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Review

The effect of growth factors for bone augmentation to enable dental implant placement: A systematic review

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Summary This systematic review assessed the potential benefits of growth factors for bone augmentation prior to the placement of dental implants in human.

A systematic online review of the Medline database, using the PubMed search machine was performed between 1966 and November 2008 by entering the MeSH terms. The primary outcome of the included studies was bone regeneration of localized alveolar ridge defects.

The initial search identified 119 papers from the electronic database. This review produced seven eligible papers that reported on bone augmentation with recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), recombinant human Platelet-Derived Growth Factor (rhPDGF) and Plasma-Rich Growth Factor (PRGF). The rhBMP-2 affected local bone augmentation with increasing volume for higher doses. Both rhPDGF and PRGF showed a positive effect in favor of the growth factor.

Differing levels and quantity of evidence were noted to be available for the growth factors evaluated, revealing that rhBMP-2, rhPDGF, and PRGF may stimulate local bone augmentation to various conditions. Especially the potential of rhBMP-2 is supportive. However, the confined number of investigators using these techniques and the low number of patient treatments reported in the literature, the generalizability of this approach is limited at this time.

Contents

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Introduction

Dental implants are the most innovative and superior treatment in dentistry, and are widely used for a variety of cases. Most of the techniques that are used are evidence-based and predictable. However, in many cases, the intended implant site is inappropriate due to the poor bone quality or to an insufficient quantity of bone. An insufficient alveolar ridge height is often related to the proximity of the implant site to other anatomical structures, i.e., the maxillary sinus or the mandibular canal.

In order to overcome some of these difficulties, autogenous bone grafts taken from the chin, the ramus of the mandible, or the iliac crest of the same patient have historically been the standard for alveolar reconstruction, specifically, due to their osteoconductive, osteoinductive, and lack of immunogenic properties. However, the adverse events and complications, such as infection, pain, sensory loss, and hematoma formation at the donor site, occur frequently upon autogenous bone graft treatment. In addition, a donor site with a sufficient quantity of bone is not always available. Allograft bones, bones taken from a different person and processed and managed by a tissue bank or commercial supplier, have often been substituted. However, this method also has limitations, including an inconsistent osteoinductive activity, unfavorable host immune responses [1], a delayed resorption, and a risk for prion and virus transmissions [2,3].

An ideal bone graft in implant dentistry should have the following properties: it should be biomimetic; it should have the ability to induce differentiation of the appropriate cells (i.e., endothelial and osteoblastic cells) for the formation of new bone; it should be easily synthesized or produced, rather than extracted from allograft materials (to eliminate all risks of disease transmission); it should be easily and quickly resorbed as the osteogenic response occurs; it should have no immune-provoking properties; it should be easily transported and stored; it should be reasonably cost-effective; it should be capable of achieving consistent and predictable results without being affected by different level of technical ability of the clinician.

In order to meet these demands, dental research has focused on the use of bioactive molecules to induce local bone formation. Since the various growth factors that have an effect on the bone regeneration have been discovered, the number of related studies has increased substantially. In particular, the factors recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) [4—7] and recombinant human Platelet-Derived Growth Factor (rhPDGF) [8—10] have been shown to induce bone formation at the compromised sites in a variety of experimental and clinical situations. These factors have also been approved by the U.S. Food and Drug Administration (FDA) for use in dentistry.

To date, there is only limited evidence to support the application of growth factors for local bone augmentation in dentistry. The aim of this systematic review was to summarize the current literature that describes the use of growth factors in conjunction with dental implants.

Material and methods

Study selection

We conducted an electronic search of the Medline database, using the PubMed search machine, for the relevant selection of studies by entering the following MeSH terms: ''Intercellular Signaling Peptides and Proteins;'' and ''Dental Implants''. We limited our results to humans, to articles published in the English language; and, in the time range of 1966 to November 2008. The references of the retrieved articles were also searched.

The inclusion and exclusion criteria

The studies included in this review met the following inclusion criteria: (1) only relevant data on bone augmentation induced by the growth factors; (2) only randomized, nonrandomized clinical trials, cohort studies, case—control studies, and case reports; (3) only studies with a clearly written amount and concentration of growth factors or using the kit with fixed concentration of growth factors; (4) only studies with a clearly defined baseline; and (5) only studies with the application of titanium root-form implants. The most recent report was used if more than one publication referred to the same data. The studies that did not meet all the inclusion criteria were excluded from the review. The studies that dealt with the following topics were excluded: (1) *in vitro* animal studies; (2) studies using gene therapy; (3) studies with a focus on periodontal regeneration; (4) studies reporting systemic treatment outcomes; (5) craniofacial surgery for total or partial reconstruction of mandibles/maxillas; (6) cleft lip and palate surgeries; (7) distraction osteogenesis; (8) osseointegration; (9) implant anchor; (10) immediate loading or (11) orthopedic surgeries. Each retrieved citation was reviewed by two independent reviewers (K.S., O.M.). Most of the citations were excluded immediately, due to the information provided by the title or the abstract. If the citation could not be excluded immediately because of its equivocal nature, then the complete article was selected by the two reviewers. Any disagreement between the reviews was resolved by a consensus. To avoid any bias, the search

process was blinded to the names of the authors, to the names of institutions, and to the names of the journals.

The data extraction

The data were independently extracted by two reviewers using data extraction tables. Any disagreements were discussed until they were resolved by a consensus. The following information were extracted: the authors, the year of publication, the study design, the number of patients, the mean age of the patients, the follow-up period, the adverse event, the applied dose of growth factor, the carrier system, the control group, the type and the dimension of the defect, the decrease in the defect of height/increased bone height/width, the newly formed bone, and the new bone density.

Result

The study characteristics

The PubMed search identified a total of 119 citations. However, most of them were excluded immediately due to the information provided by the title or the abstract (Fig. 1). Only 20 articles were selected for further text review [11—30]. The main reasons for excluding some studies ($n = 13$), after the full text was obtained, were as follows: poor-quality data for bone augmentation induced by growth factors, any reports based on animal studies, and a lack of or insufficient discussion of the clinical, radiographic, or histological treatment outcomes (only descriptive presentation of results). Of the seven eligible articles, three studies reported on bone augmentation with rhBMP-2 [14,15,17], three studies discussed the effect of rhPDGF [11—13], and one study examined the effect of Plasma-Rich Growth Factor (PRGF) [16]. Two of the rhBMP-2 studies were randomized control trials (RCT) with a clearly stated random allocation of subjects. The other BMP-2 study was a prospective, human clinical trial without a control. All of three rhPDGF studies and the PRGF study were case reports.

Table 1 shows the characteristics of the included studies. A total of 76 patients were treated with growth factors for local intra-oral bone regeneration. The mean age of the patients was 54.8 years and the mean follow-up period was 47.1 months. Table 2 shows the operative data reported in the included studies. The growth factors were always administered locally, and the root form dental implant was used in every study. The applied dose of the rhBMP-2 ranged from 0.43 to 1.5 mg/ml or from 0.2 to 24 mg/patient. However, the rhPDGF and the PRP studies lacked this type of information. Two different carrier systems were used for the application of rhBMP-2. An absorbable collagen sponge (ACS) was used in two studies [14,17], whereas rhBMP-2 was applied to a demineralized bovine bone matrix (xenogenic bone substitute mineral, Bio-Oss®) in another study [15]. With respect to the application of rhPDGF, the carriers used were Bio-Oss®, beta-tricalcium phosphate (β-TCP) and a freeze-dried mineralized bone allograft (FDBA). For the PRGF treatment, a combination of Bio-Oss® and autogenous bone was used. The types of local bone augmentations observed were sinus floor augmentations [14,16,17], preservations of extraction socket [13,17], alveolar ridge bone augmentation [11], and lateral ridge augmentation in combination with simultaneous implant placement [12,15,16]. A meta-analysis of the outcomes was not performed because of the heterogeneity of the studies (various indications, RCT, or cohort)

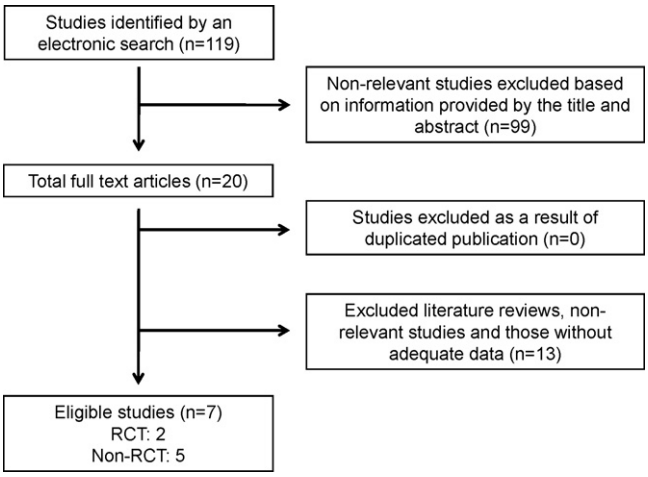

Figure 1 Outline of the literature search.

Bone height increase/defect size decrease

An increase in bone height, ranging from 10.16 ± 4.7 to 9.47 ± 5.72 mm for the sinus lift procedures, and a change in bone depth of 6.8 ± 0.2 mm, for the extraction socket augmentations, were reported for the sites treated with rhBMP-2 (Table 3). Two RCTs included control groups without the application of the rhBMP-2 [14,15]. In comparison to the controls, the effect of rhBMP-2 showed substantial variability. Boyne et al. presented negative data for the bone height, and the average gain in the bone height was 11.29 ± 4.12 mm for the control sites and 9.47 ± 5.72 mm for test sites with a low dose of rhBMP-2, respectively. There were no statistically significant differences in the control group with respect to the increase in ridge height, and the decrease in ridge width with the use of rhBMP-2 [14]. Only one RCT reported a positive effect in comparison to the control group, when the factor was applied to the lateral ridge augmentation [15].

On the other hand, rhPDGF seemed to have a positive role in enhancing the healing of soft and hard tissues, even though there was no clear mention and evaluation of bone regeneration. The result of the bone augmentation was clearly presented by the use of pictures and dental X-rays that showed successfully filled bone defects within 5—7 months after the operation [11—13].

New bone formation

Jung et al. and Boyne et al. reported the new bone formation as a percentage of the original defect or as new bone density, respectively (Table 3). The dose of the applied factor seemed to have an impact on the treatment outcome, with a higher local bone regeneration for the higher doses of rhBMP-2. For a lower dose of rhBMP-2, a positive, but not a statistically significant effect was observed on the bone formation, whereas, for a higher dose, a positive and statistically significant effect was reported. Boyne et al. reported a significant difference in new bone density in favor of the bone

Table 1 Characteristics of included studies.

Study	Year of publication	Type of study	Type of surgical procedure	No. of enrolled patient			Mean follow-up (month)	Mean age		M/F ratio		Outcome
				Treatment group	Control group	Total		Treatment group	Control group	Treatment group	Control group	
Simion et al.	2008	Case report	Alveolar ridge augmentation	1	0	1	14	36 years	—	0	—	X-ray
Byun et al.	2008	Case report	Socket preservation	1	0	1	ND	65 years	—	0	—	X-ray
Fagan et al.	2008	Case report	Socket preservation	1	0	1	3	52 years	—	1	—	X-ray, histology
Boyne et al.	2005	RCT	Sinus floor augmentation	Low dose: 18; high dose: 17	13	48	52	Low dose: 57 years $\pm$ 12; high dose: 52 years $\pm$ 7	57 years $\pm$ 11	Low dose: 0.80; high dose: 0.54	0.625	CT, histology, success and survival rate
Jung et al.	2003	RCT	Alveolar ridge augmentation	11	—	11	ND	53 years $\pm$ 16.9	—	0.57	—	Defect filling rate, histology
Anitua	2001	Case report	Alveolar ridge augmentation Sinus floor elevation	2	0	2	36	61 years $\pm$ 4.2	—	1	—	Histology
Cochran et al.	2000	Prospective clinical trial	Alveolar ridge augmentation Socket preservation	12	0	12	36	ND	—	ND	—	Defect filling rate, histology

Table 2 Operative data investigated in the included studies.

Study	Treatment group				Control group	Implant system	Number of implant
	Type of growth factor	Dose of growth factor	Delivery vehicle	Concentration of growth factor	Type of bone graft		
Simion et al.	rhPDGF-BB (GEM21S®; BioMimetic)	ND	Bio-Oss® + autogenous bone	1.2 mg/ml	—	MK3 Natural Platform 3.3 mm × 15 mm, Speedy Groovy 4 mm × 15 mm, Nobel biocare	2
Byun et al.	rhPDGF-BB (GEM21S®; BioMimetic)	ND	β-TCPalloplast, autogenous bone	0.3 mg/ml	—	Tapered ScrewVent 3.7 mm × ND mm, Zimmer Dental	1
Fagan et al.	rhPDGF-BB (GEM21S®; BioMimetic)	ND	FDBA	0.3 mg/ml	—	Osseotite implant 4 mm × 13 mm, BIOMET/3i	1
Boyne et al.	rhBMP-2 (Medtronic)	Low dose: 8.9 mg (5.2—12.0 mg); high dose: 20.8 mg (10.8—24.0 mg)	Autogenous bone or ACS	Low dose: 0.75 mg/ml; high dose: 1.5 mg/ml	Autogenous bone graft	ND	219
Jung et al.	rhBMP-2	0.18 mg	Bio-Oss®	0.5 mg/ml	Bio-Oss®	Machine surface, Nobel biocare	34
Anitua	PRGF (PRP)	ND	Bio-Oss® + autogenous bone	ND	—	ND	5
Cochran et al.	rhBMP-2	Alveolar ridge augmentation 0.27 mg (0.1—0.9 mg), Socket preservation 0.83 mg (0.2—1.7 mg)	ACS	0.43 mg/ml	—	Titanium plasma sprayed implant	13

Table 3 Summary of the clinical bone assessment.

Study	Group		Defect fill			Histological analysis			CT analysis	
			Base line (mm)	Change from base line (mm)	Percent vertical defect fill (%)	Woven bone (%)	Lamellar bone (%)	Bone substitute mineral (%)	Bone density at 4 months (mg/cm^3)	Bone density 6 months post-functional loading (mg/cm^3)
Simion et al.										
Control	–	–	–	–	–	–	–	–		
Test	rhPDGF-BB/Bio-Oss® + autogenous bone	Depth	20	ND	ND	ND	ND	ND		
		Width	15	ND	ND					
Byun et al.										
Control	–	–	–	–	–	–	–	–		
Test	rhPDGF-BB/P-TCP + autogenous bone	Depth	ND	ND	ND	ND	ND	ND		
		Width	ND	ND	ND					
Fagan et al.										
Control	–	–	–	–	–	–	–	–		
Test	rhPDGF-BB/FDBA	Depth	15	ND	ND	48	19	14		
		Width	8	ND	ND					
Boyne et al.										
Control	Autogenous bone graft	Height	11.29 ± 4.12	ND	ND				350 ± 243	448 + 213
		Width at 1/4	4.66 ± 2.75	ND	ND					
		Width at 1/2	10.17 ± 2.98	ND	ND					
		Width at 3/4	10.56 ± 3.17	ND	ND					
	rhBMP-2/ACS 0.75 mg/ml	Height	9.47 ± 5.72	ND	ND				84 ± 50	456 ± 131
		Width at 1/4	2.02 ± 2.73	ND	ND					
		Width at 1/2	8.54 ± 5.47	ND	ND					
		Width at 3/4	11.86 ± 5.15	ND	ND					
Test	rhBMP-2/ACS 1.50 mg/ml	Height	10.16 ± 4.7	ND	ND				137 ± 77	508 ± 126
		Width at 1/4	1.98 ± 2.41	ND	ND					
		Width at 1/2	7.8 ± 3.87	ND	ND					
		Width at 3/4	10.78 ± 4.63	ND	ND					
Jung et al.										
Control	Bio-Oss®	Depth	5.8 ± 1.8	5.4 ± 2.2	91 ± 15.1	13 ± 6.7	17 ± 8.1	17 ± 11.0		
		Width	ND	ND	ND					
Test	rhBMP-2/Bio-Oss®	Depth	7.0 ± 2.7	6.8 ± 0.2	96 ± 6.9	8 ± 5.0	29 ± 11.3	23 ± 11.1		
		Width	ND	ND	ND					
Anitua										
Control	–	–	–	–	–					
Test	PRGF (PRP)	Depth	10	ND	ND					
		Width	ND	ND	ND					
Cochran et al.										
Control	–	–	–	–	–					
Test	Alveolar ridge augmentation	Height	ND	-0.8 ± 2.5	ND					
		Width	ND	0.4 ± 0.9	ND					
	Socket preservation	Depth	ND	10.4 ± 6.6	ND					
		Width	ND	4.9 ± 2.4	ND					

graft group (350 ± 243 mg/cm^3) in comparison to the low (84 ± 50 mg/cm^3) and to the high (137 ± 77 mg/cm^3) dose treatment groups at 4 months after the operation. However, after 6 months of functional loading, the density of the newly induced bone increased significantly for the low (456 ± 131 mg/cm^3) and the high (508 ± 126 mg/cm^3) dose treatment groups, and its value was comparable to that of the bone graft group (448 ± 213 mg/cm^3). Jung et al. reported a positive, but not statistically significant, effect of rhBMP-2 on the amount of newly formed bone ($37 \pm 11.2\%$) in comparison to the control group ($30 \pm 8.9\%$). However, a statistically significant increase in mature lamellar bone ($29 \pm 11.3\%$) for the test site was found in comparison to the control site ($17 \pm 8.1\%$).

Safety

From the various studies, Boyne et al. [14] and Cochran et al. [17] reported the adverse events of the rhBMP-2 application that occurred during the procedure (Table 4). The most frequent adverse events occurred during the first 4 months after the operation. These events were transient and consistent with the surgical procedures performed (a maxillary sinus floor augmentation procedure, or a bone graft harvest procedure). The majority of the events were equally distributed among the treatment groups. However, the incidence of edema, rash and pain in the bone graft group were much higher than in the rhBMP-2 groups. These complaints of edema, rash (erythema), and pain were experienced from the autograft harvest site. Notably, the 1.50 mg/ml rhBMP-2/ACS treatment group had significantly greater facial edema during the first 4 months after surgery than did the bone graft group and the 0.75 mg/ml rhBMP-2/ACS group.

Discussion

This systematic review assessed the potential benefits of growth factors for bone augmentation prior to the placement of dental implants. The rhBMP-2 (INFUSE®, Medtronic) and the rhPDGF (GEM21S®, BioMinetic Therapeutics) have been approved by the FDA for dentistry. In addition, the rhBMP-7 (OP-1, Stryker Biotech) has been approved in Australia and Europe, and by the orthopedic community in the USA. Various growth factors are now entering clinical practice in dentistry. Hence, a systematic assessment of the effect of the growth factors on the bone augmentation for dental implants is very important.

The number of satisfactory studies was assumed to be low; therefore, in this systematic review with the prospective cohort studies and case reports, a lower level of evidence was used. Instead of performing a formal quality assessment of the included studies and a sensitivity analysis, this review used stringent inclusion criteria. The electronic search selected the studies, that used growth factors for bone augmentation prior to the placement of dental implants in human, by applying the following MeSH terms: ''Dental Implant'' and ''Intercellular Signaling Peptides and Proteins''. The term, ''Intercellular Signaling Peptides and Proteins'', belongs to the chemical and drug category, and is located at the upper level of the MeSH tree that contained all the growth factors. However, only seven studies of the

Table 4 Number of frequent adverse experiences according to the body system.

Study	Group	Body as a whole						Digestive system			
		Dehiscene	Edema	Face edema	Headache	Pain	Infection	Mouth pain	Oral edema	Oral erythema	Colitis
Boyne et al. (*n* = number of patient)	Bone graft (*n* = 13)	2	6	5	0	5	ND	8	8	6	ND
	rhBMP-2/ACS 0.75 mg/ml (*n* = 18)	2	0	7	2	1	ND	14	10	3	ND
	rhBMP-2/ACS 1.50 mg/ml (*n* = 17)	1	0	14	3	3	ND	15	8	4	ND
Cochran et al. (*n* = number of event)	Alveolar ridge augmentation (*n* = 532)	ND	ND	ND	ND	ND	1	6	1	ND	2
	Socket preservation (*n* = 528)	ND	ND	ND	ND	ND	1	4	2	ND	0

rhBMP-2, the rhPDGF, and the PRGF were available for an analysis. Two human RCTs for rhBMP-2 were found, but for rhPDGF and PRGF no human RCT was found. Almost all the articles were old, and no RCT evaluation of the effect of the growth factors for the dental implants had been published recently. Seven eligible articles demonstrated that the application of growth factors was safe and effective for bone formation.

Three articles related to rhBMP-2, includes this systematic review, showed a positive effect on the rhBMP application for bone formation. Cochran et al. reported a prospective, human clinical trial without a control in order to examine the effect and safety of rhBMP-2/ACS on the alveolar ridge augmentation and on the socket preservation. This study showed that bone formation was successful when using rhBMP-2/ACS at a concentration of 0.43 mg/ml. Jung et al. reported a prospective, controlled, randomized, double-masked clinical study on alveolar ridge augmentation. This study was designed to investigate the test site and the control site of the same patient's jaw, which required a lateral ridge augmentation. Despite the small number of patients, this experimental design allows the direct comparison of the test site and the control site by eliminating the differences such as the patients and the doctors or other possible variables. In addition, this is the only report that tested rhBMP-2 with grafting material (xenogenic bone substitute; Bio-Oss®) for lateral bone augmentation. The report concluded that the combination of Bio-Oss® with the rhBMP-2 was able to enhance the maturation process of bone regeneration and increase the graft-to-bone contact in humans. The most recent RCT study was reported by Boyne et al., and it was designed to evaluate the effect of two different concentrations of BMP-2 on the safety and efficacy of the sinus floor augmentation. It was demonstrated that the higher dosage produced better results. Based on the data, they concluded the following: (1) both the high (1.50 mg/ml) and the low (0.75 mg/ml) concentrations of rhBMP-2 were safe, with a safety profile similar to that of bone graft; (2) both concentrations of rhBMP-2 induced a similar amount of bone formation which was similar to that induced by the bone graft; and (3) the higher concentration of rhBMP-2 induced bone formation more rapidly in comparison to the lower concentration. The results support the use of rhBMP-2/ACS at a concentration of 1.50 mg/ml for the future studies of maxillary sinus floor augmentation. In these studies, the most frequent adverse events occurred within the first 4 postoperative months [14,17]. The majority of the events were equally distributed among the treatment groups and control groups. However, the high (1.50 mg/ml) concentration of rhBMP-2 treatment group had a significantly greater facial edema during the first 4 months after surgery in comparison to the bone graft group and the 0.75 mg/ml rhBMP-2/ACS group. On the other hand, we could not obtain a clear outcome from the three case reports that evaluated the rhPDGF efficacy and that met our inclusion criteria. However, the results of every study were consistent with respect to the positive effect of rhPDGF. In addition, there is no well-designed RCT study of rhPDGF. Therefore, the information was not sufficient to draw any definitive conclusions, particularly with respect to the long-term evaluation.

In addition to this systematic review, we also obtained another six eligible articles [31—36] by means of a hand-search of the articles listed in the retrieved list of References. These studies assessed — only the bone grafts. They were most likely automatically excluded on the PubMed during our selection process because the word "Dental Implant" was not associated strongly with these articles. The first studies were clinical trials, one of which was a multicenter cohort study of the effect of rhBMP-2 maxillary sinus floor augmentation and socket preservation [31,32] that supports the beneficial effect of BMPs. Fiorellini reported a randomized, masked, placebo-controlled multicenter clinical study to evaluate the effect of two concentrations of rhBMP-2 on the safety and efficacy of socket preservation [33]. The trend of this study was the same as that of the Boyne's study; 1.5 mg/ml of rhBMP-2 was safe for clinical application and the higher dosage produced better results. Van den Bergh et al. [34] and Groeneveld et al. [35] have used rhBMP-7 as an aid to increase the bone height in sinus, prior to the placement of implants. The results from these clinical trials indicated that the OP-1 (2.5 mg in 1 g of collagen carrier) had the potential to initiate bone formation in the human maxillary sinus within 6 months after a sinus floor elevation operation. However, the behavior of this material cannot be fully predicted.

Dickinson et al. [36] reported about the economic result of the rhBMP-2 treatment on the alveolar bone grafting in the older cleft patients, in order to improve poor wound healing, graft exposure, recurrent fistula, and failure of tooth eruption. According to the report for the autogenous bone graft group, seven of the nine patients underwent the procedure on an outpatient basis. The procedure was applied to the iliac bone graft patients on an inpatient basis. The donor-site pain intensity and the frequency were significant in the traditional iliac bone graft, but it was not significant in the rhBMP-2 treated group. Furthermore, the mean length of stay was greater for the iliac bone graft patients at 1.8 ± 0.8 days in comparison to the patients treated with rhBMP-2 at 0.4 ± 0.4 days ($p < 0.05$). Hence, the mean overall cost of the procedure, including the surgeon, the facility, the equipment, and the anesthesia fees, was greater for the iliac bone graft group ($21,800) in comparison to the rhBMP-2 treated group ($11,100).

On the other hand, the price of those growth factors is still relatively costly for treatment. The price of INFUSE® kit which contains 4.9 mg of rhBMP-2 cost more than $3000 in the United States. The rhBMP-2 and the rhBMP-7 have been used in orthopedic spinal surgery with decreased donor-site morbidity. In addition, these proteins showed promise for the tissues that are characterized by poor wound healing, such as irradiated tissue [37]. However, there are several reports on the side effects associated with the high BMPs dosage and the repeated regimens, which are required for the stable bone regeneration in the orthopedic field [38—40]. As shown here, the use of growth factors in humans undergoing craniofacial and oral maxillofacial procedures has only recently been documented. There have been investigative reports of ectopic bone growth with rhBMP-2 and, consequently, its use in growing patients is being studied carefully [41]. In order to overcome some of these difficulties, a variety of pre-clinical studies are carried out; such as testing new optimized carrier systems to decrease the dosage of growth factors, producing the growth factors by using *E-coli* system [42,43], or finding the new bioactive small peptide which have osseoinduction

ability [44] to reduce the production costs and developing a genetically engineered mutant growth factors to improve the binding property to the extracellular matrix in order to prevent rapid diffusion.

BMPs have been shown to increase the formation of bone nodules *in vitro* [45—56] and stimulate bone formation *in vivo*. But the dosage applied in these clinical studies was several orders of magnitude higher than the concentration of naturally occurring BMPs [57]. It is believed that small animals require a much lower dose of BMPs to bridge bone defects in comparison to larger animals, although this correlation is expected to change appropriately for specific carriers [58]. Hydroxyapatite, natural bone mineral, collagen, gelatin hydrogels and other biodegradable polymers compose the range of carriers that are currently being investigated as vehicles for the implantation of osteogenic factors. More recently, the attention of researchers in the biomaterial field was directed at the relationship between tissue engineering and bone morphogenesis. The fundamental principle governing these investigations is the production of more ''intelligent'' materials that could influence protein pharmacokinetics to modulate the delivery of rhBMP-2 at the site of implantation, or to enhance osteogenesis with these factors by altering the geometry of the environment [59—62].

Recently several groups have developed genetically modified mutant rhBMP-2, which is generated from *E-coli*, and this rhBMP-2 possesses an improved binding property to the extracellular matrix in order to prevent its rapid diffusion [42,43]. Wurzler et al. reported a genetically engineered mutant rhBMP-2 (rhBMP-2 T4), which was developed with two additional repeats of a positively charged epitope, called the heparin-binding domain, in the N-terminal sequence. Bing et al. reported a genetically engineered collagen targeting rhBMP-2 (rhBMP-2-v), which was fused with collagen bonding peptide to the N-terminal of rhBMP-2. Their rhBMP-2-v contained a collagen-binding domain which modified from von Willebrand factor, and this collagen-binding domain was flanked by linker regions to minimize steric hindrance. Both genetically engineered mutant rhBMP-2 have been shown to have higher extracellular matrix binding and stronger osteoinductivity than the wild-type rhBMP-2 *in vitro* and *in vivo*. By concentrating at the targeted wound site, these BMP-2 mutants can be avoids being washed away by extracellular fluids, which will eventually lead to not only a more effective osteogenesis but also a reduction of the undesirable systemic side effects.

Therefore, many questions must be answered before the growth factors can attain widespread clinical usage. Knowledge of the cellular and molecular basis of the bone regenerative signaling pathways, and the development of appropriate carriers will certainly stimulate a great revolution in dentistry, thus allowing the dominance of regenerative over cicatricial processes. However, the number of well-designed blind and randomized clinical trials is still too small to establish the clinical protocols for the improvement of a recipient bone bed prior to implant placement, or to enhance the integration process of an implant. The dissimilarities in the experimental designs, as well as, the use of nonstandardized concentration of growth factors, or the type of carriers of growth factors by different authors make it difficult to compare the outcomes of the growth factor applications in implant dentistry. A better-designed RCT, using growth factors for intra-oral bone augmentation, especially longitudinal clinical studies with a wider patient population, is necessary. However, these studies in this paper will set a golden standard for examining the effect of following new therapeutics.

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