque and Stability Quotient were excluded.

Inclusion and exclusion criteria: Healthy animals without systemic diseases or medication which may compromise osseous healing were included. Implants used must be SLA titanium implants. In vitro studies, animal studies without ethical approval, BMP placed as scaffolds at the implant site, BMP in the form of solution/gel/carrier dependent placed as a simultaneous guided bone regeneration procedure but not coated on the implant were excluded. Studies involving BMP-7, BMP-4, nanotube delivery and gene vector delivery of BMP were also excluded.

Intervention planned: Implant surface modification with rhBMP-2 adsorbed or as a covalent attachment or a carrier delivered on the surface of the implant.

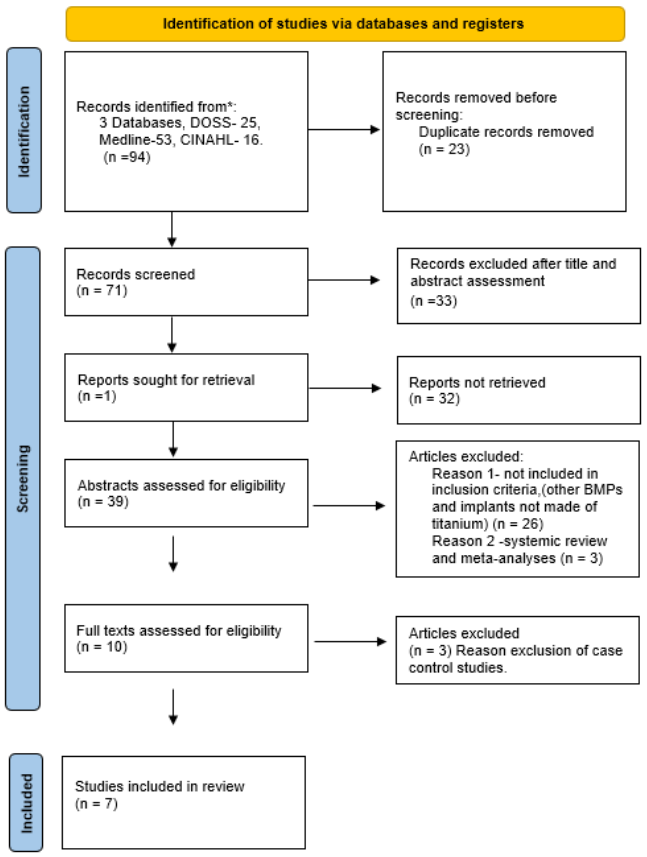
Outcomes: New bone formation measured by bone area, BV, bone height or density. Osseointegration measured by bone-implant contact which is the amount of bone in contact with the determined surface or length of the implant.

Stability measured by removal torque or Stability Quotient. Removal torque is measured by the torque required to remove an osseointegrated implant. Resonance frequency analysis is the resonance measured of the implant oscillating at the first flexural stress translated as Stability Quotient [12].

Search methods for selection of studies: The three databases Medline on Ebscohost platform, CINAHL Ultimate, Dentistry and Oral Sciences Sources were searched using the strategy planned according to the inclusion criteria and outcomes decided. MeSH terms like dental implants, oral implants, titanium implants, osseointegration, bone morphogenetic proteins, rhBMP-2, reversal torque, removal torque, bone implant contact, implant stability quotient and resonance frequency analysis were employed. The limiters used were the publication period 2013-2023 to gather up to date studies and publications in English. Systematic reviews and meta- analyses on the same subject were consulted to supplement the selection of papers. The PRISMA protocol was followed for selection of studies (Table 1). A total number of 94 papers were identified from all the databases. The rationale for excluding studies was in accordance with the exclusion criteria for study selection, participants, interventions, and the removal of duplicate papers. The final studies selected were 7 (Table 2).

Missing data: Pang et al. (2021) [13] were emailed to request missing data, but the information could not be obtained. As it was not very critical to the review, the study was still included in the selection.

Table 1: Prisma flowchart for selection of studies.



Risk assessment of bias in the included studies: The risk of bias for the included studies was assessed based on the OHAT risk of bias tool for evaluating human and animal studies (Table 3). This tool was developed from guidance by the Agency for Healthcare research and Quality, the Cochrane Handbook, the Cochrane risk of bias tool for non-randomised trials, the SYRCLE tool for animal studies, comments from advisors and staff and other sources (OHAT Risk of bias tool, 2015).

The following domains were assessed across individual studies.

Selection bias.

Allocation concealment.

Internal Validity- appropriate comparison groups.

Confounding variables.

Identical experimental conditions.

Attrition/Exclusion bias.

Detection bias.

Outcome assessment.

Other bias.

The risk of bias was graded on a 4-point scale as definitely high, probably high, probably low, and definitely low with "not reported" data classed as probably high. The study by [20] Soo Yeon Yoo et al 2015 had an overall definitely low risk of bias. The study by [17] Kim et al. 2015 was a pilot study with only mean values assessed and no statistical analysis was performed, hence the risk of bias for internal validity was graded as probably high. In the study [14] Cardoso et al. 2017, the use of phosphate carriers masks the reliable outcome measurement of the effect of the addition of BMP, hence the confounding variables

Table 2: List of studies included.

No.	Author and Year	Title of study	Full reference
	Pang K et al. (2021) [13]	'Effects of the combination of bone morphogenetic protein-2 and nano-hydroxyapatite on the osseointegration of dental implants'	Pang K, Seo Y, Lee J. (2021). Effects of the combination of bone morphogenetic protein-2 and nano-hydroxyapatite on the osseointegration of dental implants. Journal of the Korean Association of Oral and Maxillofacial Surgeons, 47(6), pp. 454-464 Available at: 10.5125/jkaoms. 2021.47.6.454.
	Cardoso MV, et al. (2017) [14]	'Titanium implant functionalization with phosphate-containing polymers may favour in vivo osseointegration'	Cardoso, M.V., de Rycker, J., Chaudhari, A., Coutinho, E., Yoshida, Y., Van Meerbeek, B., Mesquita, M.F., da Silva, W.J., Yoshihara, K., Vandamme, K. and Duyck, J. (2017). Titanium implant functionalization with phosphate-containing polymers may favour in vivo osseointegration. Journal of clinical periodontology, 44(9), pp. 950-960 Available at: 10.1111/jcpe.12736.
	Pan H., et al. (2016) [15]	'Effect of sustained release of rhBMP-2 from dried and wet hyaluronic acid hydrogel carriers compared with direct dip coating of rh-BMP-2 on peri-implant osteogenesis of dental implants in canine mandibles'	Pan, H., Han, J.J., Park, Y., Cho, T.H. and Hwang, S.J. (2016). Effect of sustained release of rhBMP-2 from dried and wet hyaluronic acid hydrogel carriers compared with direct dip coating of rh-BMP-2 on peri-implant osteogenesis of dental implants in canine mandibles. Journal of cranio-maxillo-facial surgery: official publication of the European Association for Cranio-Maxillo-Facial Surgery, 44(2), pp. 116-125 Available at: 10.1016/j. jcms.2015.11.018.
	Yoo, S., et al. (2015) [16]	'Biochemical Responses of Anodized Titanium Implants with a Poly(lactide-co-glycolide)/ Bone Morphogenetic Protein-2 Submicron Particle Coating. Part 2: An In Vivo Study'	Yoo, S., Kim, S., Heo, S., Koak, J., Lee, J. and Heo, J. (2015). Biochemical Responses of Anodized Titanium Implants with a Poly(lactide-co-glycolide)/Bone Morphogenetic Protein-2 Submicron Particle Coating. Part 2: An In Vivo Study. The International journal of oral & maxillofacial implants, 30(4), pp. 754-760 Available at: 10. 11607/jomi. 3701b.
	Kim, N., et al. (2015) [17]	'Effects of rhBMP-2 on Sandblasted and Acid Etched Titanium Implant Surfaces on Bone Regeneration and Osseointegration: Spilt-Mouth Designed Pilot Study'	Kim, N., Lee, S., Ryu, J., Choi, K. and Huh, J. (2015). Effects of rhBMP-2 on Sandblasted and Acid Etched Titanium Implant Surfaces on Bone Regeneration and Osseointegration: Spilt-Mouth Designed Pilot Study. BioMed research international, 2015, pp. 459393 Available at: 10. 1155/2015/459393.
	Kim, S. E., et al. (2014) [18]	'Improving osteoblast functions and bone formation upon BMP-2 immobilization on titanium modified with heparin'	Kim, S.E., Kim, C., Yun, Y., Yang, D.H., Park, K., Kim, S.E., Jeong, C. and Huh, J. (2014). Improving osteoblast functions and bone formation upon BMP-2 immobilization on titanium modified with heparin. Carbohydrate Polymers, 114, pp. 123-132 Available at: 10.1016/j.carbpol.2014.08.005.
	Lee, S., et al. (2014) [19]	'Hydroxyapatite and collagen combination-coated dental implants display better bone formation in the peri-implant area than the same combination plus bone morphogenetic protein-2-coated implants, hydroxyapatite only coated implants, and uncoated implants'	Lee, S., Hahn, B., Kang, T.Y., Lee, M., Choi, J., Kim, M. and Kim, S. (2014). Hydroxyapatite and collagen combination-coated dental implants display better bone formation in the peri-implant area than the same combination plus bone morphogenetic protein-2-coated implants, hydroxyapatite only coated implants, and uncoated implants. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons, 72(1), pp. 53-60 Available at: 10.1016/j.joms.2013.08.031.

Table 3: Risk of bias analysis of included studies.

	Kang Mi Pang et al, 2021	Marcio V. Cardoso et al. 2017	Hui Pan et al. 2016	Soo Yeon Yoo et al. 2015	NH Kim et al. 2015	SE Kim et al.2014	SW Lee et al.2014
Selection Bias	+	++	+	++	++	+	+
Allocation concealment	-	++	-	++	-	-	-
Internal validity-appropriate comparison groups	++	++	++	++	-	++	++
Confounding variables	++	-	++	++	++	++	++
Identical Experimental conditions	++	++	++	++	++	++	++
Attrition /exclusion bias	+	++	++	+	++	++	++
Detection bias	++	++	++	++	++	++	++
Outcome assessment-	+	+	+	+	+	+	+
Other bias	++	++	++	++	++	++	++

Key

definitely low	probably low	probably high	definitely high
++	+	-	--

are graded as probably high risk of bias. No study was excluded as the overall risk of bias for all studies were low.

Data extraction and management: The seven randomised controlled studies selected for review included over 252 implants. A comprehensive data extraction template inclusive of all characteristics, interventions, outcomes measured, results and statistical data was planned and tabulated for easy reference. The Gradepro GDT tool was used to create a summary of findings table and assess the quality of evidence. Further, the data was analysed and described as a narrative synthesis with inferences and implications.

The following information was extracted:

General information: Author, publication year, Title, Journal of publication, location, aims and study design.

Study eligibility: Inclusion and exclusion criteria

Participants: Animal used, Number of animals and implants, ethical approvals, site of implantation.

Interventions: Type and concentration of BMP used, carrier, method of implant surface modification, BMP release tests, details of surgical procedure, pre and post medications.

Comparators: Type of implant or carrier used as control.

Outcomes: Schedules, bone area, BV, bone-implant contact, Stability Quotient.

Others: Statistical analysis, significance, conclusions, conflict of interest, overall risk of bias.

Characteristics of included studies: In the randomised controlled trials by [13] Pang etal. 2021, carried out on rabbit tibia, 200 ng rhBMP-2 was added to a composite of collagen and nano-hydroxyapatite and adsorbed onto the implant surface.

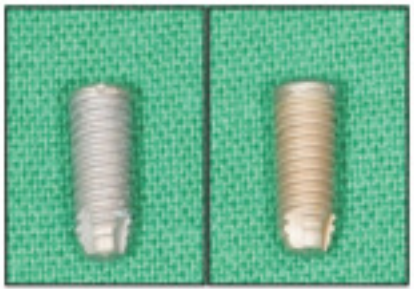


Figure 1: Photograph of titanium implant (left) and Col/nHAp/BMP-2-coated implant (right) [13] (Pang et al. 2021).

The BMP release tests were conducted as invitro tests. New bone area, bone-implant contact, and removal torque were assessed at 4 weeks [13]. In 2017, Cardoso et al. [14] studied the effects of 1 µg rhBMP-2 with Phosphorylated Pullulan (PPL) adsorbed onto the implant surface. These randomised controlled trials involving 120 implants, also tested the effects of phosphates on osseointegration by coating implants with 10% polyphosphoric acid, 1% PPL and 10% PPL against SLA titanium implants as controls. BV and bone-implant contact B were measured at 1 month and 3 months [14]. In the study by [15]. Pan et al. 2016, hyaluronic acid hydrogel with 10 µg/ml.

BMP was employed in dried, wet, and immediate dip coated on dried gel forms on 28 implants. BMP release tests were determined up to day 3. Bone area and bone-implant contact were measured at 1 week and 4 week [15]. (Pan et al. 2016) [16]. Yoo et al. 2015, conducted a randomised controlled trial on 8 rabbits with 32 implants and BMP at 50 µg/ml (PLGA) molecules electrosprayed on the implant surface. Bone area and bone-implant contact were measured at 3 weeks and 7 weeks [16]. In the pilot study by [17]. Kim et al. 2015, 24 implants were used and different concentrations of BMP 0.1 mg/ml, 0.5 mg/ml and 1.0 mg/ml were adsorbed directly and dried. The BMP release test were measured from the first 6 hours to 4 days. BH, BV, bone-implant contact and changes in Stability Quotient were measured at 8 weeks [17].

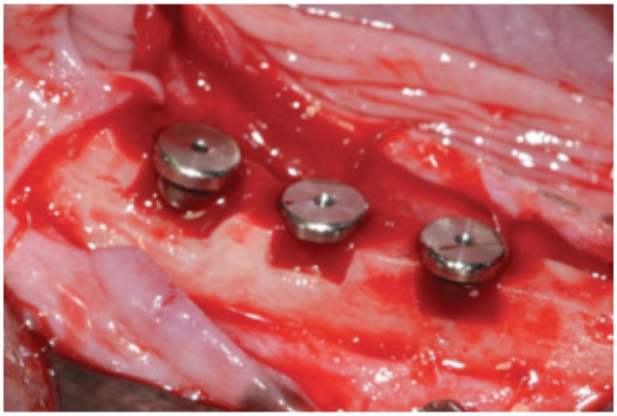


Figure 2: Implant surgery procedure for the in vivo study; 5.5 mm width peri-implant defects were created using a trephine bur. The implant was placed within its prepared site, and peri-implant defect areas were covered using a 5.5 mm diameter cover screw [18]. In the randomised controlled trials by Kim et al. in 2014, 24 implants and 0.75 mg/ml of BMP were employed. BMP was electrostatically strongly bonded with the heparinized implant surface and the BMP release was tested for 28 days.

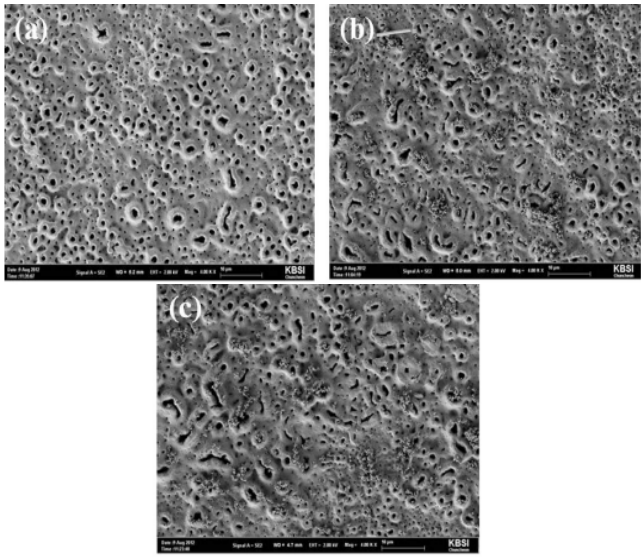


Figure 3: Scanning Electron Microscopy (SEM) for the surface morphologies; the control and surface-modified groups had similar morphologies. **(a)** Ti, **(b)** BMP-2/Ti, **(c)** BMP-2/Hep-Ti. (Magnification: ×4000). BH, bone density and bone-implant contact were measured at 8 weeks [18]. The study by [19] Lee et al. 2014, was a randomised controlled trial with 12 rabbits and 24 implants. 200 ng/ml of BMP and hydroxyapatite and collagen were adsorbed using an aerosol deposition system. The new bone formation and bone-implant contact were measured at 6 weeks.

Results

This review compared the effect of rhBMP-2 on the implant surface to the existing SLA surface on the indicators of the extent and quality of osseointegration. Of the seven selected in-vivo studies, six studies modified the titanium implants with rhBMP-2 added onto a carrier and one directly in wet and dried layered coatings. The analyses at the bone-implant surface were performed at [3,4,6-8] weeks measuring the bone area, BH, BV and bone-implant contact. The de novo bone formation increased in the initial weeks in all implants biofunctionalized with rhBMP-2. A significant increase was seen in [2] studies in bone area, in 1 study in BH at 3, 4 and 8 weeks respectively. Later follow up analysis in 3 studies showed no statistical difference except for the heparinized implant with BMP-2 coating. The bone-implant contact showed statistically significant difference at [6,8] weeks in the implants with BMP-2 on Hydroxyapatite and collagen and Heparin carriers and none in all others, though the mean values were high in [6] studies. Both the removal torque and the Stability Quotient at 8 weeks increased compared to the control but had no statistical difference. The most efficient carrier releasing BMP-2 was heparin which provided prolonged and constant dose delivery up to 28 days.

Question: Does rhBMP-2 biofunctionalized implant surface compared to SLA implant surface provide better osseointegration?.

Population: Animal studies-healthy animals without systemic diseases or medication affecting bone physiology.

Intervention: rhBMP-2 functionalization of implant surface with carriers or dip coated.

Comparison: SLA titanium implant surface.

Discussion

The rhBMP-2 is a dosage dependent growth factor. Lower concentrations promote bone formation, but higher concentrations can trigger osteoclasts, resulting in bone loss. For significant new bone formation, rhBMP-2 must be released in an initial burst and have a sustained release over days or weeks [21]. To favour bone formation, the release of BMP should be at a low constant dose by incorporating it into a carrier [22].

At very high doses, BMP-2 can cause formation of haematomas as reported in an experimental study by Bouyer et al. [23]. Other side effects of BMP at large doses were swelling and pain. In 2021, [13] Pang et al. studied the effects of Hydroxyapatite and collagen as a carrier for rhBMP-2. The BMP release was sustained over 5 days in the col/Hydroxyapatite/BMP group. The outcomes of bone area, bone-implant contact and removal torque measured at 4 weeks showed higher values but there was no statistically significant difference [13] (Pang et al. 2021). In the study by [14] Cardoso et al. a remarkable decrease in the bone formation was seen in all the outcomes compared between PPL-10/BMP and PPL10. In comparison with the negative control, the outcomes of PPL10/BMP group were similar at 1 month and lower at 3 months [14]. Hence, phosphates cannot be preferred as a carrier for BMP-2. The PPA and PPL themselves may promote osseointegration in unfavourable bone conditions.

The study by Pan et al. employed Hyaluronic Acid (HA) as a carrier for BMP. At 4 weeks, the BA measured significantly higher values in the dip coated group, but the bone-implant contact showed no significant difference among the groups though higher values were seen in the dried coated group [15]. The randomised controlled trials by Yoo et al. 2015, at 3 weeks, there was seen a significant difference but none at 7 weeks in the BMP group in bone area. The bone-implant contact measures showed no significant difference at 3 and 7 weeks [16]. The pilot study by Kim et al. 2015, measured the outcomes for different concentrations of BMP-2 and found higher values in BH, BV and bone-implant contact at 8 weeks for 0.5 mg/ml and 1.0 mg/ml groups.

Table 4: Summary of findings using gradepro assessment tool.

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
New bone area (follow-up: range 1 weeks to 7 weeks)									
4	randomised trials	not serious	not serious	not serious	not serious	None	Mean values were higher in all 4 studies. Significant difference was observed in 2 studies at 3 weeks and 4 weeks.	⊕⊕⊕⊕ High	CRITICAL
Bone volume (follow-up: range 1 months to 3 months)									
2	randomised trials	not serious	not serious	not serious	not serious	None	No significant difference in 1 study at 1 month and 3 months. Mean values were higher.	⊕⊕⊕⊕ High	IMPORTANT
Bone Implant Contact (follow-up: range 1 weeks to 3 months)									
7	randomised trials	not serious	not serious	not serious	not serious	None	BIC mean values were higher in 6 studies and statistically significant in 2 studies.	⊕⊕⊕⊕ High	CRITICAL
Bone height (follow-up: mean 8 weeks)									
2	randomised trials	not serious	not serious	not serious	not serious	None	Mean values of vertical bone height were higher in 1 study and statistically significant increase in 2nd study.	⊕⊕⊕⊕ High	IMPORTANT
Removal Torque (follow-up: mean 4 weeks)									
1	randomised trials	not serious	not serious	not serious	not serious	None	Mean values were higher but not statistically significant	⊕⊕⊕⊕ High	IMPORTANT
Implant Stability Quotient (follow-up: mean 8 weeks)									
1	randomised trials	not serious	not serious	not serious	not serious	None	Mean values were higher at 8 weeks. No statistical analysis done.	⊕⊕⊕⊕ High	IMPORTANT

CI: Confidence Interval: 95% $p<0.05$ was considered statistically significant.

Table 5: Results and significance.

Author and Publication Year	Statistical significance	Clinical significance/Results
Kang Mi. Pang et al. 2021	At 4 weeks, the Col/nHAp/BMP-2 implant demonstrated slightly more new bone area than the negative control (P=0.07) hence not statistically significant, whereas BIC and removal torque showed no significant differences, although the mean values were higher. The Col/nHAp/BMP-2 demonstrated a greater BIC (33.46%±6.91%) than the titanium implant (31.36%±3.22%), but the differences were not statistically significant. New bone area in the Col/nHAp/BMP-2 (73.69%±5.88%) was slightly higher than that of the titanium implant surface (62.24%±12.52%). Similarly, Col/nHAp/BMP-2 had a greater removal torque (26.63±4.41 Ncm) than the negative control (22.90±2.33 Ncm).	Slightly higher values were seen with BMP but not statistically significant. HAp exhibits a high affinity for BMP-2, evenly distributes BMP-2 under pressure, and causes minimal foreign body reactions, and is therefore considered useful as a BMP carrier.

Marcio V. Cardoso et al. 2017	A significant lower BV was found in the BMP-2 group. After 3 months, no statistically significant difference was observed between the PPA10 group and PPL10 BMP group ($p<0.05$) More BIC was observed in PPA10 implants compared to the PPL10 BMP group after 1 month ($p<0.05$). Significantly higher BIC values between PPL10 and PPL10 BMP at 3 months ($p<0.05$). Over 3 months, no statistically significant difference was found ($p>0.05$) among all groups.	Both PPA10 and PPL10 seem to induce faster peri-implant osseointegration and bone regeneration. Use of PPL as a carrier for BMP-2 was not efficient on stimulating peri-implant bone formation. PPA10 and PPL10 may promote more favourable conditions for early implant loading, particularly in unfavourable clinical situations.
Hui Pan et al. 2016	1) The dried coating of BMP-HAH resulted in a significantly greater BA than the wet BMP-HAH ($p<0.006$) and implants without any coating ($p<0.022$), while the simple dip coating of rhBMP-2 represented significantly greater BA than the other 3 groups ($p<0.0005$). 2) BIC was significantly higher for the dried coating of BMP-HAH than the wet coating of BMP-HAH($p<0.014$); otherwise, there were no significant differences. BIC was 42.36+/-4.75% in the control, 30.27+/-5.03% for the wet coating, 50.36+/-2.72% for the dried coating, and 41.78+/-3.50% for the dip coating of rhBMP-2.	Implants coated with dried rhBMP-2 hydrogel composite showed enhanced new bone formation in peri-implant defects relative to non-coated implants alone or implants coated with in situ-forming rhBMP-2 hydrogel composites. However, the simple dip coating of rhBMP-2 presented significantly greater BA than the other three groups.
Soo-Yeon Yoo et al. 2015	Bone area- Significant difference between groups B-3 and A-3 ($p<0.05$). There was no significant difference between BIC in B-3 and A-3($p=0.065$), and the same at 7 weeks ($p>0.05$). Bone area values were not significantly different at 3 weeks ($p=0.050$). There was also no significant difference in bone area between groups A-7 and B-7 ($p>0.05$)	Titanium implants coated with the submicron sized PLGA+rhBMP-2 showed enhanced bone area and bone-implant contact during early healing, though not statistically significant.
Nam-Ho Kim et al. 2015	Statistical analysis of the data was not performed. Mean VBHs of buccal defect areas were higher in the 0.5 (1.88±0.52) and 1.0 groups (2.06±0.60) than in the control (−0.02±0.62) and in the 0.1 groups (0.71±0.62). Mean BIC values in the 0.5 (24.47±6.63) and 1.0 groups (18.42±8.65) in buccal defect areas were higher than in the control (0.67±1.15) and 0.1 groups (10.24±10.99). Intergroup difference was not observed in lingual defect areas. However, mean buccal BV (%) values of the 0.5 (33.67±5.24) and 1.0 groups (35.67±8.80) were greater than those of the 0.1 (13.30±11.24) and control groups (2.77±3.71).	In the 1 mm coronal bone defect area surrounding the implant, bone mass and density were increased merely by the SLA implant surface, but in the open bone defect area, the 0.5 and 1.0 mg/mL concentrations of rhBMP-2 were more effective at promoting bone regeneration and osseointegration in this pilot study.
Kim SE et al. 2014	The IntraThread Bone Density and the BIC in the new bone area of BMP-2/Ti and BMP-2/Hep-Ti was significantly greater than that of Ti ($P<0.05$), and no significant difference was observed between BMP-2/Ti and BMP-2/Hep-Ti ($P>0.05$). The BIC and IntraThread Bone Density within the old bone area at 8 weeks after surgery were not different between the groups. Pronounced peri-implant bone re-modeling and vertical bone growth was observed in the BMP-2/Ti and BMP-2/Hep-Ti groups.	The BMP-2 released from BMP-2/Hep-Ti showed sustained BMP-2 release profiles compared to that from BMP-2/Ti. BMP-2/Hep-Ti substrates induced new bone formation at the defect area with statistical significance.
Lee SW et al. 2014	Mean new bone formation was 47.04+/-17.82% in CH group. This value was 23.34-/+13. 28%, 22:85+/-12.55%, and 27.72+/-13.42% in the UC, HA, and CHB groups, respectively. There was significant difference between CH and CHB group ($p=0.002$) and no significant difference between UC and CHB group ($p>0.05$). The mean BIC appeared higher at 41.45+/-6.77% in the CH group. The value was 21.38+/-6.76%, 24.18+/-8.21%, and 30.72+/-5.51% for the UC, HA, and CHB groups, respectively. The mean BIC values of the UC and CHB groups also were significantly different ($p=0.011$).	BMP-2 coating did not have a significant effect compared with the other groups. The CH group displayed significantly greater new bone formation and BIC than the other groups.

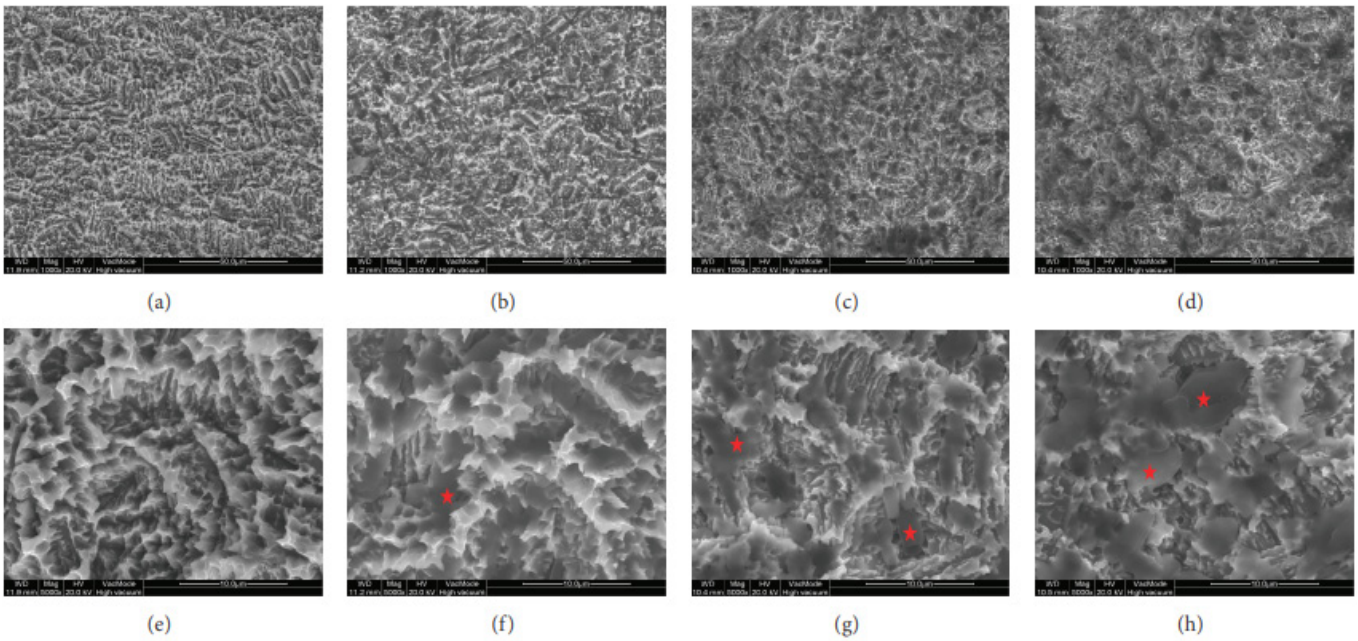


Figure 4: SEM images of each group. **(a,e)** The control group, **(b,f)** the 0.1 group, **(c,g)** the 0.5 group, and **(d,h)** the 1.0 group. Asterisk: freeze dried rhBMP-2: **(a-d)** ×1000, **(e-h)** ×5-000. (Kim et al. 2015). The Stability Quotient difference at placement and 8 weeks showed higher changes in the 0.5 and 1.0 mg/ml group. As only 4 animals were used, the authors couldn't present the statistical significance from 2 observations per group [17] (Kim et al. 2015).

Group	At surgery	At 8 weeks	ISQ change
Control	46.83 ± 3.97	60.17 ± 3.25	13.33 ± 5.43
0.1	48.00 ± 4.00	64.83 ± 3.19	16.83 ± 4.67
0.5	49.83 ± 5.95	71.67 ± 6.15	19.83 ± 9.56
1.0	52.67 ± 7.61	72.00 ± 2.68	18.17 ± 6.94

At surgery: ISQ value at surgery.
At week 8: ISQ value 8 weeks after implantation.

Figure 5: Results of Stability Quotient (ISQ) values and changes from at surgery to week 8 [17]. In the randomised controlled trials by Kim et al. 2014, the bone density and bone-implant contact showed significant increase compared to the control groups but there was none between the dried coated BMP group and the heparinized BMP group [18].

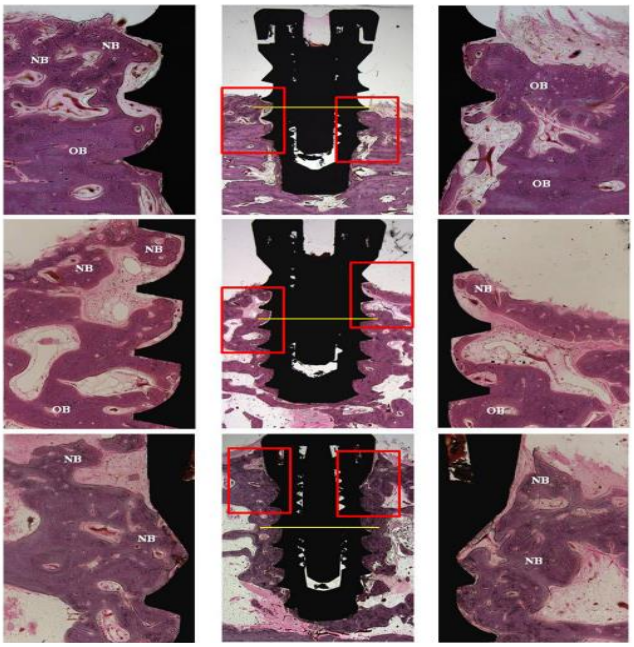


Figure 6: Histological specimens of the three groups **(a-c)** Ti, **(d-f)** BMP-2/Ti, **(g-i)** BMP-2/Hep-Ti). Note pronounced peri-implant bone remodeling and vertical bone growth in the BMP-2/Ti and BMP-2/Hep-Ti groups [18]. The study by Lee et al. 2014, the new bone formation and bone-implant contact at 6 weeks showed significant increase in Hydroxyapatite/collagen compared to Hydroxyapatite/collagen/BMP group [19].

The study by Lee et al. 2014, the new bone formation and bone-implant contact at 6 weeks showed significant increase in Hydroxyapatite/collagen compared to Hydroxyapatite/collagen/BMP group [19].

The review of these studies indicates a boost in new bone formation and bone-implant contact values when rhBMP-2 is present on the implant surface. However, the statistical analysis showed effectiveness in only 2 studies. As the study participants are animals, it is difficult to design a larger cohort which would have shown better statistically significant results. Some carriers like hydroxyapatite, collagen, hyaluronic acid, and phosphates, being osteoconductive themselves caused confounding outcomes. The studies should have measured removal torque and Stability Quotient and further follow-up. As different concentrations of BMP-2 were used in each of the studies, it was difficult to ensure homogeneity among the outcomes. The most effective dosage of BMP-2 being 20-100 µg/g of coating [24]. The effects of the carriers themselves should be considered and the inclusion criteria modified accordingly to the use of inert carriers.

Conclusion

Numerous investigations have revealed rhBMP-2 is a promising osseoinductive growth factor which can accelerate bone remodeling [25,26]. In the studies selected for this review, the rhBMP-2 was coated onto implants using carriers like Hydroxyapatite and collagen, Phosphorylated pullulan, Polylactide (L,D, co-gylcolide) PLGA, Heparin and Hyaluronic acid in 4 studies. The gradual liberation of rhBMP-2 from a depot, in these studies over a period of 3-5 days from the different carriers, aided the sustained de novo bone formation [22]. The study of the heparinized implant surface with BMP-2 bound as an electrostatic interaction and dried coated BMP measured the sustained release over 28 days and showed no statistically significant difference among them. Thus, the author concludes that the effectiveness of biofunctionalising an implant surface with rhBMP-2 as an osseoinductive agent is largely dependent on its sustained constant release into the peri-implant tissues. This can be achieved by dried coating or by carriers.

Implications for practice and future research: The review included SLA titanium implants as controls which are widely used nowadays. Establishing a successful implant surface which provides even better osseointegration will provide remarkable reduction in failures even in the presence of compromised bone physiology. Hence, further research involving carriers or techniques for sustained release of rhBMP-2 should be conducted to assess the true effectiveness of biofunctionalization of the implant surface with rhBMP-2.

Abbreviations: BMP-2: Bone Morphogenic Protein-2; CINAHL: Cumulative Index To Nursing and Allied Health Literature; DOPA: Dopamine Hydrochloride; ELISA: Enzyme-Like Immunosorbent Assay; Hap: Hydroxyapatite; Mesh: Medical Subject Headings; OHAT: Office of Health Assessment and Translation; PICO: Population, Intervention, Comparison and Outcome; PLGA: Poly (D,L Lactide-Co-Glycolide); PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RFA: Resonance Frequency Analysis; SLA: Sand-Blasted, Large Grit Acid Etched; SYRCLE: Systematic Review Centre for Laboratory Animal Experimentation.

References

1. United Nations Department of Economic and Social affairs world Population Ageing. 2020: Highlights/Statistical Papers - United Nations (Ser. A), Population and Vital Statistics Report. 2021.

2. White DA, Tsakos G, Pitts NB, Fuller E, Douglas GV, et al. Adult Dental Health Survey 2009: Common oral health conditions and their impact on the population. British dental journal. 2012; 213(11): 567-572. 10. 1038/sj. bdj. 2012. 1088.

3. Bosshardt DD, Chappuis V, Buser D (2017). Osseointegration of titanium, titanium alloy and zirconia dental implants: Current knowledge and open questions. Periodontology. 2017; 73(1): 22-40 Available at: 10. 1111/prd. 12179.

4. Gupta A, hanraj M, Sivagami G. Status of surface treatment in endosseous implant: A literary overview. Indian Journal of Dental Research. 2010; 21(3): 433-438. 10. 4103/0970-9290. 70805.

5. Albrektsson T, Brånemark PI, Hansson HA, Lindström J. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthopaedica Scandinavica. 1981; 52(2): 155-170. Available at: 10. 3109/17453678108991776.

6. Bosshardt DD, Chappuis V and Buser D (2017). Osseointegration of titanium, titanium alloy and zirconia dental implants: current

knowledge and open questions. Periodontology. 2000; 73(1): 22-40 Available at: 10. 1111/prd. 12179.

7. Sayin Ozel G, Inan O, Secilmis Acar A, Alniacik Iyidogan G, Dolanmaz D, et al. Stability of dental implants with Sandblasted and Acid-Etched (SLA) and modified (SLActive) surfaces during the osseointegration period. Journal of dental research, dental clinics, dental prospects. 2021; 15(4): 226-231. Available at: 10. 34172/joddd. 2021. 037.

8. Termaat MF, Den Boer FC, Bakker FC, Patka P, H J Th M Haarman. Bone morphogenetic proteins: Development and clinical efficacy in the treatment of fractures and bone defects. Journal of Bone and Joint Surgery. 2005; 87(6): 1367-78.

9. Cottrell JA, Keane O, Lin SS, O'Connor JP. BMP-2 modulates expression of other growth factors in a rat fracture healing model. Journal of Applied Biomedicine. 2014; 12(3) 127-135. 10. 1016/j. jab. 2014. 02. 003.

10. Haimov H, Yosupov N, Pinchasov G, Juodzbalys G. Bone Morphogenetic Protein Coating on Titanium Implant Surface: A Systematic Review. Journal of oral & maxillofacial research. 2017; 8(2): 1. 10. 5037/jomr. 2017. 8201.

11. Alenezi A, Chrcanovic B, Wennerberg A. Effects of Local Drug and Chemical Compound Delivery on Bone Regeneration Around Dental Implants in Animal Models: A Systematic Review and Meta-Analysis. International Journal of Oral & Maxillofacial Implants. 2018; 33(1): 1-18. Available at: 10. 11607/jomi. 6333.

12. Sennerby L ,Meredith N. Implant stability measurements using resonance frequency analysis: Biological and biomechanical aspects and clinical implications. Periodontology. 2000; 47: 51-66. 10. 1111/j. 1600-0757. 2008. 00267. x.

13. Pang K, Seo Y and Lee J. Effects of the combination of bone morphogenetic protein-2 and nano-hydroxyapatite on the osseointegration of dental implants. Journal of the Korean Association of Oral and Maxillofacial Surgeons. 2021; 47(6): 454-464. 10. 5125/jkaoms. 2021. 47. 6. 454.

14. Cardoso MV, de Rycker J, Chaudhari A, Coutinho E, Yoshida Y et al. Titanium implant functionalization with phosphate-containing polymers may favour in vivo osseointegration. Journal of clinical periodontology. 2017; 44(9): 950-960. 10. 1111/jcpe. 12736.

15. Pan H, Han JJ, Park Y, Cho TH, Hwang SJ. Effect of sustained release of rhBMP-2 from dried and wet hyaluronic acid hydrogel carriers compared with direct dip coating of rhBMP-2 on periimplant osteogenesis of dental implants in canine mandibles. Journal of cranio-maxillo-facial surgery: Official publication of the European Association for Cranio-Maxillo-Facial Surgery. 2016; 44(2): 116-125. Available at: 10. 1016/j. jcms. 2015. 11. 018.

16. Yoo S, Kim S, Heo S, Koak J, Lee J, et al. Biochemical Responses of Anodized Titanium Implants with a Poly(lactide-co-glycolide)/ Bone Morphogenetic Protein-2 Submicron Particle Coating. Part 2: An In Vivo Study. The International journal of oral & maxillofacial implants. 2015; 30(4): 754-760. 10. 11607/jomi. 3701b.

17. Kim N Lee S, Ryu J, Choi K, Huh J. Effects of rhBMP-2 on Sandblasted and Acid Etched Titanium Implant Surfaces on Bone Regeneration and Osseointegration: Spilt-Mouth Designed Pilot Study. BioMed research international, 2015; 459-393. 10. 1155/2015/459393.

18. Kim SE, Kim C, Yun Y, Yang DH, Park K, et al. Improving osteoblast functions and bone formation upon BMP-2 immobilization on titanium modified with heparin. Carbohydrate Polymers. 2014; 114: 123-132. 10. 1016/j. carbpol. 2014. 08. 005.

19. Lee S, Hahn B, Kang TY, Lee M, Choi J, et al. Hydroxyapatite and collagen combination-coated dental implants display better bone formation in the peri-implant area than the same combination plus bone morphogenetic protein-2-coated implants, hydroxyapatite only coated implants, and uncoated implants. Journal of oral and maxillofacial surgery: Official journal of the American Association of Oral and Maxillofacial Surgeons. 2014; 72(1): 53-60. 10. 1016/j. joms. 2013. 08. 031.

20. Soo-Yeon Yoo, Seong-Kyun Kim, Seong-Joo Heo, Jai-Young Koak, Joo-Hee Lee et al. Biochemical Responses of Anodized Titanium Implants with a Poly(lactide-co-glycolide)/Bone Morphogenetic Protein-2 Submicron Particle Coating. Part 2: An In Vivo Study. International Journal of Oral & Maxillofacial Implants. 2015; 30(4): 754-760. 10. 11607/jomi. 3701b.

21. Brown KV Li B, Guda T, Perrien DS, Guelcher SA, Wenke JC. Improving bone formation in a rat femur segmental defect by controlling bone morphogenetic protein-2 release. Tissue engineering. Part A. 2011; 17(13-14): 1735-1746. 10. 1089/ten. TEA. 2010. 0446.

22. Hunziker EB, Enggist L, Küffer A, Buser D, Liu Y. Osseointegration: The slow delivery of BMP-2 enhances osteoinductivity, Elmsford, NY: Pergamon. 2012.

23. Bouyer M, Guillot R, Lavaud J, Plettinx C, Olivier C, et al. Surface delivery of tunable doses of BMP-2 from an adaptable polymeric scaffold induces volumetric bone regeneration. Biomaterials. 2016; 10(4): 168-181. 10. 1016/j. biomaterials. 2016. 06. 001.

24. Hunziker EB, Jovanovic J, Horner A, Keel MJ, Lippuner K, et al. Optimisation of BMP-2 dosage for the osseointegration of porous titanium implants in an ovine model. European cells & materials. 2016; 32: 241-256. 10. 22203/eCM. v032a16.

25. Wang C, Liu Y, Fan Y ,Li X. The use of bioactive peptides to modify materials for bone tissue repair, Oxford: Published by Oxford University Press in association with the Chinese Society for Biomaterials. 2017.

26. Jang J, Yun J, Lee K, Jang J, Jung U, et al. Osteoinductive activity of biphasic calcium phosphate with different rhBMP-2 doses in rats, New York, NY: Elsevier Inc. 2012.