

Bone Morphogenetic Protein Coating on Titanium Implant Surface: a Systematic Review

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ABSTRACT

Objectives: The purpose of the study is to systematically review the osseointegration process improvement by bone morphogenetic protein coating on titanium implant surface.

Material and Methods: An electronic literature search was conducted through the MEDLINE (PubMed) and EMBASE databases. The search was restricted for articles published during the last 10 years from October 2006 to September 2016 and articles were limited to English language.

Results: A total of 41 articles were reviewed, and 8 of the most relevant articles that are suitable to the criteria were selected. Articles were analysed regarding concentration of bone morphogenetic protein (BMP), delivery systems, adverse reactions and the influence of the BMP on the bone and peri-implant surface *in vivo*. Finally, the present data included 340 implants and 236 models.

Conclusions: It's clearly shown from most of the examined studies that bone morphogenetic protein increases bone regeneration. Further studies should be done in order to induce and sustain bone formation activity. Osteogenic agent should be gradually liberated and not rapidly released with priority to three-dimension reservoir (incorporated) titanium implant surface in order to avoid following severe side effects: inflammation, bleeding, haematoma, oedema, erythema, and graft failure.

Keywords: bone morphogenetic protein; dental prosthesis implantation; osseointegration; surface-coated materials; surface properties.

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INTRODUCTION

Currently, implantation is a daily routine especially in dental field. Endosseous dental implants are the ideal replacements for missing teeth. They give to the patient the opportunity to restore its masticatory function, improve mobility and alleviate pain. Dental implants are now often implanted immediately after tooth extraction, which, by forestalling the mechanical loading phase, necessitates for earlier establishment of physical stability via implant osseointegration [1].

However, osseointegration is often compromised in a large bone defect area [2,3]. Usages of biocompatible materials for micro as well as macro implants have greatly increased implantation success rates. In the dental implantation field, titanium (Ti) implants are most popular due to their excellent mechanical properties, biocompatibility, chemical stability, low toxicity, bioactivity and great corrosion resistance [4-6]. Yet, Ti implants cannot overcome poor bone quality or quantity conditions and results in poor healing as well as regeneration abilities [7]. Another drawback of Ti implants is the long fixation time of the bone to the implant that usually takes several months for healing [8]. Bone is a dynamic organ, it resorbs and forms steadily in the human body, and the massiveness of bone resorption over the years requires bone augmentation which plays a crucial role in compensation of damaged sites [9,10]. Nowadays, osseous autograft considers the gold standard for large bony defects repair, even though the amount of the bone is restricted [11].

In the current literature, different agents were suggested for bone stimulation as; hydroxyapatite (HA), type-I collagen (CO) and bone morphogenetic protein (BMP). CO found to be a major component in bone composition, causing increases in tissue vascularization, decreases in inflammation by decelerating macrophage and osteoclast activity. However, CO coating alone is not sufficient to accelerate the differentiation of osteoblasts. HA which is a main inorganic component in bone tissue, serves also as bone graft material, even though its usage regarding the long term survival is controversial [12].

BMPs belong to transforming growth factor beta (TGF- β) superfamily, are biological factors which play major roles in the osteogenesis process [11], by regulation of osteogenic cells and differentiation of bone mesenchymal stem cells (MSCs) [6]. BMPs are widely used as an additive for bone graft material; its addition contributes for bone to implant contact (BIC) [12].

In various studies the usage of BMP reported to improve and enhance osteogenesis process, osteoblasts activity, chondroblast activity and osseointegration after dental implantation. From the variety of BMPs, BMP-2 and BMP-7 derivatives showed to be the most effective for inducing bone morphogenesis [13]. Moreover, recombinant human BMP-2 has been available for therapeutic use given its rapid ability to trigger the differentiation of osteoblasts [14].

BMP-2 has an important role in regulating the osteogenic differentiation of MSCs and also in the response of bony and tissue formation [15]. BMP-7 also known as osteogenic protein-I which plays a major role in transformation of MSCs into bone and cartilage [11].

Preclinical and clinical studies have shown that local application of BMP-2 and BMP-7 can promote and perform cellular differentiation that raise the potential for bone repair in variety of situations including bony defects, non-union fractures, extraction sockets and osseointegration [1,15].

Even though supra-physiological amount of BMP is required for successful bone healing, high doses can result in rapid and inefficient BMP escape from its carrier which in turn can cause complications as: ectopic bone formation, excessive bone resorption and formation of malignant processes, which was not specified in the study. The same study proved that a prolonged presence of BMP-2 within the defected site will result in increased amount of bone formation. It was also found that prolong presence of BMP-2 within the defected site will lower the amount of the BMP required for sufficient effect. The applications of BMPs on Ti surface can improve the osseointegration of dental implants and shorten the time period for implant integration [15].

The purpose of the present review is to investigate the osseointegration process improvement by bone morphogenetic protein coating on titanium implant surface.

MATERIAL AND METHODS

Protocol and registration

Analysis and inclusion criteria methods were specified in advance and documented in a protocol. The review is registered in an international prospective register of systematic reviews 'PROSPERO' [16]. The protocol registration number: CRD42016051836.

The protocol can be assessed:

https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016051836

Focus question

The following focus questions were developed according to the data extracted from the current literature:

1. Does osseointegration process of Ti dental implant can be enhanced with administration of BMP? What kind of side effects it may develop?
2. What is the most recommended delivery method for BMP in order to accelerate osseointegration and in the same time avoid adverse effect?

Types of publication

The review included case reports, case reviews, and retrospective and prospective studies that were published *in vivo* in the English language. Excluded were articles in non-English language and abstracts lacking full text.

Types of studies

The review included any experimental model *in vivo*.

Information sources

The information sources were the MEDLINE (PubMed) database and EMBASE databases.

Population

Studies *in vivo* included healthy animals without systemic diseases or immunological disorders. The animals underwent BMPs treatment.

Literature search strategy

According to the PRISMA guidelines [17] an electronic search was conducted using MEDLINE (PubMed) database and EMBASE databases, in order to locate articles concerning the efficacy of BMP coated titanium implants' surface on implant osseointegration.

The Keywords used for the search included: (bone morphogenetic protein") and (((“surface-coated materials”) OR (“osseointegration”) OR (“dental prosthesis implantation”) OR (“surface properties”). The search was restricted to English language. Articles published from October 1, 2006 to September 2016 were searched.

Inclusion and exclusion criteria

Inclusion criteria for the selection

The full text articles with possible relevance were

assessed with the following inclusion criteria:

- Clinical article on experimental model.
- Treatment had to be completed on healthy animals without systemic diseases and immunological disorders.
- Studies involving at least 3 models. If less so statistically irrelevant.
- Studies involving diagnostic parameter and/or clinical, histological, histomorphometrical, push out test and/or radiological.
- Minimum follow-up of 3 weeks post operation.

Exclusion criteria for the selection

- Studies that included unclear data, with authors who could not be contacted for any reason.
- Not enough information regarding selected topic.
- Articles irrelevant to the study of BMP coating Ti implants' surface and its relation to implants osseointegration.

Sequential search strategy

The selected articles were subjected independently to clear inclusion and exclusion criteria by 3 reviewers as follows. The three reviewers resolved differences obstacles through discussion, consulting a third party who was an experienced senior reviewer. Following the initial literature search, all articles were chosen according title relevancy, considering the exclusion criteria. Following, studies were excluded based on irrelevant data obtained from the abstracts. The final stage of screening involved reading the full texts and confirming each study's eligibility based on the inclusion criteria.

Data extraction

The data were independently extracted from studies in the form of variables, according to the aims and themes of the present review, as listed onwards.

Data items

Data were collected from the included articles and arranged in the following fields:

- “Author/Year” - revealed the author and year of publication.
- “Model investigated”- indicates the model which was examined.
- “Carriage mode” - described the type of delivery mode.
- “BMP type”- describes the tissue BMPs have been used.

- “Bone formation after “n” week” - indicates the bone formation follow-up after “n” week, while “n” indicates number of weeks.
- “Evaluation method” - methods which evaluate the amount of new bone formed.

- Blinding of outcomes assessment (-/+/?);
- Incomplete outcome data (-/+/?);
- Selective reporting (-/+/?).

Risk of bias across studies

To assess the quality of the studies and to identify papers with intrinsic flaws that could affect the cumulative evidence. Cochrane collaboration bias summary for potential bias was used [18].

Risk of bias assessment parameters:

- Random sequence generation (-/+/?);
- Allocation concealment (-/+/?);
- Blinding of participant’s and personnel (-/+/?);

RESULTS

Study selection

The search delivered 225 search results, from which 41 abstracts were reviewed (Figure 1). A total of 41 articles were ultimately reviewed in full. Preliminary exclusion was made by the title and its relevancy and later by abstract relevancy. Finally, studies which did not meet the inclusion criteria were filtered. Eighth studies met the inclusion criteria and the present data was included on 340 implants and 236 models.

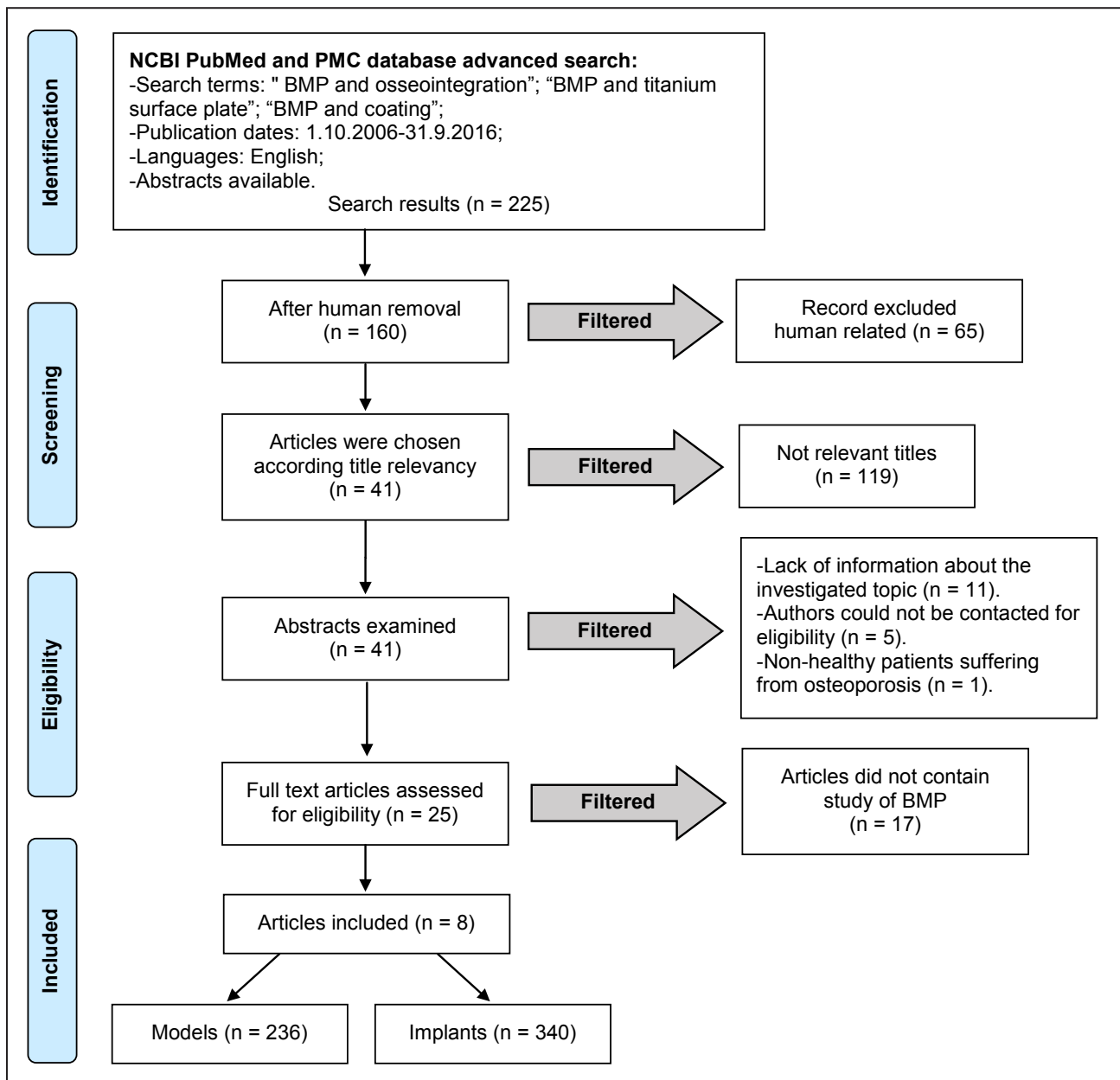


Figure 1. PRISMA flow diagram.

Study exclusion

The reasons for excluding studies after full-text assessment were as follows: articles [19-29] that lack information about the investigated topic, articles [30-34] with no full text available. Article [35] with non-healthy patients.

Quality assessment

The results of risk of bias assessment (quality) for included article RCTs (random control trial) were summarized in Table 1. The result show that three [1,2,9] studies were considered to have a low risk of bias while another five [6,7,12,14,15] were considered to have an unclear (unknown) risk of bias.

Study characteristics

In 2013, Jiang et al. [15] performed a study on 15 rabbits in order to evaluate if hBMP-2 which formed on sandblasted/roughened Ti implants will enhance bone formation *in vivo*. To determine the effect of BMP Jiang et al. [15] compared the roughed and sandblasted coated implants with uncoated control implants. Histomorphometric evaluation was applied after 2, 4 and 8 weeks and the result revealed that even though, BIC was higher for uncoated implants the amount of bone and cells cultured on coated surfaces sandblasted/roughened Ti implants had much higher cell viability than the control uncoated surfaces, furthermore, no difference was observed between 2 type of implant surfaces. They concluded that Ti implants coated with BMP-2 genes accelerated bone formation around the implants.

In 2014, Kim et al. [7] made an experimental analysis *in vivo* and *in vitro* to improve osteoblast function and bone formation in 3 examined dogs using heparin

delivery method in order to immobilize BMP-2 to Ti implants surface. Four Ti implants were installed in each dog’s mandible and maxilla in its left and right sides. ALP (alkaline phosphatase) activity, calcium deposition, and gene expression levels showed that, cells found on Ti implants containing BMP-2 can increase significantly the bone regeneration; this was in contrast to the case of implants without BMP-2. They also demonstrated that BMP-2/Heparin (Hep)-Ti substrates significantly enhancing osteogenic differentiation compared to those of Ti substrates. The conclusion of this article is that BMP-2 stimulates early and late osteoblast differentiation.

However, there have been conflicting results with other articles found in current literature.

Lee et al. [12] compared peri-implant bone formation among different bone stimulating agent such as; HA, CO and HA, CO in combination with HA and BMP-2. Each group included 3 rabbits and in total 12 rabbits participated in the experiment and 24 implants were implanted in their tibia bone. Histomorphometric analysis was used to evaluate the bone formation results (Table 2). The results showed that HA and CO group gain greater peri-implant bone formation then with other stimulating agent.

Additionally, adding superficially adsorbed two-dimensional BMP-2 to Ti implant surface did not show any advantage compared to HA and CO group, therefore they concluded that the addition of BMP-2 will not increase peri-implant bone formation and the mixture of HA and Co will display greater amount of new bone in compare to the other groups analysed in this study.

Mantripragada et al. [9] got also surprising results when used another isoform of BMP; BMP-7. The goal was to examine the bone repair after application of different delivery method on implants in defected femur of 80 rats.

Table 1. Bias summary

Study	Year of publication	Random sequence generation	Allocation concealment	Blinding of participant’s and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting	Other bias
Hunziker et al. [1]	2012	-	+	+	+	+	?	+
Sun et al. [2]	2012	-	+	+	+	+	+	+
Xiao et al. [6]	2016	?	+	+	+	+	+	?
Kim et al. [7]	2014	+	?	?	+	+	+	+
Mantripragada et al. [9]	2016	+	?	+	+	+	+	?
Lee et al. [12]	2014	?	?	+	+	+	?	?
Bouyer et al. [14]	2016	+	?	?	+	+	+	+
Jiang et al. [15]	2013	+	?	?	+	+	+	+

+ = low risk; ? = unclear risk; - = high risk.

Table 2. Characteristics of the included studies

Study	Concentration	Carriage mode	BMP type	Model	Bone formation first week (%)	Bone formation second week (%)	Bone formation third week (%)	Bone formation after > 4 weeks (%)	Evaluation method
Hunziker et al. [1]	12.95 µg	Incorporated into coating	BMP-2	Miniature pigs	60	83	> 90	NA	Histomorphometric
	12.95 µg (incorporated) + 10 µg (adsorbed)	Incorporated into and adsorbed onto coating			74	83			
	10 µg	Adsorbed onto coating			17	70	75		
	NA	Coating alone			5	50			
Sun et al. [2]	NA	NA	Control	Minipigs	NA	6.04	20.55	27.88	Histomorphometric
	0.05 µg/µL 4 mM HCl solution containing BSA 0.1%	Absorbable CO	rhBMP-2 homodimers			19.7	25.72	43.07	
			rhBMP-7 homodimers			14.5	31.61	36.42	
			rhBMP-2/7 heterodimers			30.41	40.72	59.44	
Xiao et al. [6]	0.1 mg/mL	AO	rhBMP-2	Rabbits	NA	NA	NA	Lowest adsorption amount	Histologically
		PT						Better adsorption than AO	
		AA						The great adsorption	
Kim et al. [7]	0.75 mg/mL	NA	BMP-2/Ti	Dogs	NA	NA	Vertical bone formation	NA	Histologically
		Heparin							
	NA	Control	Failure of osseointegration						
Mantripragada et al. [9]	7 mg	Chitosan-TPP	Microparticle	Rats	NA	NA	NA	6.41 NBF (1/mm)	New bone fragments (1/mm)
	200 ng with PBS		BMP-7 coated microparticle					6.53 NBF (1/mm)	
			BMP-7 encapsulated microparticle					4.89 NBF (1/mm)	
	NA		Control					7.52 NBF (1/mm)	
Lee et al. [12]	NA	CP	HA	Rabbits	NA	NA	NA	22.85 NBF, 24.18 BIC	Histomorphometric
			HA/Co					47.04 NBF, 41.45 BIC	
			HA/CO/BMP-2					21.72 NBF, 30.72 BIC	
		NA	Control					23.34 NBF, 21.38 BIC	
Bouyer et al. [14]	5 µg/mL	EDC-10	BMP-2	Rats	NA	NA	NA	0	Histomorphometric
	25 µg/mL							62.5	
	50 µg/mL							100	
	100 µg/mL							100	
	5 µg/mL	EDC-30						0	
	25 µg/mL							50	
	50 µg/mL							100	
	100 µg/mL							NA	
Jiang et al. [15]	100 mg of EGFP-C1 with 5 mg/ml	PEI	BMP-2	Rabbits	NA	37.4	31.7	41.5	Histomorphometric
	NA	NA	Control					34.4	

NA = not applicable; BMP = bone morphogenetic protein; HA = hydroxyapatite; EDC = ethylene imine linear poly; CP = calcium phosphate; HCl = Hydrogen chloride; BSA = bovine serum albumin; AO = anodic oxidation; PT = polished titanium; AA = acid alkali; TPP = sodium tri-polyphosphate; BIC = bone implant contact; NBF = new bone fragments.

Chitosan-TPP and chitosan-TPP-BMP-7 scaffolds used as delivery method. Control group without any coating was also evaluated in their study for comparison. Histological and computerized tomography data showed that femoral defect around microparticle coated Ti implants was greater than the one in the control group. The control group presented with no complete healing. No significant difference was observed between microparticle with or without BMP-7. The factors that were suggested to influence the obtained results were:

- The fibrous capsule around microparticle which could have prevented the release of BMP.
- The quantity of BMP or the inflammatory process.

BMP-2 and BMP-7 homodimers have been proven to be efficacious in accelerating bone formation in animal models; however its high cost, potential side effect and heterodimers were proposed to overcome those drawbacks [2].

Sun et al. [2] investigated the formation of new bone in peri-implant bone defect. Eighteen minipigs models were treated with same dose of rhBMP2/7 while different dimer was compared to homo/ hetero dimers. The result showed that the control group had no sufficient bone regeneration in compare to the test group which showed significant results, also after 6 weeks follow-up, bone regeneration with BMP-2 homodimer showed 43.07% while bone regeneration with BMP-7 homodimer showed 36.42%. It was concluded that the use of BMP will result in better bone formation and BMP-2 has greater effect than BMP-7. The group of BMP-2/7 in their heterodimers form induced stronger bone regeneration than BMP-2 and BMP-7 homodimers, by this they conclude that BMP-2/7 homodimers which are more expensive and have more risk for side effects, can be replaced with cheaper dimer as BMP-2/7 heterodimers for bone engineering with the same dose.

Bouyer at al. [14] made an experimental analysis in order to assess the effect of BMP-2 concentrations with EDC10 (ethylene imine linear poly) and EDC30 crosslinking levels. It was assessed while trying to fill volumetric femoral size defect. Comparison between BMP-2 in different concentrations was assessed with different delivery methods, as mentioned in Table 2. The BMP25 and BMP50 groups on EDC30 films exhibited similar levels to those of EDC10. It led them to conclude that EDC crosslinking levels have no significant influence on the bone volume ratio. The bone regeneration kinetics depended on the BMP-2 dose. The kinetics was extremely rapid for BMP50 and BMP100. However, encapsulated haematomas were found with these high doses of BMP-2.

They showed that better result will be presented with experimental group containing osteoinductive surface coating than control group and volume ratio increase with increasing BMP concentration. However, there was a direct correlation between increased bone volumes to higher chance for haematoma. To the best of our knowledge a several methods of local BMP delivery were proposed in the literature to enhance peri-implant osteogenesis.

In 2012, Hunziker et al. [1] compared the osteoinductive effectiveness of different modes of BMP-2 carriage within a defined osteoinductive space using the same experimental models. Ti Implants bore either a direct depot of BMP-2 or a coating adsorbed depot of BMP-2, a coating incorporated or a coating incorporated and a coating-adsorbed reservoir of the BMP-2, 6 implants with different coating were inserted into the maxillary bone of 18 pigs. The histomorphometric analysis evaluated the volume of newly formed bone 1, 2 and 3 weeks after surgery and revealed that the rate of this process is initially most rapid when the coating bore an adsorbed and an incorporated depot of BMP-2. Adsorbed group generate an initial high local concentration of BMP-2, but by the end of the third week, more than 90% of the coating had been degraded by activity of osteoclast and bone resorption appear.

Implants that bore a coating-incorporated depot of BMP-2 had a peak of osteogenic activity being attained during the first week and sustained thereafter. The osteoinductive efficacy index showed slightly lower for implants that bore a coating-adsorbed depot and lowest for implants that bore both a coating incorporated and a coating adsorbed BMP-2.

In three models inflammatory activity was noted adjacent to implant chamber.

Their findings demonstrate that the capacity of BMP-2 to induce local bone formation can be affected by its mode of delivery to the peri-implant space. Gradual liberation from a coated incorporated depot will present higher osteogenic response in compare to a rapid release from coating adsorbed depot.

It is well known that the change of the surface topography can affect the conformation of the adsorbed BMP-2 and normally, proteins tend to adsorb on the hydrophobic surface [6].

In 2016, Xiao et al. [6] made an experiment on 36 rabbits in order to investigate the mechanism of BMP-2 functional change induced by modified Ti surface. They checked how different surface topography, polished Ti (PT) acid alkali (AA) and anodic oxidation (AO) can influence osteogenic function. Six Ti implants were implanted on both femurs while half of the implants were adsorbed with rhBMP-2.

The evaluation performed in 2 methods; half of the participant subjected to push out test and the other half subjected to histological study.

The result revealed that adsorption amount of rhBMP-2 on AO treated implants was lowest while adsorption amount with AA treated implants was highest. PT group had the median adsorption amounts. They found also that structure is influenced by different surface topography. Even though largest amount of rhBMP-2 absorbed on AA and promoted osteogenic differentiation of mesenchymal stem cell (MSCs), this phenomenon didn't sustain for long time. On the other hand, AO treated implants which presented low adsorption amounts, retained for long term. It was also found that osteogenic function of BMP-2 is not only influenced by the concentration. But also on surface modification which can regulate structure of rhBMP-2 and can further influence its osteogenic function.

DISCUSSION

Autogenous bone has been the most popular for augmentation procedures based on the high success rate, though, the harvesting may require another surgical area with a result of high morbidity. Additionally, Triplett et al. [36] reported that the use of autogenous bone had greater prevalence of oedema, pain, sinusitis and erythema than BMP-2.

Since the eruption of BMP's in to the dental field, most of the research focus had been on the therapeutic application of specific BMP in regenerative therapy [37].

The purpose of this review was to investigate the osseointegration process affected by BMP coating on titanium implant surface as well as to find out the most efficient delivery system method and in the same time avoid adverse effects.

The result of current review demonstrated that the use of BMP-2 enhance bone regeneration, this statement was proved by Jiang et al. [15] study which presented much higher cell viability on hBMP-2 coated surfaces on sandblasted or roughened Ti implant than the uncontrolled surfaces, hence BMP-2 genes found to be important osteoinductive accelerators around Ti implants.

Additionally, Kim et al. [7] made an experimental analysis on mandible and maxilla of 3 examined dogs. The implants were also coated with BMP-2 and found to be valid in stimulation of early and late osteoblast differentiation. Bone regeneration was significantly increased around the coated implants in compare with the uncoated implants.

In current data, conflicting results were presented by different authors. Lee et al. [12] compared various bone stimulating agent as; HA, CO and BMP-2. It can be seen that greater peri-implant bone formation was formed with HA and CO group, while, with the peri-implant insertion of BMP bone didn't increase. Moreover, HA and CO will display in greater amount of new bone.

Mantripragada et al. [9] tried to examine bone repair follow application of BMP-7 by different delivery methods and no significant difference was observed between the comparable groups around coated Ti implants.

The factor that was suggested to influence the obtained results could be the fibrous capsule formed around microparticle which could have preclude the release of BMP and (1) affect the quantity of released BMP or (2) to result in inflammatory process, which can lead to increase in interleukins values resulting in (3) delay osseointegration, healing and bone formation.

To prevent these symptoms, anti-inflammatory medications may be prescribed [38]. Besides inflammatory response, following complications can develop with usage of BMPs: ectopic bone formation, osteoclast activity, cancer risk, pseudarthrosis, graft failure, swelling, infection, bleeding, oedema and erythema [37-39]. Moreover, in the current literature data on serious adverse effect was shown after the use of BMP-2 in oral and maxillofacial procedures resulting in additional surgical intervention and additional suffering for the patient. To deal with the adverse Tan et al. [40] suggested the use of systemic steroids in order to reduce soft tissue oedema that associated with BMP-2 application. Bouyer et al. [14] made an experiment in order to assess the effect the BMP-2 in different concentrations and they found that the kinetics of bone regeneration was extremely rapid for BMP50/100 however encapsulated haematoma was found with those high doses. They revealed that better result will be present with osteoinductive surface but in lower concentrations. From this we can conclude that BMPs needs to be delivered to target sites gradually, at a low level and continuously, not in a single high dose burst. There are many methods suggested in literature for delivery of BMP to the target side [1,6,7]. Attempts to use directly adsorbed BMPs to implant surface were made but with no success in osteoinductive efficacious [1]. Hunziker et al. [1] made an experiment to identify the osteoinductive efficacious with different modes of BMP-2 carriage within a defined osteoinductive space using the same experimental model.

Their findings demonstrate that the capacity of BMP-2 to induce local bone formation can be affected by its mode of delivery to the peri-implant space and gradual liberation from a coated incorporated depot will present higher osteogenic response in compare to a rapid release from coating adsorbed depot BMPs.

The efficacy of BMP homodimers has been proved to be successful in many experiments. However, series of potential side effects and high costs resulted into a search for another dimer. Heterodimers were proposed to overcome these drawbacks. Heterodimer can induce cell migration with significant lower concentration needed which will be kept for longer period in a respect to homodimers. Sun et al. [2] investigated the formation of new bone in peri-implant bone defect while comparing these 2 dimers. The results strengthen the use of heterodimers after they showed higher bone regeneration amount.

Ti implant surface topography may provide a way to regulate the function of BMP. Surface topography is the key factor for long term success rate of dental implant and successful osseointegration of Ti implant to bone tissue [11,41]. Recently article was published by Xiao et al. [6] in order to investigate how different surface topography can influence osteogenic function. They found that AA had the largest adsorption amount and suggested that osteogenic function is not only influenced by concentration however, surface modification has a big role on bone regeneration and osteoinduction.

Regulation of Ti implant surface topography may provide a way to regulate the function of BMP [6]. Yeo et al. [41] reported that acid etch topography has four times greater resistance to removal test, along with roughened sandblasted surface which was found

to increase significantly bone contact. Both surfaces will have higher resistance to implant removal.

Certainly, BMPs have been used to promote osseointegration and bone regeneration as suggested by Yeo et al. [41], who reported that BMP coated on an oxidized Ti surface induced more bone osseointegration, regeneration and volume in compared with Ti oxidized layer who was luck in BMP coating [41].

By all authors topographically Ti implants surface reported to show high success rates and better result of osseointegration.

CONCLUSIONS

It's clearly shown from most of the examined studies that bone morphogenetic protein increases bone regeneration. Further studies should be done in order to induce and sustain bone formation activity. Osteogenic agent should be gradually liberated and not rapidly released with priority to three-dimension reservoir (incorporated) titanium implant surface in order to avoid following severe side effects: inflammation, bleeding, haematoma, oedema, erythema, and graft failure.

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The authors confirm that this review content has no conflict of interest with any financial organization regarding the material discussed in the review.

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