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Changes of peri-implant bone density in relation to local application of alendronate and/or recombinant human bone morphogenetic protein-2: A randomized controlled clinical study

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KEYWORDS Bisphosphonates, Recombinant human bone morphogenetic proteins, Peri-implant bone density, CBCT.

ABSTRACT

Aim This study aimed to prospectively evaluate the changes in peri-implant bone density (BD) in response to local application of bisphosphonates/alendronate (ALN) alone or combined with recombinant human bone morphogenetic protein-2 (rhBMP-2) in Hounsfield units (HUs) using cone beam computerized tomography (CBCT).

Materials and methods Seventy-one dental implants were used for replacing missing tooth/teeth in 27 patients. According to the local application of ALN and/or rhBMP-2, the dental implants were allocated randomly into 4 groups: group 1, local application of ALN gel; group 2, local application of rhBMP-2 gel; group 3, local application of a mixed formula of both gels, the gel was applied immediately before implant insertion; group 4, implant insertion without application of any medication (control). The changes in BD around each implant were assessed at 3 time points; immediately after implant insertion (baseline), immediately after insertion of the prosthesis (preloading), and after functional loading.

Results Peri-implant BD values in HUs were significantly increased post implant insertion in all study groups from baseline to the postloading measurements. ALN and rhBMP-2 groups showed also increase in bone density from baseline to the preloading time points, and representing the highest differences in BD although not statistically significant.

Conclusions Within the limitations of this study, the results concluded that there was a continuous increase of peri-implant BD throughout the study period, irrespective of the local application of ALN and rhBMP-2 alone or combined on BD compared to the control group at the end of the study, with significant increase in BD in ALN and rhBMP-2 comparing with MIX and control groups in preloading period.

INTRODUCTION

It has been reported that alveolar bone density was considered one of the most crucial factors that influence dental implant osseointegration. Owing to its cortical (or compact) bone compared to the maxillae, many studies demonstrated higher implant success rate in the mandible (1). The bone density may be determined by various techniques including the general location, radiographic evaluation, and/or tactile sensation during surgery (2). In recent years, preoperative quantitative and qualitative assessment of implant sites has been commonly done with the use of a computed tomography (CT) scan, the bone density (BD) is objectively determined by Hounsfield unit (HU). Due to the need for less expensive image acquisition protocols or for scanners with lower radiation dose (3, 4), cone beam CT (CBCT) has been introduced as an alternative diagnostic modality for dental applications, for accurate diagnosis and treatment planning especially for dental implant placement. Many authors maintained that CBCT could be considered an appropriate tool to assess BD in planning osseointegrated implants (5). However, the higher radiation doses than two-dimensional imaging and the presence of various types of artifacts produced by metal objects are considered the main disadvantages of CBCT (6).

Despite the importance of surface topography, it has been suggested that a level of surface activity is necessary for osteopromotive capacity (7). Implant surface modification may enhance the interactions with biological fluids and cells and accelerates peri-implant bone healing as well as improves osseointegration, especially at sites of low density (8). Thus, most

works still favor surface treatment of dental implants via coating and acid etching over other methods in producing good substrate surfaces that could lead to better osseointegration and successful dental implants. New coating strategies have been developed to improve implant osseointegration that involve a dedicated drug-loading ability to locally target bone around dental implants more effectively (9, 10).

Several animal studies have reported that the osseointegration of metal implants was improved when an antiresorptive drug, bisphosphonate (BP), was administered systemically, applied locally (11), or bound to the implant (12), with positive effects upon fixation. The positive effect of systemic or local BP was also demonstrated clinically when oral alendronate or local ibandronate were used in knee arthroplasty: results demonstrated that these drugs could lead to improved implant stability and also contribute to improvement of BD postoperatively (13, 14). Adding to that, many systematic reviews concluded that local application of BPs with different agents and concentrations had favorable effects and seemed to promote osseointegration (15, 16). With regard to the importance of enhancing bone formation onto implant surface, the use of BMPs as coating for dental implants has been increased due to their favorable effect on bone implant contact (17), with rhBMP-2 is considered, from a clinical stand point, the only commercially available BMP (18).

Previous studies have been conducted to assess the effects of local application of BPs with different methods (either coating, immersion, or site irrigation) (19, 20, 21), and other ones reported the effects of rhBMP-2 on dental implants with different concentrations and methods of application (22, 23). The changes of peri-implant BD have been rarely reported in these studies, since implant stability and marginal bone changes were the outcome of interest. For this reason, the aim of this study was to evaluate the effects of local application of antiresorptive agent/ALN alone or combined with rhBMP-2 on the peri-implant BD, obtained by the CBCT in HU values. The null hypothesis was that there is no significant effect between these 2 agents and a control group.

MATERIALS AND METHODS

A randomized prospective clinical study was conducted at the Department of Oral and Maxillofacial Surgery, College of Dentistry, University of Baghdad during the period from July 2019 through February 2021. The study was approved by the Research Ethics Committee (protocol number 034118), it was guided by the Consolidated Standards for Reporting Trials (CONSORT) statement and was registered at ClinicalTrials.gov (NCT04140006). The procedure was clearly described to all patients who were included in the study, and who provided a signed informed consent.

A total of 27 patients who required dental implant rehabilitation for single or multiple missing teeth in the posterior maxilla or mandible were enrolled for this study. The inclusion criteria were: patients above 18 years of age with edentulous gap of a minimum of 6 months after extraction and sufficient vertical and horizontal dimensions of the alveolar bone that are considered surgically straightforward cases according to SAC classification (24). The exclusion criteria were: active or chronic infection in the implant zone; patients with a history of or under treatment with BPs or other drugs that may alter bone metabolism; history of radiotherapy to the head and neck; and heavy smokers or severe periodontitis.

The enrolled patients received a total of 71 bone level tapered DIs (Straumann®. Basel, Switzerland). The implants were randomly assigned into 4 groups using Microsoft Excel (2019): Group 1, 2, and 3 (study groups) involved injection of medicated gel immediately before DI installation, while in group 4, DIs were installed without injection of any medication (control group). The patients were informed about the different local applications, but were blinded to the assignment.

Medicated gel preparation

According to Kassem et al. (25). Carbopol based gel was prepared from a combination of Carbopol (C, Carbopol 934, GRM6761-500G, HiMedia, India) and Hydroxypropylmethyl Cellulose (H, HPMC, K15M, Alpha Chemika, India) in a ratio of 1:2.5. The C/H combination was obtained by mixing calculated amounts of polymeric dispersions. The resultant solutions were thoroughly mixed, and the pH was adjusted to 6.8±0.2. The medicated gels were prepared by dissolving 2 mg powder of each drug in 0.2 ml of distilled water to form a solution with concentration of 2 mg/0.2 ml. Then each solution was added to 1.8 ml of the C/H polymeric system that resulted in medicated gel for both drugs with concentration of 2 mg/2 ml, without any preservatives. The prepared ALN gel formulation was sterilized by autoclaving for 30 minutes at 121±1°C, while for rhBMP-2, the gel base was sterilized before protein addition.

Surgical protocol and gel application

All DIs were installed according to the manufacturer instructions with extensive flapped approach. The implant sites were prepared through sequential drilling and the implants were inserted about 0.5 mm subcrestally. DIs used in this study were 3.3 and 4.1 mm in diameter and 8, 10, 12 mm in length. For standardized insertion, DIs were placed in the upper then lower jaw, right then left side, and posterior to anterior position in case of replacement of multiple missing teeth.

In the study groups 1 and 2 and before implant installation, 0.05 ml of ALN or rhBMP-2 gel, with concentration of 100µg/0.05 ml., was injected into the

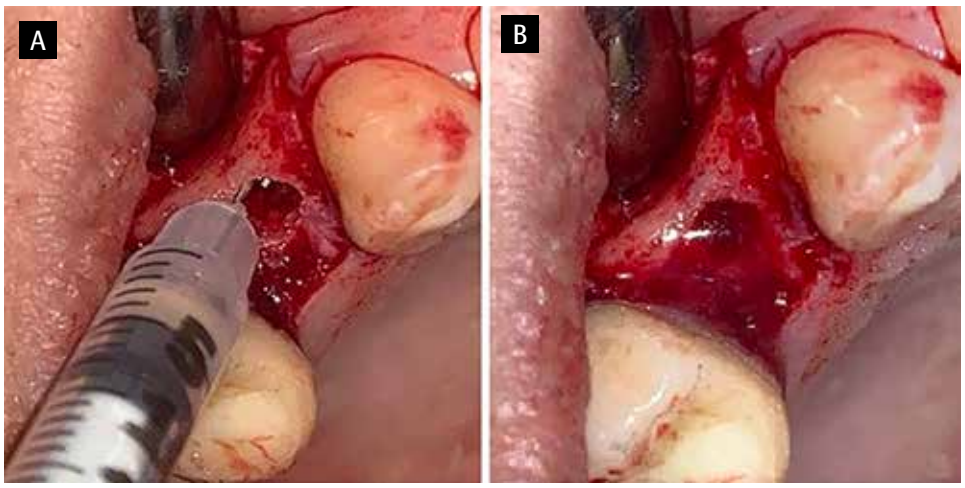

FIG. 1 Injection of the medicated gel. Syringe with 0.05 ml of medicated gel inserted in the implant site (A); implant site filled with the gel (B).

implant bed (Fig. 1). For the study group 3 (MIX, mixed formula), 0.025 ml of both ALN and rhBMP-2 gels (50 µg/0.025 ml for each) were injected into the implant bed before implant insertion, while implants in the control group were inserted without injecting any gel.
Following implant installation, implant stability was measured using the Osstell Mentor (Göteborg, Sweden), then a cover screw was placed and the flap was sutured. Postoperative antibiotics and analgesics were prescribed. Eight weeks later, the implants were uncovered with a second stage surgery and healing abutments were placed allowing the peri-implant mucosa to heal.

Radiographical assessment of peri-implant bone density

For BD evaluation, a full view with axial, coronal, and sagittal sections for each patient was acquired by CBCT (KAVO OP 3D Model, Germany). The exposition and reconstruction parameters were set at: field of view (FOV) 13 × ⌀ 15 cm; voxel size 38µm; effective dose 33µSv; exposure time 8.1 seconds; scanning time 38.2 seconds; a default 5mA; and a tube voltage 90 kV. The first CBCT scan was performed immediately after implant placement (baseline, T1), the second one was after insertion of prothesis (preloading, T2), and the third after about 25 weeks post functional loading (T3). Using the OnDemand software, peri-implant BD was measured in HUs. In order to avoid the titanium artifact in CBCT images which is approximately 0.5 mm distance from implant-bone interface (26), the measurements in this study were registered in a spot diameter of 1 mm and in a distance of 1 mm from the implant perimeter in 3 regions of interest: apical, middle, and cervical regions of the radiological implant length, with exclusion of the compact most coronal 2 mm. Then a mean of HU value (± SD) for all these points was recorded as mean peri-implant BD. To achieve this the following method was adopted: with three-dimensional rotation of the sagittal axis about 20°±1° (Fig. 2A), being aligned with the dental arch, the density values of the bone around each implant were measured in the three areas of interest along the buccal (B) and palatal (P) sides in the coronal view (Fig. 2B), and the mesial (M), and distal (D) sides in the sagittal view (Fig. 2C).
Then, after distal rotation of the coronal axis of about 20°±1° (Fig. 3A), the BD was measured at distobuccal (DB)-mesiopalatal (MP) and mesiobuccal (MB)-distopalatal (DP) sections, that were represented by coronal (Fig. 3B) and sagittal views respectively (Fig. 3C).

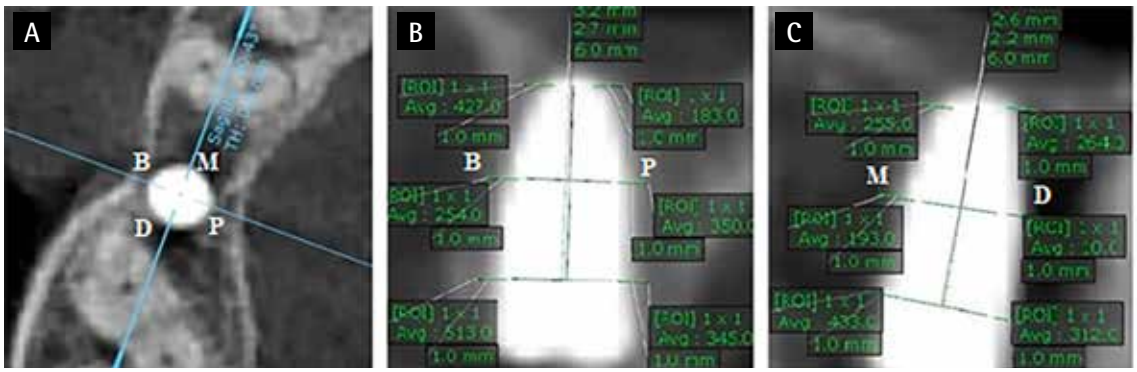

FIG. 2 Cone beam computed tomography sections immediately after implant insertion. A: Axial view with sagittal rotation 20°±1° shows B (buccal), P (palatal), M (mesial), and D (distal) sides for measurements of peri-implant bone density. B: Coronal view with B and P measurements of BD. C: Sagittal view with M and D measurements of bone height.

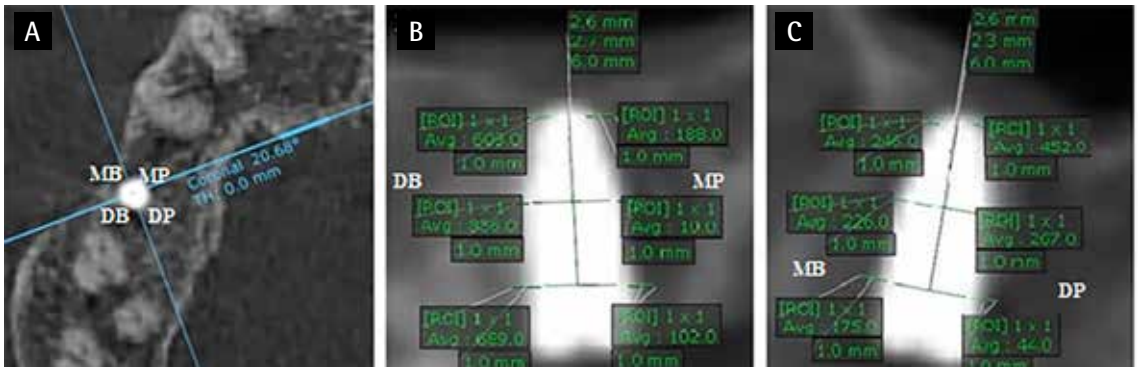

FIG. 3 Cone beam computed tomography sections immediately after implant insertion. A: Axial view with distally coronal rotation 20°±1° shows MB (mesiobuccal), DB (distobuccal), MP (mesiopalatal), and DP (distopalatal) aspects for measurements of peri-implant bone density. B: Coronal view with DB and MP measurements of bone density. C: Sagittal view with MB and DP measurements of bone density.

The method was standardized for BD assessment for all measurement intervals.

With regards to the evidence that the use of filters to improve the CBCT image influence the accuracy of bone lesion detection and BD assessment, peri-implant BD was measured without filters which were used only to clarify the image in order to properly localize the points and distances of measurement. All assessments done with default brightness and by a blinded observer.

The predictor variable was the local application of ALN gel, rhBMP-2 gel, or a combination thereof before insertion of implants compared to a control group, while the outcome variable was the change in peri-implant BD at 3-time intervals after insertion of DI, before loading, and post functional loading.

Study group	No. of analyzed DIs	
Group 1/ ALN	17	
Group 2/ BMP	15	
Group 3/ MIX	18	
Group 4/ CON	17	
DI site	No. / %	
Maxilla	28 (41.8%)	p-value
Mandible	39 (58.2 %)	.102
DI size	No. / %	
RC	46 (68.7%)	p-value
NC	21 (31.3%)	.918
Treatment outcome		
Success	67 (94.4%)	p-value
Failure	4 (5.6%)	.246

DI; dental implant, ALN; alendronate, BMP; bone morphogenetic protein, MIX; mixed formula, CON; control, RC; Regular CrossFit (4.1mm in diameter), NC; Narrow CrossFit (3.3mm in diameter).

TABLE 1 Distribution of DIs in the study.

Statistical analysis

Data were analyzed using SPSS statistical software (SPSS Statistics for Windows, version 25, Armonk, NY: IBM Corp.). Statistical analysis of peri-implant BD values between the study groups, which were presented with mean ± standard deviation, were analyzed by Kruskal-Wallis test with Mann Whitney U and Wilcoxon Rank Sum corrected post hoc tests. In all statistical tests, which was done by a blinded statistician, the significance level was defined as $p < .05$.

RESULTS

A total of 27 patients was included in this study, with a mean age ±SD of 43±9.5 years (range 24-61). They were 18 females (66.7%) and 9 males (33.3%). The patients

Implant Group	Time point	Mean ± SD	P-value	
ALN n = 17	T^1-implant placement	364.1 ± 139.8	T1 vs T2	.013*
	T^2-preloading	471.4 ± 140.6	T2 vs T3	.227
	T^3-postloading	511.9 ± 137.5	T3 vs T1	.001*
BMP n = 15	T^1-implant placement	453.9 ± 67.00	T1 vs T2	.001*
	T^2-preloading	606.5 ± 178.7	T2 vs T3	.865
	T^3-postloading	633.5 ± 253.0	T3 vs T1	.005*
MIX n = 18	T^1-implant placement	437.9 ± 147.8	T1 vs T2	.154
	T^2-preloading	478.2 ± 98.06	T2 vs T3	.105
	T^3-postloading	509.3 ± 104.3	T3 vs T1	.018*
CON n = 17	T^1-implant placement	461.72 ± 94.24	T1 vs T2	.308
	T^2-preloading	500.37 ± 114.81	T2 vs T3	.381
	T^3-postloading	550.01 ± 123.80	T3 vs T1	.022*

*BD, bone density; HU, Hounsfield unit; ALN, alendronate; BMP, bone morphogenetic protein; MIX, mixed formula; CON, control; SD, standard deviation, * statistically significant.*

TABLE 2 Intragroup comparisons of peri-implant BD with mean HUs.

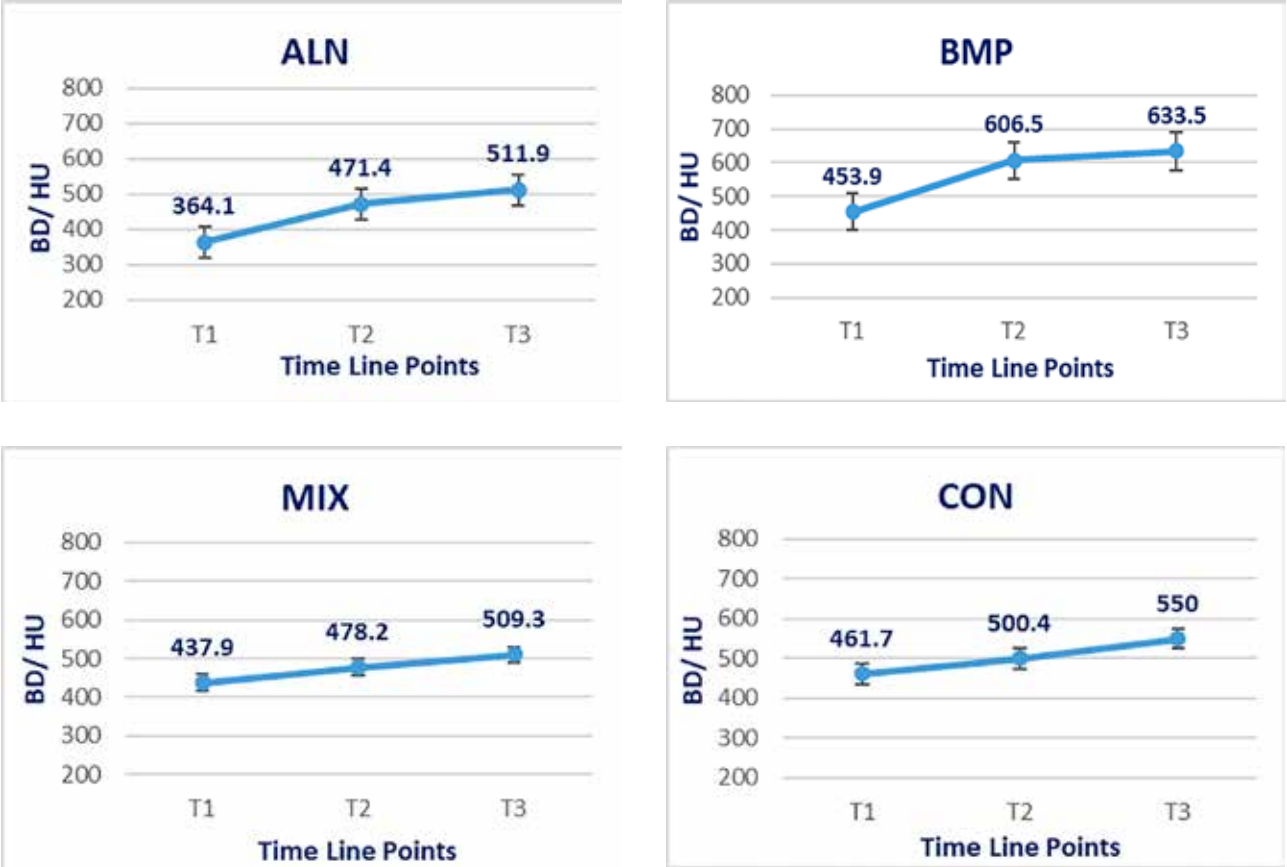

FIG 4 Linear graphs illustrating the differences in the bone density (BD) of study groups in the measurement intervals. HU; Hounsfield unit, ALN; alendronate, BMP; bone morphogenetic protein, MIX; mixed formula, CON; control, T1; implant placement; T2; preloading; T3; post functional loading.

received a total of 71 DIs, 4 of which failed during the healing period. For the 67 analyzed DIs, there was no significant difference regarding their distribution according to the recipient jaw and their dimensions as well as the study outcome (Table 1). So, none of these factors acted as a confounding factor that may affect the outcome of the study.

Intragroup peri-implant bone density comparison

The mean density values (HUs) of peri-implant bone in relation to the measurement intervals for each group are shown in Figure 4. The results showed a continuous increase in BD around the implants in all groups throughout the study period.

There was significant difference in BD for ALN and BMP

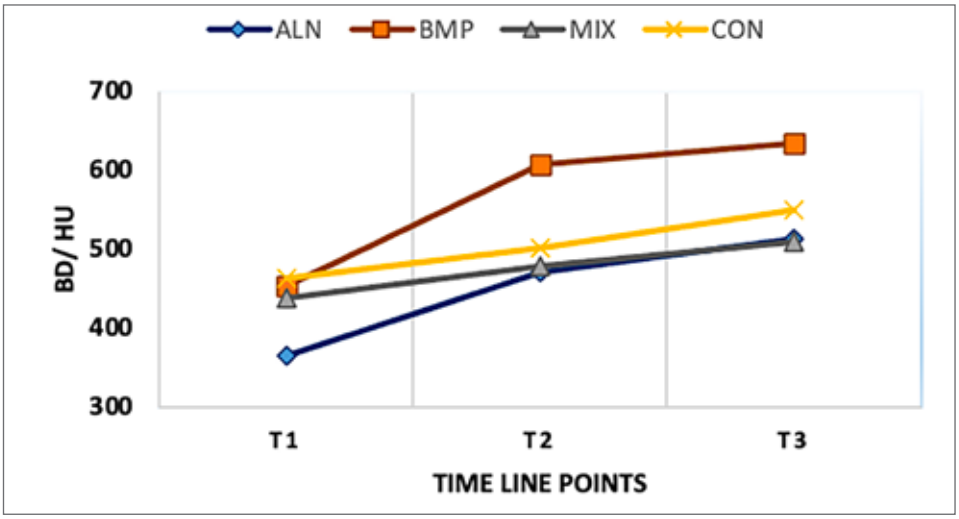

FIG. 5 Differences in the bone density of the study groups in the measurement intervals.
BD, bone density; HU, Hounsfield unit; ALN, alendronate; BMP, bone morphogenetic protein; MIX, mixed formula; CON, control; T1, implant placement; T2, preloading; T3, post functional loading.

Time point	Implant Group				p-value
	ALN (n= 17)	BMP (n= 15)	MIX (n= 18)	CON (n= 17)	
T^2-T^1	107.3	152.6	40.3	38.7	.017*
T^3-T^2	40.5	27	31.1	49.6	.119
T^3-T^1	147.8	179.6	71.4	88.3	.061

*BD, bone density; HU, Hounsfield unit; ALN, alendronate; BMP, bone morphogenetic protein; MIX, mixed formula; CON, control; T1, baseline; T2, preloading; T3, postloading; *statistically significant*

TABLE 3 Inter-group comparison of BD measurement intervals (HU values)

	Implant Group		
	BMP (n= 15)	MIX (n= 18)	CON (n= 17)
ALN (n= 17)	.375	.187	.278
BMP		.051	.033*
MIX			.869

*BD, bone density; ALN, alendronate; BMP, bone morphogenetic protein; MIX, mixed formula; CON, control; *statistically significant*

TABLE 4 Post-hoc Inter-group comparison of BD for T2-T1 time point (p-value).

groups between T1 and both T2 and T3 time points, with no significant difference between pre and postloading. For both MIX and control groups, the only significant differences in BD were between T1 and T3 (Table 2).

Intergroup peri-implant bone density comparison

The differences in the mean BD for the total sample in each group according to each measurement interval are shown in Figure 5.

For measurement intervals, inter-group comparisons using multivariate test showed that the best results regarding the differences in T2-T1 and T3-T1 intervals were in BMP and ALN groups, although it was not significant (Table 3). A significant difference among the study group was found for the first measurement interval (T2-T1) only. Post Hoc analysis, using Mann Whitney U test for exact differences, revealed that the difference was between the BMP and control groups as shown in Table 4.

Complications

Apart from the common post implant insertion complications (pain and swelling), none of the patients showed signs of infection, or dehiscence at the first week post-surgery as well as throughout the study period except for four implants that failed (2 implants from each ALN and BMP groups), 2 at second stage surgery (8 weeks post insertion), and the other 2 about 3 weeks post healing abutment insertion.

DISCUSSION

The quality of bone plays a major role in the initial bone-to-implant contact and in certain areas of the jaws (particularly the maxillary posterior region) and in certain conditions (such as osteoporosis) the bone may have trabecular morphology. Trabecular bone is less dense compared with cortical bone, this in turn, will affect the degree of firmness with which the implant has been placed, thus influencing its success rate (27). Since bone is composed of a mineralized matrix, a logical solution to the problem of bone targeting is the development of delivery systems that possess hydroxyapatite affinity such as BPs (28), or agents that have bone stimulating effect such as BMPs (29).

The use of BPs in implant dentistry has been studied extensively, both their systemic use (30, 31) and local application by different methods such as coating or implant immersion and/or irrigation of surgical site (32, 33, 34). Meanwhile, many preclinical and clinical studies hypothesized that titanium implants coated with rhBMP-2 can trigger enhanced bone formation providing better osseointegration in the peri-implant region (35, 22).

Some studies have investigated the local effect of ALN on osseointegration by means of applying it in the form of a solution (21, 36), whereas in the present study, the gel formula was chosen in order to contain the drug in the osteotomy site and keep it in contact with the bone walls during implant placement. Local application of ALN could be also considered as a safer method to overcome the adverse effects of its systemic use. Adding to that, application of rhBMP-2 in a gel formula may be a proper method for efficient delivery of the protein due to hardly maintaining its biological function in situ (37). Although the effect of ALN gel, as an adjunct method for periodontal treatment, has been investigated in many clinical trials (38), and has been shown to have a significant effect on the inhibition of bone resorption and increase bone neoformation, this study, to the best of our knowledge, is the first randomized clinical study in the field of dental implantology that uses polymer gel-based system for local application of ALN and rhBMP, alone or combined, with a specific concentration and amount, to assess their effect on peri-implant BD changes both in the preloading healing period and after

functional loading.
The rationale of using ALN for local application in this study was the encouraging results from previous studies, furthermore, ALN has the strongest data supporting its efficacy, the highest long-term safety information, a broad range of indication, and convenient dosing (39, 40). In addition, the findings of many studies provided evidences that rhBMP-2 showed positive effects on alveolar bone height, maxillary sinus lift, as well as improvement of bone healing around dental implants (41, 42).
Despite prior evidence that the local application of BPs resulted in improvement in implant fixation with an increase in peri-implant BD (43, 44), the results of this study are not in concordance with previous studies and this could be explained by the heterogeneity of samples and the methodologies of assessment and/or the agents used. Clinical studies that assessed the effects of local BPs on dental implants, whether coating or solution, used implant stability quotient values or marginal bone level differences with no BD evaluation and all these studies reported positive effects on both implant stability and peri-implant bone level (19-21, 32-34, 36). While those studies which reported the effect of this local therapy on peri-implant BD were done in animal models using removal torque, histomorphometric parameters, or micro-computed tomography for analysis and demonstrated positive effects with different agents and concentrations and mode of application whether coating the implant or mixing the drug with bone graft and most of these studies were in orthopedic surgery (45, 46), which also may explain the different results.
However, other preclinical and clinical studies reported comparable or non measurable difference in BD with local application of BPs, that could be considered similar to our study (47, 48), though, these studies were also carried out with different methods. On the other hand, Guimarães et al. in their rabbit model, reported a negative influence of ALN gel and the drug reduced the percentage of bone-implant contact.
With the same objective, many authors studied the effects on immediate implants of applying rhBMP-2 onto the implant surface or in the extraction site with absorbable collagen sponge. The results reported improved implant stability with statistically significant differences in bone mineral density between the control group and BMP-2 group (22, 23, 35). While other studies showed no measurable differences on peri-implant bone healing or when used in alveolar ridge augmentation (50, 51).
The results of this study demonstrated significant improvement in BD for ALN and BMP groups for the preloading healing period (from implant placement to the insertion of prosthesis). While, the alveolar bone surrounding the DIs in all study groups was significantly denser from baseline to the post functional loading time point, with no significant difference between the study groups. Although the ALN and BMP reported the best BD values, the increase in BD was related mainly with time from implant insertion to post functional loading which could be explained by Wolff's law (52), that relates to the response of bone to mechanical stimulation and states that bone adaptation will occur in response to a repeated load and the bone will remodel itself over time to become stronger. This significant increase in BD was in agreement with the results from other studies which reported that continuous loads resulted in an increased peri-implant BD (53, 54).
The null hypothesis of the present study could be accepted for peri-implant BD in relation to local application of ALN and/or rhBMP-2 in long-term results, because all groups showed a similar pattern of BD changes at the end of the study, although implants in ALN and BMP groups demonstrated better results, nevertheless they were statistically not significant. Regarding, the significant results of peri-implant BD in both ALN and rhBMP-2 in preloading phase of the study, these results need to be studied by further clinical trials to clarify the significant effects, if any, of these agents on BD in the field of dental implantology.
The limitations of this study are related to the relatively small sample size and the short follow up period, comparing the results of this study to the others was rather difficult and/or problematic due to the scarcity of those studies that investigate the peri-implant BD clinically. Also, many studies used animal models in their investigations and their results cannot be extrapolated for the clinical use, in addition to the heterogeneity of agents, concentrations, local application formulas, indications for use, variables of interest, and evaluation tests.

CONCLUSION

The results of this study concluded that there was a continuous increase of peri-implant BD through-out the study period irrespective of the local application of ALN and rhBMP-2 alone or combined on BD compared to the control group at the end of the study. However, the significant increase in BD in ALN and rhBMP-2 comparing with MIX and control groups in preloading period is noteworthy and need more studies to explore their real effects.
Further clinical trials are needed to investigate the effects of these agents with different concentrations and/or formula as well as other agents on peri-implant BD in improving the clinical outcome.

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