Effect of Application of Growth Factors with Dental Implant for Enhancing Bone Formation and Osseo Integration: A Review

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Abstract

Purpose

Evaluation the effect of application of growth factors with dental implants in enhancing bone formation and osseointegration.

Study Selection

Electronic database (PubMed & Midline) searches were performed to identify scientific articles, published in English, between 2001-2017 reporting on growth factors, bone morphogenetic proteins, platelets rich plasma and platelets rich fibrin with dental implants.

Result

Histometric and radiographic evaluations data were collected from all studies and comparison was made between the different studies to evaluate the amount and quality of bone surrounding dental implants to evaluate the effect of growth factors on bone when used with dental implants.

Conclusions

From the results of all studies, it was found that growth factors could enhance bone formation around dental implant which leads to good prognosis of the dental implants.

Keywords

Cytokines; Morphogenetic Protein; Growth Factors; Dental Implants; Platelets Rich Plasma; Platelets Rich Fibrin

Introduction

Success of any dental implant is related to the quality and quantity of bone implant contact and osseointegration which refers to a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant which is important to stabilize the dental implant [1]. Many studies discus the effect of growth factors on induction of bone formation with dental implants.

Growth factor is a naturally occurring substance...
capable of stimulating cellular growth proliferation, healing, and cellular differentiation. Usually it is a protein or a steroid hormone. Growth factors are important for regulating a variety of cellular processes. They often promote cell differentiation and maturation, which varies between growth factors [2].

The available growth factors types are, Transforming growth factor beta (TGF-β), Insulin like growth factor I and II (IGF-I; IGF-II), Fibroblast growth factor (FGF), Epidermal growth factor (EGF), Platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF).

Growth factors and cytokines are signaling molecules that control cell activities in an autocrine, paracrine or endocrine manner. They can have various functions on different cell types while distinct growth factor or cytokines can exert similar or overlapping functions on certain cells. Growth Factors and cytokines affect a wide variety of physiological processes such as cell proliferation, differentiation, apoptosis, immunological or hematopoietic response, morphogenesis, angiogenesis, metabolism, wound healing, and maintaining tissue homeostasis in adult organisms. The abnormal production or regulation of growth factors and cytokines can cause various diseases such as cancer [3], liver fibrosis [4] and broncho-pulmonary dysplasia [5]. Historically, growth factors were thought to be biological moieties that have a positive effect on cell growth and proliferation while cytokines were typically considered to have an immunological or hematopoietic response. However, as different lines of research have converged, it has been found that ‘cytokines’ and ‘growth factors’ can have similar functions and therefore, these terms are now used interchangeably. Bone morphogenetic proteins (BMPs) are multi-functional growth factors that belong to the transforming growth factor beta (TGFbeta) super family. The activity of BMPs was first identified by Urist [6]. He coined the term “bone morphogenetic protein” (BMP) to describe the activity of a complex protein extract of bone matrix. He implanted cylinders of bone that had been decalcified in a variety of acids in muscle pockets in rabbits and observed new bone formation.

Now the human BMP is produced by using recombinant techniques. Therefore, the available protein is free from the risk of infection or allergic reaction. Twenty proteins have already been purified and cloned; they are called BMP-1 through BMP-20. In 2002 FDA approved OP-1 (BMP-7) for long bone defects and BMP-2 in a collagen carrier within a cage for anterior lumbar interbody [7].

The role of growth factors on induction of bone formation may have resulted from the stimulated proliferation of osteoblast precursors rather than stimulated osteoblastic differentiation which could stimulate BMP activity in the early phases of bone healing, just before the BMPs exert their effects. While BMPs are key regulators of osteoblast and chondrocyte differentiation during skeletal development and of osteogenic differentiation in healing fractures [8].

The aim of our review to summarize the scientific articles dealing with using of growth factor with dental implant to improve bone formation and osseointegration.

**Criteria for Considering Studies for this Review Inclusion Criteria**

2. In vivo studies.
3. Implant and growth factors, bone morphogenetic proteins, platelets rich plasma and platelets rich fibrin,
4. Evaluation of effect of growth factors, bone morphogenetic protein, platelets rich plasma and platelets rich fibrin on bone formation and osseointegration around dental implant.
5. Histological and radiographic evaluation of the effect of growth factors on prei –implant defect found or Intentional creation.

**Exclusive Criteria**

1. In vitro studies.
2. Expression of growth factors in the peri-implant soft tissues.
3. Evaluation of the effect of growth factor in bone formation or ridge augmentation before implant installation.

**Searching Methods**

Electronic database (PubMed & Midline) searches were performed to identify scientific articles, published in English, between 2001-2017 reporting on growth factors, bone morphogenetic protein, platelets rich plasma and...
platelets rich fibrin with dental implants.

**Growth Factors and Dental Implant**

Sykaras et al. [9], studied the effect of recombinant human bone morphogenetic protein-2 on bone regeneration and osseointegration of dental implants. In this study, bilateral extractions of mandibular premolars of dogs were performed and surgical implantation of 104 hollow cylinder implants followed after 8 weeks of healing. For test group, implants had their hollow chamber filled with 20 mg of rhBMP-2 delivered with a bovine collagen carrier, whereas the control group implants had their apical chamber left empty. Dogs were followed for 2, 4, 8 and 12 weeks. Histomorphometric evaluation and immunohistochemical analysis were performed. Minimal bone was regenerated at 2 weeks for both groups. At 4 weeks, bone fill averaged 23.48% for the rhBMP-2 and 5.98% for the control group. At 8 weeks, mean bone fill was 20.94% and 7.75% for the rhBMP-2 and the controls, respectively. At 12 weeks, mean bone fill was 31.39% and 24.31% for the rhBMP-2 and control implants, respectively. Bone-implant contact (BIC) increased for both groups over time and at 8 weeks the rhBMP-2 BIC value was 18.65% and for the control 7.22%. At 12 weeks, the BIC was 43.78% and 21.05% for the rhBMP-2 and the control group [9].

Becker et al. [10], studied the effect of recombinant human bone morphogenetic protein-2 (rhBMP-2) biocoated and rhBMP-2 nonbiocoated titanium implants after implantation in the mandible and tibia of dogs. Implantation of sand-blasted and acid-etched implant (c) (n=6), chromo- sulfuric acid surface-enhanced (CSA) (n=6), 2and rhBMP-2- biocoated CSA [BMP-A: noncovalently immobilized rhBMP-2 (596 ng/cm20) (n=6), BMP-B: covalently immobilized rhBMP-2 (819 ng/cm2) (n=6). Histomorphometric result revealed that BIC values appeared to be highest in the BMP-B group, followed by BMP-A, CSA, and C. While there no differences in BD between groups were observed at a distance of >1 mm [10].

Nikolidakis et al. [11], studied the effect of local application of autologous platelet-rich plasma (PRP) on bone healing in combination with the use of titanium implants with 2 different surface configurations was investigated. Thirty-six implants (6) CaP coated implants (CaP), (6) CaP coated implants + PRP liquid (CaP/liquid), (6) CaP coated implants + PRP gel (CaP/gel), (6) Non-coated implants (Ti), (6) Non-coated implants + PRP liquid (Ti/liquid), and (6) Non-coated implants + PRP gel (Ti/gel) were placed into the goat femoral condyles (trabecular bone). The animals were sacrificed at 6 weeks after implantation and histo-morphometrical variables were evaluated (the bone-implant contact and the bone mass adjacent to the implant). Significantly more interfacial bone-to-implant contact was observed for all 3 groups of CaP-coated implants and the titanium/liquid group (non-coated implant with PRP liquid) than for the other 2 non-coated titanium groups (with PRP gel or without PRP). The evaluation of the bone mass close to implant surface indicated that all the groups induced a significant increase of the bone mass except the PRP gel groups, whereas PRP in a liquid form showed a significant effect on bone formation in group II was greater than that in group III at 8 weeks, but there was no significant difference between groups I and II (although bone formation in group II was greater than that in group I at 4 weeks). The bone formation in group II was greater than that in group III at 4 or 8 weeks. The formed bone in group I was also greater than the one in group III at 8 weeks, but there was no difference at 4 weeks [12].

Park et al. [13], applied liposomal vectors carrying bone morphogenetic protein (BMP)-2 cDNA directly into freshly created peri-implant bone defects on pig calvariae, with or without autologous bone graft, (Group A: BMP/
liposome (n=18) Group B: collagen carrier only (n=18) Group C: BMP/liposome with autologous bone graft (n=18) Group D: autologous bone graft only (n=18). The animals were sacrificed on 7 and 28 days. The peri-implant bone area was divided into three different regions of interest (ROI) was confined to the central area of the peri-implant bone defect, ROI II were designated along the margin of the bone defect and (ROI III) was the bone-implant interface area without a peri-implant bone defect.

Within a week of BMP-2 gene delivery with bone grafts, most osteoblastic cells lining the grafted bone chips also produced BMP-2. Particulated bone was immediately reorganized into newly formed trabecular bone. Grafted bone without BMP-2 gene delivery was still scattered and new bone matrix formation was not detected until 4 weeks after bone grafting. At week 4 most of the bone defect area around ROI II was filled with newly formed bone matrix in group A, while in group B (collagen group) new bone formation with a thin, loose trabecular pattern was observed only around the border of the defect Loose fibrous tissue filled the defect center with no bone matrix detectable at ROI I 4 weeks after surgery [13].

Hayashi et al. [14] they used twenty- four implants placed into edentulous areas of mandible of four beagles dogs with the upper four screw threads exposed. bFGF-gelatin hydrogel complex with concentration 0.0.1,1,10 & 100 μg and auto genus bone as control was used to cover exposed threads. After 8 weeks histological observation showed new bone formation around exposed screw in the groups with 1,10, &100 μg. The highest values for regenerated bone height and height of bone in contact with implant were obtained in the autogenous bone group, whereas the highest values of bone volume ratio and bone contact ratio were found in 10 μ.

Wikesjo et al. [15], Studied whether adsorbing rhBMP-2 onto a titanium porous oxide (TPO) implant surface might increase or accelerate local bone formation and support osseointegration in the posterior mandible (type II bone) in dogs. Implants with a TPO surface were adsorbed with rhBMP-2 at 0.2 mg/ml or 4.0 mg/ml, whereas TPO implants without rhBMP-2 served as controls. After 8 weeks of healing, implants coated with rhBMP-2 (4.0 mg/ml) exhibited markedly increased bone formation and bone metabolic activity compared with that observed for implants coated with rhBMP-2 (0.2 mg/ml) and controls. BIC bone implant contact appeared significantly lower for rhBMP-2-coated implants when compared to the control, however, the BIC (Bone implant contact) in BMP-2 coated implants is clinically respectable. Finally, it was concluded that rhBMP-2 adsorbed onto TPO implant surfaces is able to induce dose-dependent peri-implant bone re-modeling, resulting in the formation of normal, physiologic bone and clinically applicable osseointegration within 8 weeks [15].

Mozar Z et al. [16], Studied the effect of platelet-rich fibrin as the sole grafting material in Sinus floor augmentation with simultaneous implant placement histologically and radiographically at six months. The study consists of consists of 25 sinus elevations performed on 20 patients, 14 females and six males and the sub sinus residual bone height was evaluated between 1.5 and 6 mm a presurgical exam and a 6-month post- surgical radiologic exam were performed and 6 months after the sinus lift, bone biopsies were taken in the center of the regenerated osteotomy window of the sinus lift, and evaluated. The histomorphometry results showed that, the general architecture of the bone looked natural, with structured trabeculae and a dense collagen matrix. At a high magnification, osteoblasts were easily identified and osteocytes in the lacunae demonstrated the vitality of this bone sample. Radiographic analysis showed that the final bone gain was always very significant with these quite long implants (bone gain: between 7 and 13 mm [mean – SD: 10.1 – 0.9 mm]). In this case series, no implant was lost, leading to a 100% success rate after 6 months [16].

Lee et al. [17], Studied the effect of basic fibroblast growth factor (bFGF) in combination with a biodegradable polymer coated onto titanium implants. The implants were inserted in rabbit tibiae, and bone growth was examined by histomorphometric analysis.

Forty-eight implants were equally divided into 4 groups and inserted into rabbit tibiae. Group 1 implants were anodized under 300 V; group 2 implants were anodized and then coated with 0.02 ml PLGA(poly lactic co glycolic acid); group 3 implants were anodized and then coated with 0.02 ml PLGA/bFGF (10 ng bFGF); and group 4 implants were anodized and then coated with 0.2 ml PLGA/bFGF (100 ng bFGF). Histomorphometric analysis was performed via light microscopy and computerized image analysis of the implants that had been in situ for 12 weeks. The mean bone-to-implant contact (BIC) percentage in group 4 (44.7%) was significantly greater than that seen in groups 1 (31.4%) and 2 (33.6%) [17].

Luo et al [18], Evaluated the synergistic effect of bone morphogenetic protein 2 (BMP-2) and vascular
Endothelial growth factor (VEGF) on the repair of bone defects around dental implants. Six adult dogs, mandibular premolars were extracted from six dogs. Surgically prepared to create six mesial bone defects (6 mm height, 4 mm in the bucco-lingual direction and 5 mm in the mesio-distal direction). Then, the 3.8 10 mm implants were installed into the bone defect. Five groups of scaffold were divided, including pure chitosan/collagen scaffold; scaffold loaded with adenoviruses expressing BMP-2, adenoviruses expressing VEGF, both adenoviruses expressing BMP-2 and adenoviruses expressing VEGF, VEGF protein and adenovirus expressing BMP-2. Study shows that BMP-2 gene and VEGF protein-combined scaffolds could supply a good controlled growth factor system for bone tissue regeneration [18].

Lee et al. [19], Analyze orthotropic bone formation and remodeling of three different dental implant surfaces, restorable blasting media (RBM); sandblasted, large-grit, acid-etched (SLA); and magnesium-incorporated oxidized (MgO) implant surfaces. The implants were placed into the proximal tibia of rabbits. Each rabbit received six different implants (three coated with ErhBMP-2 in one tibia and three uncoated implants in the other tibia), and the sites were closed, submerging the implants. Histo-morphometric analysis at 8 weeks revealed that Mean bone-to-implant contact (± standard deviation) for the ErhBMP-2/RBM (35.4% ± 5.1%) and ErhBMP-2/MgO (33.4% ± 13.2%) implants was significantly greater compared with RBM (23.6% ± 6.2%) and MgO (24.9% ± 2.7%) implants (P < .05). Considering the mean bone-to-implant contact in cortical bone, ErhBMP-2/SLA implants (32.9% ± 7.8%) showed lower bone-to-implant contact in cortical bone than all other implant variations (range, 39.9% ± 18.1% to 51.3% ± 9.2%; P < .05) [19].

Kim et al. [20], Studied the effects of rhBMP-2 on osseointegration in dogs. Three different concentrations of rhBMP-2 (0.1, 0.5, and 1 mg/mL) were applied to sandblasted and acid etched (SLA) implants and served as test group, while SLA implants were used as a control group. Two months after tooth extraction, four animals received implants coated with 3 different concentrations of rhBMP-2 in one side of the mandible while the contra lateral side received SLA implants. BIC, bone volume (BV) and implant stability were analyzed at 8 weeks after implant placement. The mean BIC and BV were greater in the 0.5 and 1.0 mg/mL rhBMP-2 groups than in the 0.1 mg/mL and control groups. Furthermore, the ISQ values were highest in the 1.0 mg/mL group. It was concluded that the SLA implants coating with 0.5 and 1.0 mg/mL of rhBMP-2 was more effective in enhancing osseointegration [20].

Kammerer et al. [21], Evaluated the effect of platelet-derived growth factor (rhPDGF-BB) on the promotion of osteogenesis around variable-thread tapered implants. Twenty-four variable-thread tapered implants were inserted in the tibia of 12 rabbits. Twelve sites received additional rhPDGF-BB released from a presoaked xenogenic bone block that was fixed supracrestally. For each implantation site, a deproteinized bovine bone block was trimmed to measure 13.5X 5X5 mm and drilled through to include a 3.5 mm diameter hole to allow implant insertion. DBB blocks were randomly soak-loaded with either 0.5 ml recombinant human platelet-derived growth factor- BB of 1 mg/ml (n = 12) or animal blood (n = 12). Each surgical site received a single variable-thread tapered implant (3.5 X 11.5 mm). The results showed considerable crestal and medullary bone remodeling could be found around all implants. After 3 weeks, both BIC (bone implant contact) and PMF (percentage of medullary bone fill around the implants) were higher in the no PDGF group (BIC: 63% ± 10 with PDGF vs. 85% ± 5 with no PDGF; PMF: 57% ± 10 with PDGF vs. 74% ± 4 with no PDGF). After 6 weeks, the BIC difference between the two groups was less distinct (BIC: 78% ± 17 with PDGF vs. 72% ± 25 with no PDGF), whereas the PDGF group showed higher PMF values (PMF: 77% ± 5 with PDGF vs. 56% ± 10 with no PDGF). We can conclude that in early phase addition of rhPDGF-BB decrease osseous crestal and medullary healing properties around dental implants. In a later phase, an increase in the cortical area as well as an increased medullar bone formation was seen [21].

Discussion
Bone healing is a complex physiological process; the simplest form involves three basic steps: inflammation, cellular proliferation and differentiation, and finally remodeling [22].

Growth factors are generally accepted to be essential mediators of tissue repair via well-established mechanisms of action that include stimulatory effects on angiogenesis and cellular proliferation, in growth, differentiation, and matrix biosynthesis [23].

The initial vascular response to injury includes the release of sub-endothelial factors that attract circulating platelets and activate coagulation proteins. The active
secretion of these growth factors begins within minutes of the start of the coagulation sequence, and more than 90% are secreted during the first hour. After this initial burst, the platelets synthesize and secrete additional growth factors for the remaining 7 days of their viability. Macrophages then arrive due to the vascular ingrowth stimulated by the platelets and regulate wound healing by secreting some of the same growth factors plus additional ones. The rate of wound healing is determined by the number of platelets in the blood clot within the graft or wound [24].

Platelets have been shown to stimulate the mitogenic activity of human trabecular bone cells and to increase the proliferation rate of human osteoblast-like cells and stromal stem cells, thus contributing to the regeneration of mineralized tissues. Growth factors released from platelets signal local mesenchymal and epithelial cells to migrate, divide, and increase synthesis of collagen and matrix, thus providing a scaffold that encourages migration of osteoblasts [24].

Platelet-rich plasma (PRP) is defined as an “autologous concentration of platelets in a small volume of plasma” and is considered to be a rich source of autologous growth factors [25]. The application of the PRP fraction with dental implant was performed via gel preparation (by mixing the PRP fraction with 10% calcium chloride solution and 300 IU of bovine thrombin) and subsequent installation in the implant site, but risk arises from bovine thrombin that is used to activate PRP. Coagulopathies due to anti-body formation against thrombin, Factor V, and Factor XI have been reported. The other form of RPR application via dipping of the implant in PRP liquid before its insertion, it was found that PRP in a liquid form showed a significant effect on bone opposition to roughened titanium implants during the early post-implantation healing phase [11]. Platelet rich fibrin (PRF) is considered as the potential second generation platelets rich products. It has many advantages compared to (PRP), such as the simple, inexpensive and effective collecting process, no added substances from outside to activate the platelets, arrested platelets into the fibrin network, and support for homeostasis, cell migration and proliferation and finally bone regeneration. The contribution of PRP and PRF to the bone healing process is thought to be based on the growth factors (GFs) stored in it. The following GFs are reported to be present in PRP: platelet derived growth factor (PDGF), transforming growth factors-P (TGF-P), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), insulin growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), as well as three blood proteins known to act as cell adhesion molecules for osteoconduction [26]. Application of growth factors for regeneration of hard tissue structures continues to gain interest because it has been shown to promote osteogenesis and osseointegration by guiding cell differentiation, tissue formation process, and vascularization of the newly formed bone [27].

Direct application of growth factors to the implant site often has limited success as a localized delivery is required to target the cells and these cytokine growth factors have short half lives (for example, platelet-derived growth factor (PDGF), isolated from platelets, has a half life of less than 2 minutes when injected intravenously) [28].

To address these issues and acquire a localized, continuous expression of growth factor in the targeted cells sustained over the many day/week healing period. All need an appropriate carrier for regular clinical use. The ideal carrier must maximize host tissue exposure to the growth factors and ensure uniform delivery without allowing spread of the substance beyond the boundaries of the graft site. The carrier should be safe and biocompatible. Several carriers have been tested, and from the latest results it seems that synthetic polymers may prove to be a reasonable carrier [29].

Many carriers were used as collagen carrier [9,13] polylactide/glycolide carrier [17], autologous bone graft [13] Composite chitosan/collagen [18,30] on other studies, they used implant surface as carrier [19] and gelatin hydro gel also used [14].

The concept of using one growth factor alone or combination of two or more growth factors with dental implant for induction of bone formation and osseointegration are still debatable.

It was mentioned that growth factor alone is not sufficient to improve bone healing. But if it was combined with BMP-2, could have a synergistic effect in promoting bone healing around dental implant [18].

While in other study used bFGF- gelatin hydrogel, the histological evaluation revealed that bFGF-gelatin hydrogel complex using an optimum amount of bFGF was useful for bone augmentation around implants [14].

What is the right dose of growth factor to be used for enhancing bone formation and without any adverse reaction? It was found that, large doses of these growth
factors can result in adverse side effects [11, 31].

The previous studies used growth factors doses ranged from ng, μg and mg with dogs, pigs, rabbits and gouts. Lan et al used rhbFGF (200 μg), rhiGF-1 (250 μg) and 1.0mg of rhBMP-2 [12]. Nikoildakis et al. used 0.5 and 1.0 μg of TGF-β1 [11], Hayashi et al. used different doses of bFGF 0.1,10 & 100 μg and the most effective doses was 1,10 & 100 μg, whereas the highest values of bone volume ratio and bone contact ratio were found in 10 μg[14]. Lee et al. used 0.02 ml PLGA/ bFGF (10 ng bFGF) and 0.2 ml PLGA/bFGF (100 ng bFGF)[17], Wikesjo et al. used rhBMP-2 at 0.2 mg/ml or 4.0 mg/ ml and with rhB MP-2 (4.0 mg/ml) exhibited markedly increased bone formation [14], and Kim et al. used different concentrations of rhBMP-2 (0.1, 0.5, and 1 mg/mL) and they found that 0.5 and 1.0 mg/mL of rhBMP-2 was more effective in enhancing osseointegration [20].

Conclusion

From the results of all previous studies, it was found that growth factors with appropriate carriers could enhance bone formation around dental implant when used alone or in combination of one or more growth factors or bone morphogenetic protein. More studied must be conducted, to study the effect of growth factors with dental implant clinically and how to calculate the suitable dose of it for enhancing bone regeneration without any side effect or adverse reaction.

There was no conflict of interest.

References


