

# Bone morphogenetic protein effect on implant stability and bone height in immediately loaded implant supported mandibular overdenture (randomized clinical trial)

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## Keywords

Bone height-bone morphogenetic protein, immediate loading, implant stability, overdenture

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## Abstract

**Background:** The applications of molecular and nanoscale-based biological materials such as bone morphogenetic proteins (BMPs), may play a role in improving the osseointegration of dental implants and shortening the time period for implant integration.

**Aim:** The aim of this clinical study was to evaluate and compare the implant stability and bone height changes of implants with two different surface topographies in immediately loaded implant supported mandibular overdenture.

**Materials and Methods:** A total of 10 completely edentulous patients were selected from the outpatient clinic, Cairo University. Patients were divided into Group (I): Five patients had received two conventional titanium implant coated with ready-made BMP and Group (II): Five patients had received two conventional titanium implant surface installed in the interforaminal area and immediately loaded with overdentures. Crestal bone height changes were evaluated with Digora system at 0, 6, 9 and 12 months after implants loading. The implant stability was evaluated with the Osstell mentor device; every 2 weeks for the 1<sup>st</sup> 3 months. Then every 3 months till the end of the follow-up period (12 months).

**Results:** Regarding bone height changes: conventional titanium implant surface had shown higher mean values of bone loss than BMP coated implant group. However, there was no statistically significant difference in mean values of bone height loss between them. Regarding implant stability: Group (I): BMP coated implant group had shown higher mean values of implant stability than Group (II): non - BMP coated implant group. There was no statistically significant difference between studied groups.

**Conclusion:** BMP coating of titanium dental implants may induce less crestal bone resorption and better implant stability in immediately loaded implant supported mandibular overdenture.

**Clinical Significance:** BMP plays a role in reducing crestal bone resorption. Further clinical studies (randomized clinical trials) should be made recommended on a larger number of patients, for longer follow-up periods. Different techniques for BMP application and release should be tried

## Introduction

Dental implants had become an integral treatment modality in prosthetic dentistry. Implant prostheses have shown dramatic improvements in masticatory performance, esthetics, and patient satisfaction. The placement of dental implants and the insertion of implant-supported prostheses have been found to substantially

reduce bone loss in the edentulous jaw, as well as promote bone deposition distal to implants.<sup>[1]</sup> Because the time frame to achieve full osseointegration, as well as the anatomy and function of the bone implant interface, is a direct consequence of the implant surface, there is a need to establish surfaces modifications that will lead to a predictive improvement of implant to bone response.<sup>[2]</sup>

Such surface modifications, whether topographical or chemical, had been successful in accelerating osseointegration at early implantation times which may shorten the total treatment period.

The applications of molecular and nanoscale-based biological materials such as bone morphogenetic proteins (BMPs), peptides, and stem cells in conjunction with calcium phosphate coatings have been and will continue to play an ever increasing role in improving the osseointegration of dental implants and shortening the time period for implant integration.<sup>[3]</sup>

BMPs are growth factors that naturally found within the bone matrix and act as pleiotropic organizer of chemotaxis, mitosis, differentiation, excitation of extracellular matrix formation, bound to matrix components, conservation of phenotype, and apoptosis. In addition, they play a role in regulation of bone volume, skeletal organogenesis and the regeneration of bone after a fracture.<sup>[4]</sup>

Liu *et al.*,<sup>[5]</sup> had assessed the effects of BMP-2 and its mode of delivery on the osteoconductivity of dental implants with either a naked titanium surface or a calcium-phosphate-coated one. The naked titanium surface bore adsorbed BMP-2, while the coated one bore incorporated, adsorbed, or incorporated and adsorbed BMP-2. They concluded that the osteoconductivity of implant surfaces can be significantly modified by BMP-2 and its mode of delivery.

Kim *et al.*,<sup>[6]</sup> suggested a new concept of bone-to-bone biologic fixation using recombinant human BMP-2 (rhBMP-2)-loaded pedicle screws.

Yoo *et al.*,<sup>[7]</sup> tested whether the application of rhBMP-2 onto plasma-sprayed hydroxyapatite implant surfaces by immersion in protein solution before implant installation would result in significantly improved bone apposition. They concluded that the combination of plasma-sprayed calcium phosphate surface and rhBMP-2 coating significantly enhanced osseointegration, which validated the postulated hypothesis.

Regarding the edentulous population, treatments with implants performed over a short period of time, in a single stage and with immediate loading are the best choice. However, no evidence was found of long-term studies to support or refute either early or immediate loading protocols for mandibular implant overdentures.<sup>[8]</sup>

Implant stability is evaluated quantitatively with the aid of resonance frequency analysis (RFA), containing a piezoelectric transducer (electrically energized) that can be fixated on the implant.

Hypothetically dental implants coated with a bone inductive factor such as a BMP may activate local bone formation and osseointegration in sites of poor bone quality or in need of augmentation.<sup>[9]</sup>

The coating of dental implant with an osteoinductive protein (rhBMP-2) in immediately loaded implant supported mandibular overdenture may improve the osseointegration and implant stability.

## Materials and Methods

This study was a randomized clinical trial (RCT) conducted on patients attending the outpatient clinic in Prosthodontics Department, Faculty of Oral and Dental Medicine, Cairo University-, Cairo, Egypt.

The protocol of this study was reviewed and approved by the staff members of Prosthodontic Department and Research Ethics Committee in Faculty of Oral and Dental Medicine, Cairo University. The protocol was registered in the Pan African Clinical Trial Registry ([www.pactr.org](http://www.pactr.org)) database, the registration number was PACTR201312000640136.

### Regarding the patient selection

A total of 10 completely edentulous patients were selected according to the following criteria: Their age was ranging from (i.e., range 45-55). The residual ridge had moderate height, width suitable for implant placement and covered by the firm and healthy mucoperiosteum. Adequate interarch space (22 mm) for implant supported overdentures construction.

Angle Class I maxillomandibular relationship. All patients were free from any systemic disease that might affect the bone quality and/or post-operative healing. After sample size calculation, experimental group will have five patients and control group will have five patients.

Patients had been divided into two groups: Group (I): Five patients had received two conventional titanium implant coated with ready-made BMP installed in the interforaminal area. Group (II): Five patients had received two conventional titanium implant surface installed in the interforaminal area. Each patient had received two immediately loaded implant supported mandibular overdentures according to random allocation.

The allocation was done by sequence generation through using website ([www.random.org](http://www.random.org)) the participants were randomly divided into titanium dental implant coated with ready-made BMP group and titanium implant noncoated with BMP group with 1:1 allocation ratio. Allocation concealment mechanism was performed as the patients who had shared in this study were allowed to select an opaque sealed envelope. It contained computer-generated random numbers which determined the kind of group that he was belongs. This study was a double-blinded study (participant and assessor).

Through medical and oral examinations were carried out in addition to specific laboratory investigations. Upper and lower complete dentures were constructed according to the conventional technique for patients decided to receive implants.

Pre-operative cone beam computed tomography was made to evaluate bone quality and quantity of edentulous mandibular ridge. Duplication of finished denture was made from barium sulfate. Two holes were made at mandibular canine regions; where implants would be installed.

Clear acrylic resin template was modified to be used as a surgical template. Two conventional titanium dental implant\* (DENTIS, S-Clean Tapered Implants) installed in the canine

areas in the two studied groups. The implants were 10 mm in length and 3.7 in diameter.

BMP coating procedures for Group (I): COWELL BMP (rhBMP-2+ $\beta$ -tricalcium phosphate [TCP]/hydroxyapatite [HA]) [Figure 1] were done as the TCP/HA graft material was transferred into a container. Normal saline (0.2 ml for 0.25 mg vial) was injected into 0.25 mg vial; saline was then mixed with BMP powder. The resultant mixture was aspirated [Figure 2] using a sterile plastic syringe. The BMP was applied onto the implant surface [Figure 3] before threading the implant into the corresponding osteotomy site. The implant coated



**Figure 1:** COWELL BMP recombinant human bone morphogenetic proteins (recombinant human bone morphogenetic protein-2+ $\beta$ -tricalcium phosphate/hydroxyapatite)



**Figure 2:** Normal saline (0.2 ml for 0.25 mg vial) was injected in to 0.25 mg vial; saline was then mixed with bone morphogenetic protein powder. The resultant mixture was aspirated using a sterile plastic syringe

with the BMP Gel layer was then installed into its implant bed. The female part of locator attachment was inserted into the corresponding implant hex and torqued to 25 Newton centimeter. Flap repositioning was carried out being made with interrupted suturing.

Evaluation of implant stability was made with Osstell mentor device. The implants corresponding smart peg was connected to the implant hex, and the RFA was measured 4 times per each implant (twice from the buccal and twice from the lingual direction). The implant stability quotient (ISQ) values were averaged for every implant. Implants showing values  $\leq 65$  were not included in the study implant stability was evaluated at the day of surgery and every 2 weeks for the 1<sup>st</sup> 3 months. Then, every 3 months till the end of the follow-up period.

Mesial and distal crestal bone levels around the implants surface was evaluated radio graphically using the Digora system. The assessment of crestal bone levels was done at 0, 6, 9, and 12 months after implants loading. Digora soredex digital imaging device and software were used for the radiographic assessment. The distance between the crestal bone level and the most apical bone-implant interface was measured in (mm) with the aid of periapical radiographs (Digital Intraoral Sensor-Digora) using the long cone technique. The images were manipulated using the software as follows: Magnification tools of the software system were used to maximize the field of vision up to 7 times the original image. Calibration of the implant length and width through the insertion of the actual implant length (10 mm). A vertical straight line was drawn from the implant shoulder to the most apical part of the fixture. A horizontal straight line was drawn from the mesial to the distal aspect of the implant shoulder. Measurement of mesial and distal bone loss was made with the aid of the same measurement tools to ensure reproducibility between follow-up, radiographs were made using the paralleling technique. A specific holder (FPS 3000 Holder-Made in China) was utilized to maintain the film position accurately every time. The holder was prepared to receive the impression coping and held tightly by the fixation done through the screwdriver and the film holder [Figure 4].

2 weeks after surgery; the loading procedures were completed: The White Block-Out Spacer (Zest order #8519 Package) was placed over the head of each Locator Abutment. A Locator Cap was inserted with Black Processing Male (Zest order #8519 Package) into each Locator Implant Abutment, leaving the White Block-Out Spacer under it. Relief was made to those areas and enough space is made. The denture was modified to receive attachments and tried intraorally to ensure complete seating. The auto polymerizing acrylic resin (Acrostone Relining Materials, Egypt) was then mixed and added into the relieved areas over the metal housing of locator attachment. The denture was inserted into position in the oral cavity. The patient was instructed to close into the maximal intercuspal or centric position, maintaining a proper relationship with the opposing arch. After acrylic resin curing, the denture was removed and discarded the white spacer. The Locator Male Removal Tool was utilized (attached to the



**Figure 3:** The bone morphogenetic protein was applied onto the implant surface before threading the implant into the corresponding osteotomy site



**Figure 4:** The holder was prepared to receive the impression coping and held tightly by the fixation done through the screwdriver for paralleling technique

Locator Core Tool, Zest order #8393) to remove the Black Processing Male from the metal denture cap. The Locator Male Seating Tool (contained in Locator Core Tool, Zest order #8393) is used to firmly push a Locator Replacement Male into the metal Denture Cap. The replacement male was seated securely into place, leveled with the rim of the cap. Finally, the occlusion was checked for any occlusal premature contacts using articulating papers. The patient was instructed to maintain strict oral hygiene measures. Data were collected, tabulated and statistically analyzed.

## Results

All patients in this study had attended all the follow-up recall visits. The results obtained from this study were tabulated and statistically analyzed.

### Bone height changes in conventional titanium implant coated with BMP group

There was a statistically significant difference in bone height loss in the period from (0 to 6 months) and from (9 to 12 months); where ( $P = 0.012$ ) in Group I or BMP coated implant group.

On the other hand, there was statistically insignificant difference in crestal bone height loss from (0 to 6 months) recording ( $0.61 \text{ mm} \pm 0.16$ ) in Group II.

### Effect of BMP on bone height [Figure 5]

Although conventional titanium dental implant group had shown higher mean values of bone loss along the study period ( $0.43 \pm 0.30 \text{ mm}$ ) than conventional titanium implant coated with (BMP) group ( $0.39 \pm 0.33 \text{ mm}$ ).

There was no statistically significant difference between conventional titanium dental implant group ( $0.43 \pm 0.30 \text{ mm}$ ) and conventional titanium implant coated with [BMP] group ( $0.39 \pm 0.33 \text{ mm}$ ), where  $P = 0.714$ .

### Evaluation of implant stability

- There was no statistically significant difference between the studied groups in the implant stability at (0 months), (half month), (1 month), (1 and half months), (2 months), (2 and half months), (3 months), (6 months), (9 months), and (12 months), where ( $P = 0.882$ ) in Group (I) or (BMP) coated titanium implant group
- There was a statistically significant difference between (0 months and half month), (1 month), (1 and half months), (2 months), (2 and half months), (3 months), (6 months), (9 months), and (12 months), where ( $P = 0.001$ ) in Group (II).

### Effect of BMP presence on implant stability [Figure 6]

- Although, conventional titanium implant coated with (BMP) group had shown higher mean value of implant stability along the period of the study ( $67.87 \pm 2.23$ ) than conventional titanium dental implant group ( $66.96 \pm 2.72$ ), there was no statistically significant difference between conventional titanium dental implant group ( $66.96 \pm 2.72$ ) and conventional titanium implant coated with (BMP) group ( $67.87 \pm 2.23$ ) where ( $P = 0.071$ ).

## Discussion

The results of this study revealed that there was a significant increase in crestal bone loss in both studied groups from 0 to 6 months and 0 to 12 months. This crestal bone loss was in the normal range documented with immediately loaded implant overdentures.<sup>[10]</sup> This bone loss may be attributed to immediate bone response to healing and reorganization combined with function stresses in addition.<sup>[11]</sup>

In the conventional titanium, dental implant group had shown higher mean values of bone loss along the study period

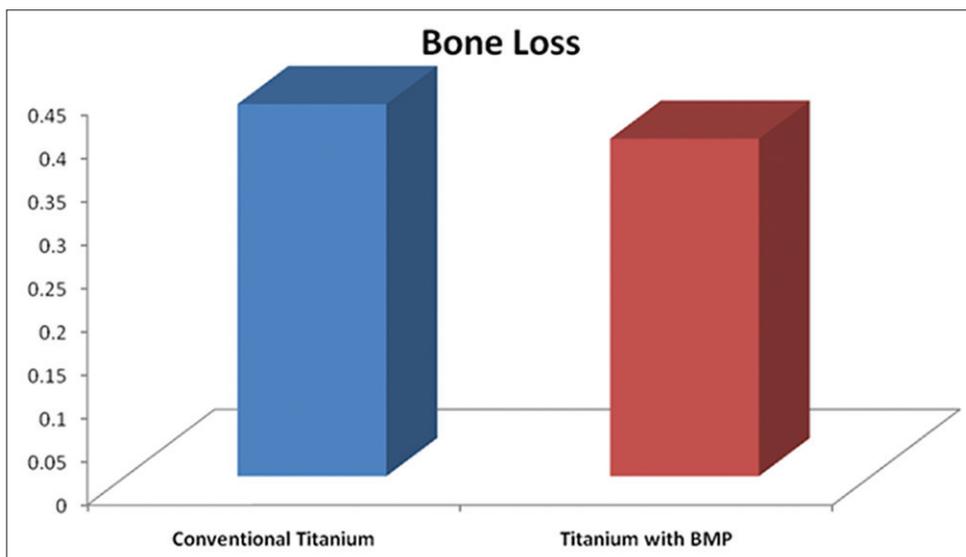


Figure 5: Effect of bone morphogenetic protein on bone height throughout the study

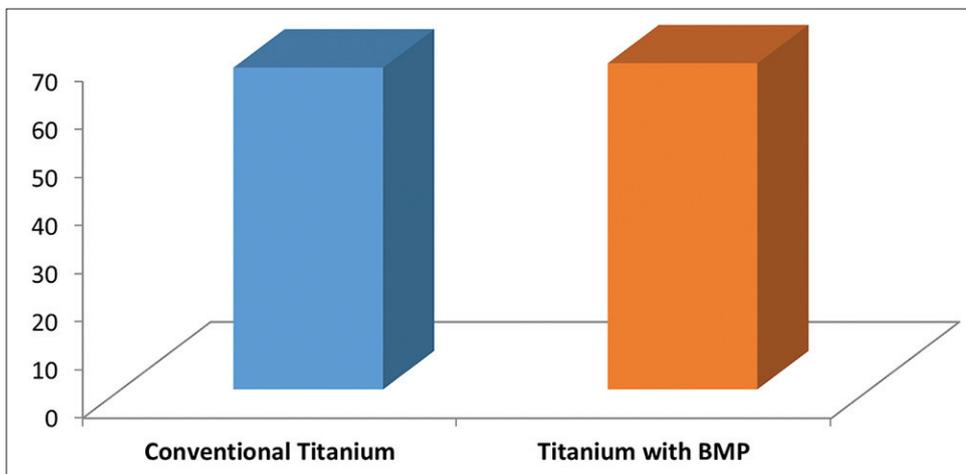


Figure 6: Effect of bone morphogenetic protein presence on implant stability along the study periods

( $0.43 \pm 0.30$  mm) than conventional titanium implant coated with (BMP) group ( $0.39 \pm 0.33$  mm), and there was no statistically significant difference between conventional titanium dental implant group ( $0.43 \pm 0.30$  mm) and conventional titanium implant coated with [BMP] group ( $0.39 \pm 0.33$  mm), where  $P = 0.714$ . This may be due to one or more of the following causes: During the first postsurgical week, the degradation of implant coatings containing the incorporated BMP-2 was mediated by foreign body giant cells. The osteoclasts may participate in the process after that. They could assume the role played by osteoclasts in physiological bone formation and in remodeling-based signaling pathways as reported by Katagiri and Takahashi.<sup>[12]</sup>

However in the BMP coated implants group; the rapid release of the BMP coating into the peri-implant bone which may have the ability to incorporate signaling factors and release them into

bone surrounding implants may explain the lower mean values of bone loss in this group than conventional one.

On the other hand, the results of bone loss in BMP coated implants had not revealed significant decrease as were expected. This finding may be attributed to the quantity of BMP-2 liberated into bone surrounding implants may be negligible and almost may lie below the osteoinductive threshold as reported by Liu *et al.*<sup>[13]</sup> This is supported by our findings for the adsorbed-BMP.

In BMP, coated implant group, a decrease in the weekly rate of bone formation was seen during the 4<sup>th</sup> week, but this reflected the prevalence of bone remodeling activities at this stage, which is expected in the absence of active stress fields.

Moreover, the high rate of coating degradation seen during and after the 3<sup>rd</sup> week, may led to a significant reduction in the coating volume by the end of the 5<sup>th</sup> week, which is most probably due to the synergistic resorptive activities of the foreign body

giant cells and osteoclasts may explain the significant increase in bone loss and implant stability during that stage.<sup>[13]</sup>

The biomimetic delivery of growth factors in the BMP into bone surrounding implants seems to be ineffective approach that might not affect peri-implant bone regeneration. If BMP compounds were incorporated into, rather than adsorbed onto, the crystal lattice works; then they would be liberated at an even slower rate, as the inorganic layer undergoes degradation. Moreover, it has been explained that surface modifications may be more strongly correlated to (bone implant contact [BIC]) values and less to bone area measurements as reported by Johansson.<sup>[14]</sup>

Although, the histomorphometric results supported that all surfaces dip-coated by rhBMP-2 presented higher implant osseointegration levels compared to uncoated surfaces.<sup>[7]</sup> However, the osteogenic agents activate the osteoprogenitor cells and bone resorbing osteoclasts at the same time explaining the cause of significant bone loss in coated implant group. Moreover, over stimulation of the osteoclasts probably had a catalytic effect on the degradation rate of the coating, since, being a bone matrix like material; it is subject to osteoclastic digestion.<sup>[13]</sup>

It was reported by Manders *et al.*,<sup>[15]</sup> that all biomimetic Ca-P coatings exhibited improved BIC rates compared with the uncoated control surface after 2 and 4 weeks.

This was a common finding of the previous studies; because it has been shown that Ca-P-based surfaces bind more attachment proteins, for the integrin-mediated binding action of osteoprogenitors compared with titanium surfaces.<sup>[15]</sup>

Although, the incorporation of growth factors into the biomimetic coating did not lead to any significant changes in BIC values at each time period. Moreover, a major increase in BIC values could not be detected for any coating, and lower BIC rates were detected for all surfaces when compared with the relevant literature.<sup>[16]</sup> These results were compatible with the results of this study as there was almost no difference between BMP coating implant and non BMP coating.

BMP coated implant group had shown higher mean value of implant stability along the period of the study ( $67.87 \pm 2.23$ ) than conventional titanium dental implant group ( $66.96 \pm 2.72$ ), there was no statistically significant difference between conventional titanium dental implant group ( $66.96 \pm 2.72$ ) and conventional titanium implant coated with (BMP) group ( $67.87 \pm 2.23$ ) where  $P = 0.071$ . Although there was no statistically significance difference in implant stability between the two studied groups, the conventional titanium implant coated with (BMP) group had shown higher mean ISQ values. This might induce clinical difference reflected by higher implant stability at different recall visits. As the implant stability depends mainly on the BIC. The BMP coated implants may have certain changes in surface composition following the incorporation of various growth factors.

The results of this study were supported by these findings as there were no statistical significance difference between the two studied groups because the initial protein adsorption controlled by the surface characteristics has an important effect

on the attachment of osteoprogenitor cells, it may be suggested that the conformational and functional changes of proteins on BMP vascular endothelial growth factor surface did not support the integrin-mediated attachment of osteoblasts that would further deposit bone matrix directly on the surface. The histomorphometric studies, there is no significant increase in BIC values for rhBMP incorporated surfaces. The reason why the BMP group offered no improvement in BIC is not quite clear.<sup>[17]</sup>

There was a statistically significant difference (0 month), (half month), (1 month), (1 and half months), (2 months), (2 and half months), (3 months), (6 months), (9 months), and (12 months) in both groups of study where  $P = 0.001$ . These results may be related to the accommodation of the bone after compression during the installation of the implant, biological changes at the beginning of the bone remodeling and of the marginal bone reabsorption. After bone remodeling period, these values may be progressively increased in the bone repairing period.

After bone mineralization, the ability of the ISQ measures is to stabilize within the dense bone or increasing slightly, in the trabecular bone.<sup>[18]</sup>

The decrease of a few points in the ISQ may not be considered a problem in the prognosis of the implants with high initial stability values at the time of surgery. This decrease in ISQ values may consider that there are problems for implants with average ISQ values as the manipulation in the production of the prosthesis, as well as mastication and food may cause micro movements on the implant, with the resultant formation of fibrous tissue at the interface.<sup>[19]</sup>

## Conclusion

**Within the limitations of this study it may be concluded that**

Conventional titanium dental implant coated with ready-made BMP may induce: Less crestal bone resorption when compared with conventional titanium dental implant in immediately loaded cases and better implant stability in comparison to conventional titanium dental implant in immediately loaded cases.

## Recommendations

Further clinical studies (RCT) should be made recommended on a larger number of patients, for longer follow-up periods. Different techniques for BMP application and release should be tried.

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