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Crestal bone changes around early vs. conventionally loaded implants with a multi-phosphonate coated surface: A randomized pilot clinical trial

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Abstract

Objectives: To compare the marginal bone level around implants with a thin multi-phosphonate coated surface after either an early or conventional loading protocol.

Material and methods: A randomized pilot clinical trial was conducted. Dental impressions were obtained after either 4 (test) or 8 weeks (control) and single crowns screwed-in 2 weeks later. Several variables were evaluated including radiographical marginal bone level (MBL), patient's level variables, and those related to the restoration and surrounding tissues. These data were obtained at several time points up to a 1-year follow-up.

Results: Thirty-four patients were included in the study, 18 assigned to the test group. No differences at implant placement were detected for tissue thickness, keratinized mucosa, nor any other clinical or radiological variable. At the time of impressions, tissue was thinner in the test group (2.30 (0.46) versus 2.78 (0.66) mm, test versus control, respectively; $p = .012$) so shorter abutments were used in this group. Regardless, no significant changes in marginal bone level were detected neither within group along time nor between groups. The average MBL at the 1-year follow-up was −0.15 (0.32) versus −0.22 (0.37) ($p = .443$) (test versus control, respectively). None of the clinical or radiological variables evaluated had a determinant influence on the MBL at any visit nor group.

Conclusion: The use of implants with a multi-phosphonate coated surface for early loading offers successful radiographical outcomes 1 year after loading. MBL over time was not affected by taking the impressions 4 or 8 weeks after implant placement and loading them 2 weeks later.

KEYWORDS

early loading, implant surface, marginal bone loss

1 | INTRODUCTION

It has been almost 50 years since introduction of the term Osseointegration. The biological process per se has been described from a histological point of view in many experimental models; the sequence of biological events that occur in bone healing around an implant inserted in the different maxillary areas are well identified (Davies, 2003). However, this knowledge does not seem to translate into daily clinical activity. In this sense, in the early years of Implantology, the recommendation was to wait 6 months before the prosthetic load in the upper maxilla, and 3 months in the jaw, due to the higher bone density of this area (Szmukler-Moncler et al., 2000). Nowadays, it is known that 8 weeks is more than enough to obtain bone healing around the implants (Ghimire et al., 2018). In in vitro experimentation, 28 days was sufficient to determine bone formation, and in animal models we have learned that bone requires a period of around 28 days for complete healing or remodeling (Cirera et al., 2020).

Thus, from this point of view, there has been a perfect clinical description of the immediate, early, or delayed loading protocols in implant dentistry, and how long we have to wait to restore the implants placed in these clinical circumstances (Cochran et al., 2004; Morton et al., 2018). Nevertheless, this is not based on precise histological support in humans. Similarly, we have a precise description of what primary and secondary stabilities are and how is the transition between the two during the bone healing process (Raghavendra et al., 2005). Subsequently, clinical recommendations on the minimum insertion torque, or others tools such as radiofrequency analysis and which values are essential to ensure long-term clinical success in such implants have been developed (Herrero-Climent et al., 2020). However, even though bone healing processes may be influenced by many local and systemic factors, based on current knowledge, dental professionals have not been able to establish clear criteria in post-surgical waiting times for the rehabilitation of our patients. In some cases, this waiting time is even established by "patient's demands."

In this sense, it must be mentioned that bone biology is simply biology, and tissue events occur as they do, beyond the consensuses and classifications we strive to establish. Therefore, research efforts in Implant Dentistry have been targeted at reducing waiting times by accelerating biological processes that are already known in bone healing. To this end, numerous strategies are being used, framed in the field of biomimetics. These include modifications of the physical-chemical features of the implant surface (Padial-Molina et al., 2011), addition of proteins with biological bone actions (Cirera et al., 2020; Sevilla et al., 2018), drugs such as melatonin (Galindo Moreno et al., 2016), adsorption of ions with certain cellular targets (Ellingsen et al., 2004), or the use chemical molecules with action on calcium and phosphate metabolism (Rupérez et al., 2016).

However, the results obtained with so many different methods have not been conclusive, mainly due to the difficulty of maintaining the integrity of the layers on the surface (Padial-Molina et al., 2009). One of those surface treatments is based on a permanently adhered monolayer of a multi-phosphonic acid on the surface of the implant that does not modify the surface topography (Viornery, Chevolot, et al., 2002). In vitro, this modified surface has been shown to induce the production of type I collagen (16%) without cytotoxic effects (Viornery, Guenther, et al., 2002). In vivo, this treated surface has shown that early bone mineralization can be increased, resulting in better fixation and stability after only 2 weeks (32% higher than control) (von Salis-Soglio et al., 2014). In fact, it was also shown that even one year after implantation, bone-to-implant contact was 39% higher for implants with treated surface compared to control (von Salis et al., 2012). An initial clinical report confirmed the clinical safety of this surface modification after a healing period of 6 months in the maxilla and 3 months in the mandible (Esposito et al., 2013). However, the main claimed advantage of this modified surface, that is, acceleration of osseointegration, has not been tested on shorter loading protocols than traditional ones. Moreover, its effect on marginal bone loss, a fundamental factor in predicting the occurrence of peri-implantitis (Galindo-Moreno et al., 2015), is unknown. As clinicians, the question using this type of modified surface is whether we can safely reduce waiting times in our patients, and whether this reduction in times will affect the long-term maintenance of the implants.

Therefore, the purpose of this study was to compare the marginal bone level around implants with a thin multi-phosphonate coated surface after either an early or conventional loading protocol.

2 | MATERIALS AND METHODS

2.1 | Study design

This controlled randomized clinical trial was designed as a consecutive enrollment prospective one-center study. A minimum of 30 patients was set to be included in the study with a parallel 1:1 allocation ratio to either a control group (conventional loading, impressions taken 8 weeks after implant placement) or test group (early loading, impressions taken 4 weeks after implant placement).

The protocol was reviewed and approved by the Ethical Committee for Research in Humans of the University of Granada, Spain (216/CEIH/2016). Moreover, this study was registered in clinicaltrial.gov under protocol number NCT03059108. The protocol was developed in accordance with the Helsinki Declaration of the World Medical Association, the Clinical Research Guide to Medical Devices for Humans (ISO 14155:2011), and the General Guide to Good Clinical Practices (2001/20/EC). Every patient was previously informed in details about the study and all of them signed a written informed consent before the study procedures were initiated.

Reporting of this trial followed the CONSORT guidelines.

2.2 | Participants

Patients referred to the Oral Surgery and Implant Dentistry Clinic of the School of Dentistry, University of Granada, Spain, were evaluated for participation in this study.

The inclusion criteria defined that the patient must be of legal age (older than 18 years) and younger than 75 years, mentally and physically

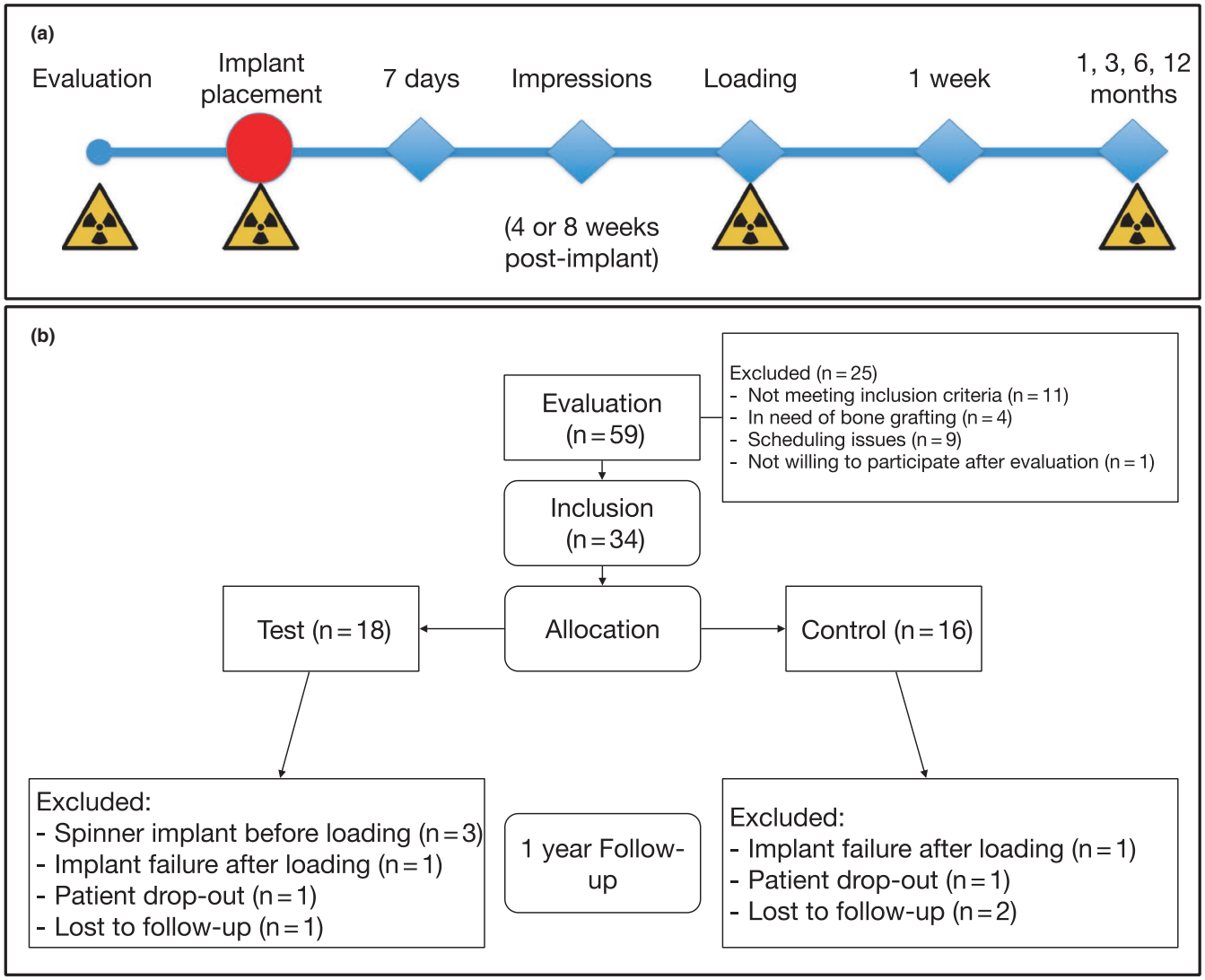

FIGURE 1 (a) Overview of the study sequence and (b) CONSORT diagram of screening, allocation, and follow-up

healthy, with an absent tooth in the premolar or molar area in the maxilla or the mandible, with the presence of natural neighboring and antagonist teeth. The main exclusion criteria listed diseases that could alter healing or bone metabolism (uncontrolled diabetes, diagnostic osteoporosis, etc.), taking drugs that could cause the same effects (bisphosphonates, long-time corticosteroids intake, RANK inhibitors, etc.), smokers of more than 10 cigarettes/day, need for bone grafting in the same therapeutic session and pregnant women. Candidates presenting clinical and/or radiographic signs of active periodontal disease or other dental conditions would be withheld from the study until treatment was adequately provided and stability was achieved.

2.3 | Interventions

During the first screening appointment, a full medical history was reviewed as well as clinical and radiological diagnostic tests. Patients which met the inclusion criteria underwent the surgical phase during a second session. All the surgeries were conducted by the same surgeon (PG-M) assisted by the same periodontist (LG-G). Control of the study's variables was done by the same person (MP-M). A full-thickness mucoperiostal supracrestal incision was made including the papillae of the adjacent teeth. The flap was raised to the limit of the inserted gingiva at the vestibular and lingual aspects. Surgical drilling of the implant bed was carried out following the C1 implant placement protocol established by the company (MIS, Bar Lev Industrial Park, Israel); it always ended with the single-use final drill. Drilling was performed at a speed of 1,200 rpm under profuse irrigation of sterile saline with a maximum 55 Ncm torque. C1 implants with the multi-phosphonate coated surface (MIS Implants Technologies) were then inserted with hand-piece and motor; maximum insertion torque was 55 Ncm, and finished with wrench if needed, always with torque below 80 Ncm. Healing followed a 1-stage protocol in order to perform faster loading. The flap was carefully sutured with 4/0 surgical silk (Laboratorios Aragó, Barcelona, Spain); it included a stitch on each adjacent papilla. Group allocation of the patient was

subsequently determined in order to blind the surgeon during the surgical procedure. Dental impressions were taken at the designated time (4 or 8 weeks after implant placement) and sent to the prosthesis laboratory technician. A metal-ceramic screw-retained crown was fabricated over a Ti-Base abutment; it was delivered approximately two weeks later. An overview of the study sequence is presented in Figure 1a.

2.4 | Outcomes

The primary outcome measure was based on marginal bone level (MBL) parameters, particularly changes from loading to the 1-year follow-up. For this purpose, standardized periapical images of the area were obtained with the assistance of an intraoral X-ray positioner at implant placement, prosthesis delivery, 3, 6, and 12 months. Linear measurements of the implant marginal bone level were measured by using the software Image J (NIH) and taking the implant shoulder as reference. Positive values indicated the bone was coronal to the shoulder while negative values were recorded when the bone was apical to the reference point. Changes over time were then calculated. Each image was internally calibrated with the implant diameter, as this was always visible in the radiography. Additionally, other obtained measurements were: the distance between the implant and each adjacent tooth, the bone level at the adjacent teeth taking the cement-enamel junction as reference, and the distance from the contact point of the crown to the bone crest. Mesial and distal measurements were obtained for each implant and then averaged.

Clinical data at the time of implant placement included the mesio-distal distance between the adjacent teeth, occlusal height, bucco-lingual width (before and after the raising of the flap), vertical soft tissue thickness, and width of keratinized mucosa. Additionally, vertical soft tissue thickness was also measured at the time of dental impressions and prosthesis delivery. From prosthesis delivery to final follow-up, the width of keratinized mucosa as well as the papilla index (Jemt, 1997) (0 = No papilla; 1=<50% of filling of the interproximal area; 2=≥50% of filling; 3 = Ideal papilla; 4 = Overgrowth) were also registered. Healing index (Morelli et al., 2011) was also evaluated up to prosthesis delivery: 0 = Mature wound healing; 1 = Erythema; 2 = Bleeding; 3 = Flap mobility; 4 = Suppuration; and 5 = Necrosis.

Additionally, samples of peri-implant crevicular fluid and intrasulcular plaque were collected at different time points for future analyses.

2.5 | Sample size

The current study was categorized as a pilot study since no previous research has been published on marginal bone levels around implants with this surface treatment neither in an early or conventional loading protocol nor with the macroscopic implant design and prosthetic connections used here. Only a previous study with a longer loading protocol compared the multi-phosphonate coated surface modification with a non-modified surface. It included 23 patients by the beginning of the trial and detected a trend on marginal bone loss after one year (Esposito et al., 2013). Therefore, it was decided to increase the sample size to at least 30 patients.

2.6 | Randomization

To prevent imbalance between groups in terms of gender, location of the missing tooth, and type of bone, a restricted randomization by minimization protocol was performed by using a software designed for this purpose (Saghaei, 2011). This was intended to maximize the statistical power and generalizability of the study findings. A clinic staff member not involved in the clinical trial performed the allocation.

2.7 | Blinding

Although neither the patient nor the restorative dentist (LL-C) could be masked because of the loading protocol, both the surgeon (PG-M), assistants in charge of examination and follow-ups (LG-G, CG-L, RR-A), and the data analyst (MP-M) were blinded, as group allocation was set after implant placement and all data was re-coded and analyzed in a blinded manner.

2.8 | Statistical analysis

An intention-to-treat plan was set for statistical analyses. Statistical significance was set at $p < .05$. Percentages, means, standard deviations, and errors were calculated for each type of variable. Categorical data have been evaluated with chi-squared test. Because of the sample size, the primary and secondary continuous outcome measures have been analyzed by non-parametric Wilcoxon rank-sum test and general linear model for over time analyses with pairwise comparisons of means further evaluated by Tukey contrasts. All tests have been performed using R (version 3.6.2) (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

59 patients were evaluated for inclusion from February 2017 to January 2019 and 34 met the enrollment criteria; 18 of them were assigned to the test group (dental impressions 4 weeks after implant placement). At the 1-year follow-up, only 12 patients were evaluated in each group; 6 and 4 patients (test and control groups, respectively) were not analyzed because of lost to follow-up (1 and 2, respectively; patients were not reached upon contact by several methods nor attended their planned follow-up visit), the patient dropped out of the study (1 in each group, decided and communicated their intention to not continue the follow-up visits) or the implant failed after loading (1 in each group). In addition, spinner implants at the time of impressions

(3 in the test group) were also excluded from the study. Inclusion, exclusion, allocation, and follow-up are summarized in Figure 1b.

Of the included patients, as summarized in Table 1, the mean age was 45 (27 – 57) and 39 (25, 58) ($p = .067$), for the test and control groups, respectively. Eight in each group were females ($p = .746$). Most of them were non-smokers nor alcohol addicted. No systemic disease was reported by any patient. The main reason for tooth extraction was extensive caries. Implants mainly rehabilitated the first and second upper premolars. Except for 3 cases in the test group in which the implant rotated at the time of impressions, all other cases were restored according to the protocol. Two implants, 1 in each group, showed signs of pain upon mastication after the 3 months follow-up and were removed, as they were mobile. No other implant was lost after 1 year. On average, 29.67 (3.53) versus 59.38 (4.73) days went from implant placement to impressions and 45.07 (3.47) versus 73.63 (8.14) from implant placement to loading in the test and control groups, respectively.

Regarding the radiographic measurements (Table 2), no differences were found for the distance between the implant and each adjacent tooth, the bone level at the adjacent teeth and the distance from the contact point to the bone crest at any visit. Within each group, the MBL from implant placement to prosthesis delivery that corresponds to post-surgical remodeling was significantly different; 0.42 (0.30) versus −0.04 (0.42) mm for the test group ($p < .001$) and 0.46 (0.31) versus 0.12 (0.31) mm for the control group ($p < .001$). These differences between the groups were not statistically significant. The average MBL change from implant placement to loading was −0.48 (0.51) versus −0.31 (0.38) mm for the test and control group, respectively; the difference was not statistically significant ($p = .312$). No other significant change was observed from prosthesis delivery to the 1-year follow-up either within or between the groups (Figure 2).

The main finding of the study was that the average MBL change from loading to the 1-year follow-up was −0.23 (0.23) versus −0.33 (0.21) mm for the test and control groups, respectively; the difference was not statistically significant ($p = .261$). Particularly, at the 1-year follow-up the differences in MBL between the test and control groups were not significant on neither the mesial side (−0.02 (0.29) versus −0.21 (0.49) mm; $p = .175$), the distal (−0.28 (0.43) versus −0.23 (0.29); $p = .773$) or average (−0.15 (0.32) versus −0.22 (0.37); $p = .443$). None of the clinical or radiological variables evaluated had a determinant influence on the MBL at any visit or group. This means that there were no significant changes from loading to 1 year either within or between the groups.

At implant placement, tissue thickness was similar for both groups, 2.72 (1.07) versus. 2.78 (0.84) mm for the test and control groups, respectively ($p = .911$); width of keratinized tissue was significantly wider for the control group, 3.53 (1.66) versus 4.38 (1.02) mm for the test and control groups, respectively ($p = .034$). Afterward, no significant differences were detected in the width of keratinized tissue up to 1 year. Interestingly, tissue thickness at the time of impressions was lower in the test group, 2.30 (0.46) versus 2.78 (0.66) mm for the test and control groups, respectively; $p = .012$); this determined the height of the Ti-Base transmucosal abutment. As a consequence, there were significant differences of the Ti-Base abutment height, shorter in the test group: 86.7% versus 50% of 1.50 mm in the test and control groups, respectively; $p = .029$). The opposite happened to the length of the crowns, longer for the test group, 9.36 (0.78) versus 8.41 (1.26) mm for the test and control groups, respectively; $p = .015$); however, the crown-to-implant ratios did not differ, 1.03 (0.07) versus 1.00 (0.15) for the test and control groups, respectively; $p = .423$). No other clinical parameter showed statistically significant differences between the groups, including the mesio-distal distance, occlusal height, and healing index. Papilla index was not different between groups at any follow-up visit either (Figure 3).

Signs of mucositis were recorded for 2 patients in the control group and 1 in the test showed at the 3- and 6-month follow-up, respectively. Irrigation with chlorhexidine and hygiene instructions resolved the condition.

4 | DISCUSSION

The aim of this study was to compare the MBL around implants with a thin multi-phosphonate coated surface after either an early or conventional loading protocol; this is, on which the prosthetic phase was initiated either 4 or 8 weeks after implant placement by taking the impressions. The crowns were placed 2 weeks later, when occlusal loading actually started. Marginal bone loss was compared between both groups at several times with the final milestone of 1-year after delivery of the final prosthesis. Our general results showed that an early loading protocol initiated 4 weeks after placing implants with a multi-phosphonate coated surface did not affect the MBL when compared to loading initiated after 8 weeks, for any milestone until 1 year after prosthesis delivery.

Comparing our main outcomes with the available literature is challenging, due to the different criteria established to categorize the loading times. The most updated definition of "early loading" refers to an implant with prosthesis in occlusion with the opposing dentition between 1 week and 2 months after implant placement (Morton et al., 2018), which is in fact a wide time frame. A fundamental factor that differentiates between immediate and early loading is based on the biomechanical and biological significance of the concept of primary stability, and that of secondary stability. Secondary stability, achieved by osteointegration, which is a dynamic concept, is what finally ensures the stability and long-term success of the implant (Raghavendra et al., 2005). In the interim time between primary stability (mechanical) and secondary stability (biological), there is a critical moment when the implant is in a compromised phase that ranges from 1 to 4 weeks (Raghavendra et al., 2005). Thus, although the definition of early loading goes from 1 to 8 weeks (Morton et al., 2018), the time between 1 and 4 weeks is actually the period when more changes occur and the implant is less stable. Thus, we have to be careful when analyzing the literature in this regard.

TABLE 1 Description and comparison of clinical variables

	Test group (dental impressions 4 weeks after implant placement) *n* = 18 (52.94%)				Control group (dental impressions 8 weeks after implant placement) *n* = 16 (47.06%)				*p* value*
Age [mean (min, max)] (years)	42 (25, 58)								
	45 (27 – 57)				39 (25 – 58)				.067
Gender [*n* (%)]									
Female	8 (44.4)				8 (50.0)				.746
Male	10 (55.6)				8 (50.0)				
Smoking [*n* (%)]									
No	14 (77.8)				11 (68.8)				.302
Low (<5 cigarettes/day)	4 (22.2)				3 (18.8)				
Low (>5, <10 cigarettes/day)	0 (0.0)				2 (12.5)				
Mesio-distal distance [mean (*SD*)] (mm)	9.0 (2.22)				8.5 (1.45)				.527
Occlusal height [mean (*SD*)] (mm)	6.82 (1.19)				7.06 (1.78)				.645
Bucco-lingual width [mean (*SD*)] (mm)									
Before flap raising	7.22 (1.35)				7.31 (2.12)				.888
After flap raising	6.83 (1.72)				7.03 (1.51)				.736
Implant diameter [*n* (%)]									
3.75 mm	10 (55.6)				11 (68.8)				.429
4.20 mm	8 (44.4)				5 (31.2)				
Implant length [*n* (%)]									
10.0 mm	9 (50.0)				8 (50.0)				1
11.5 mm	9 (50.0)				8 (50.0)				
Days from implant placement to impressions [mean (*SD*)]	29.67 (3.53)				59.38 (4.73)				<.001 *
Days from implant placement to prosthesis delivery [mean (*SD*)]	45.07 (3.47)				73.63 (8.14)				<.001 *
Abutment height [*n* (%)]									
1.50 mm	13 (86.7)				8 (50.0)				.029 *
3.00 mm	2 (13.3)				8 (50.0)				
Tissue thickness [mean (*SD*)] (mm)									
Implant placement	2.72 (1.07)				2.78 (0.84)				.911
Impressions	2.30 (0.46)				2.78 (0.66)				.012 *
Width of keratinized tissue [mean (*SD*)] (mm)									
Implant placement	3.53 (1.66)				4.38 (1.02)				.034 *
Prosthesis delivery	2.87 (1.36)				3.75 (1.39)				.067
1 week post-loading	2.92 (1.71)				3.63 (1.36)				.235
1 month post-loading	2.93 (1.58)				3.70 (1.33)				.163
3 months post-loading	3.07 (1.73)				3.43 (1.09)				.509
6 months post-loading	3.54 (1.33)				3.50 (0.85)				.860
12 months post-loading	3.66 (1.15)				3.54 (0.78)				.798
Papilla index [% within visit] (MESIAL) **	0	1	2	3	0	1	2	3	
Prosthesis delivery	13.3	73.3	13.3	0.0	6.2	62.5	31.2	0.0	.441
1 week post-loading	7.7	30.8	46.2	15.4	0.0	6.2	87.5	6.2	.107
1 month post-loading	0.0	20.0	60.0	20.0	0.0	0.0	86.7	13.3	.140
3 months post-loading	0.0	7.1	35.7	57.1	0.0	21.4	28.6	50.0	.555

(Continues)

TABLE 1 (Continued)

	Test group (dental impressions 4 weeks after implant placement) $n = 18$ (52.94%)				Control group (dental impressions 8 weeks after implant placement) $n = 16$ (47.06%)				*p* value*
6 months post-loading	0.0	0.0	7.7	92.3	0.0	7.1	28.6	64.3	.202
12 months post-loading	0.0	0.0	25.0	75.0	0.0	0.0	30.8	69.2	.748
Papilla index [% within visit] (DISTAL) **	0	1	2	3	0	1	2	3	
Prosthesis delivery	13.3	66.7	20.0	0.0	6.2	56.2	37.5	0.0	.508
1 week post-loading	0.0	30.8	53.8	15.4	0.0	12.5	81.2	6.2	.284
1 month post-loading	0.0	20.0	60.0	20.0	0.0	0.0	93.3	6.7	.079
3 months post-loading	0.0	7.1	42.9	50.0	0.0	14.3	28.6	57.1	.670
6 months post-loading	0.0	0.0	30.8	69.2	0.0	0.0	42.9	57.1	.516
12 months post-loading	0.0	0.0	8.3	91.7	0.0	0.0	23.1	76.9	.315

**p* value: Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical variables; **: There were no cases with papilla index higher than 3.

In some studies, the implant loading is done quite early. For instance, in 27 patients, to restore mandibular molars, Salvi and coworkers compared implants loaded at two weeks (test) versus 6 weeks (control) after implant placement with cemented single-tooth crowns. Two test and one control implants rotated at the time of abutment connection (one week [test] and 5 weeks [control] after implant placement). No statistical differences were found in mean crestal bone loss measurements (0.57 ± 0.49 versus 0.72 ± 0.50 mm) (Salvi et al., 2004). Although this study is similar to the current one in many aspects, it is important to note that the implants in Salvi's study test group had their prosthetic abutments connected only a week after surgery, and posteriorly, one week later, the crowns were cemented. Some other differences with our protocol are that 1.- these implants were placed in mandibular bone, therefore, denser, in contrast to our study in which most of the implants were placed in the maxilla; 2.- primary stability after a week of bone healing is still well-maintained while bone remodeling is still not at full activity; and, finally, 3.- these implants were never subjected to anti-torque force, for example in the impression phase, because crowns were cemented; while in our protocol we had multiple screw-in and screw-out episodes (removing the healing abutment to screw-in the impression coping, and back to screw-in the healing abutment again). Thus, it could be said that, in our case, implants were subjected to higher mechanical demands with the most potentially deleterious movement at the time of transition from primary to secondary stability.

With a more similar time frame to our study, Grandi and coworkers compared the clinical outcomes of single implants with immediate non-occlusal loading, early non-occlusal loading at 3 weeks, or conventionally loaded at 4 months. There were no statistically significant differences for any of the outcome measures up to 1-year post-loading (Grandi et al., 2015). In terms of complications, our study also shows similar outcomes as in Grandi's study two implants failed, one in the immediately loaded and one in the early loaded group ($p = .601$). Bornstein and coworkers with an early loading protocol after 3 weeks of healing of implants placed in the mandible also found similar outcomes but in a shorter follow-up, only 6 months (Bornstein et al., 2009). Some of their implants, as in Salvi´s study, were considered "spinner," and left unloaded for a longer period of time. In our study, when this occurred, it was decided to exclude those implants from further analysis. Thus, survival rates may vary, but this circumstance has to be considered.

In contrast, other protocols established early loading protocols after 6 weeks of bone healing. In this case, using implants with an internal conical connection, Mitsias et al. (2018) found similar outcomes to those reported in this study: peri-implant marginal bone loss was 0.19 ± 0.44 mm at immediately loaded implants (2 days), 0.18 ± 0.66 mm at early loaded implants (6 weeks) and 0.25 ± 0.28 mm at conventionally loaded implants (3 months). There were no statistically significant differences in complications ($p = 1.000$) and bone loss ($p = .806$) between the three loading strategies (Mitsias et al., 2018). Similarly, a series of studies led by our group using the same early loading protocol found similar results in terms of survival and MBL, in short- (Galindo-Moreno et al., 2012), medium- (Maiorana et al., 2015), and long-term follow-ups (Galindo-Moreno, Nilsson, et al., 2017). Many other protocols using different implant surfaces and clinical restorations have also demonstrated clinical effectiveness and no differences in terms of bone maintenance and clinical success in comparison with delayed protocols (Han et al., 2018; Kim et al., 2016; Makowiecki et al., 2017). This happens, in our opinion, because bone healing is completed for functional loading after 6 weeks (Berglundh et al., 2003); so, all these protocols, longer than 6 weeks, are totally reliable from a biological and clinical point of view, although they might be influenced by several factors such as specific bony substratum, implant surface, or dimension of the gap between the bone and the implant.

We have not found any differences in terms of other clinical variables. It should be noted that we used a single-stage protocol

TABLE 2 Description and comparison of radiographical variables (mean (*SD*) in mm except the crown-to-implant ratio)

	Test group (dental impressions 4 weeks after implant placement)	Control group (dental impressions 8 weeks after implant placement)	*p* value*
Distance from implant to anterior tooth	2.83 (1.09)	2.18 (1.00)	.143
Distance from implant to posterior tooth	2.67 (1.19)	2.37 (1.00)	.576
Crown length	9.36 (0.78)	8.41 (1.26)	.015 *
Crown-to-implant Ratio	1.03 (0.07)	1.00 (0.15)	.423
Implant MBL (MESIAL)			
Implant placement	0.53 (0.45)	0.54 (0.35)	.602
Prosthesis delivery	0.01 (0.56)	0.13 (0.45)	.678
3 months post-loading	−0.16 (0.63)	0.10 (0.17)	.618
6 months post-loading	0.01 (0.23)	−0.08 (0.39)	.592
12 months post-loading	−0.02 (0.29)	−0.21 (0.49)	.175
Anterior Tooth MBL			
Implant placement	2.63 (0.77)	2.27 (0.68)	.143
Prosthesis delivery	2.77 (0.70)	2.38 (0.58)	.120
3 months post-loading	2.79 (0.82)	2.31 (0.68)	.237
6 months post-loading	2.79 (0.68)	2.62 (0.46)	.376
12 months post-loading	2.79 (0.68)	2.75 (0.58)	.974
Implant MBL (DISTAL)			
Implant placement	0.32 (0.26)	0.39 (0.33)	.706
Prosthesis delivery	−0.10 (0.44)	0.10 (0.25)	.659
3 months post-loading	−0.25 (0.45)	0.05 (0.24)	.109
6 months post-loading	−0.24 (0.45)	−0.20 (0.33)	.771
12 months post-loading	−0.28 (0.43)	−0.23 (0.29)	.773
Posterior Tooth MBL			
Implant placement	2.01 (0.85)	1.98 (1.08)	.860
Prosthesis delivery	2.06 (0.85)	2.07 (1.27)	.567
3 months post-loading	1.95 (0.59)	1.91 (0.95)	.473
6 months post-loading	2.08 (1.02)	1.92 (0.91)	.687
12 months post-loading	2.10 (0.93)	1.92 (0.86)	.478
Average Implant MBL			
Implant placement	0.42 (0.30)	0.46 (0.31)	.571
Prosthesis delivery	−0.04 (0.42)	0.12 (0.31)	.507
3 months post-loading	−0.20 (0.49)	0.07 (0.17)	.129
6 months post-loading	−0.11 (0.30)	−0.14 (0.33)	.645
12 months post-loading	−0.15 (0.32)	−0.22 (0.37)	.443
MBL change from Implant placement to Loading			
Mesial	−0.55 (0.70)	−0.38 (0.55)	.841
Distal	−0.43 (0.40)	−0.25 (0.25)	.349
Average	−0.48 (0.51)	−0.31 (0.38)	.312
MBL change from Loading to 1 year			
Mesial	−0.24 (0.33)	−0.34 (0.25)	.196
Distal	−0.23 (0.18)	−0.33 (0.29)	.902
Average	−0.23 (0.23)	−0.33 (0.21)	.261

*p value: Wilcoxon rank sum test.

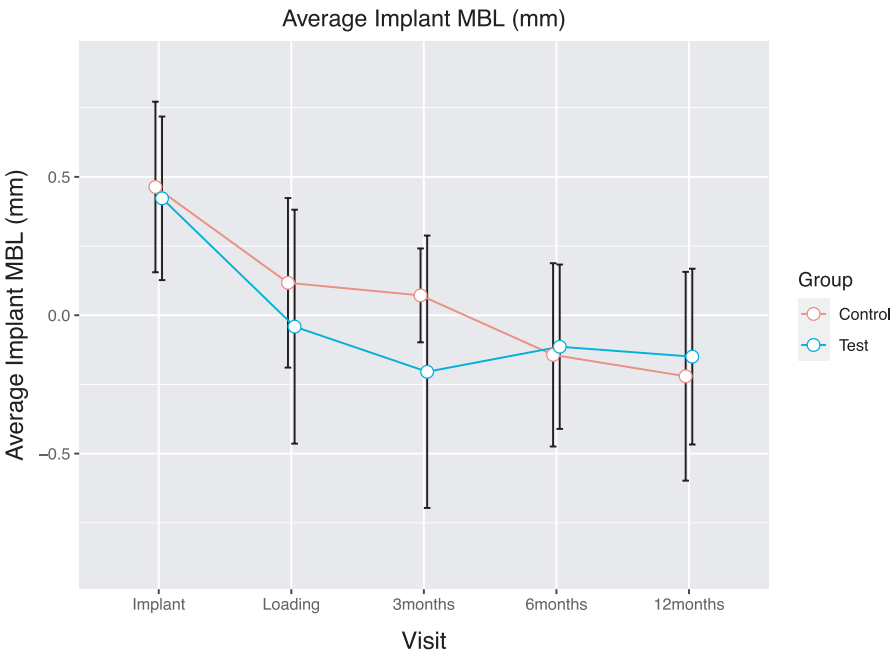

FIGURE 2 Representation of the distal and mesial average of implant MBL over time

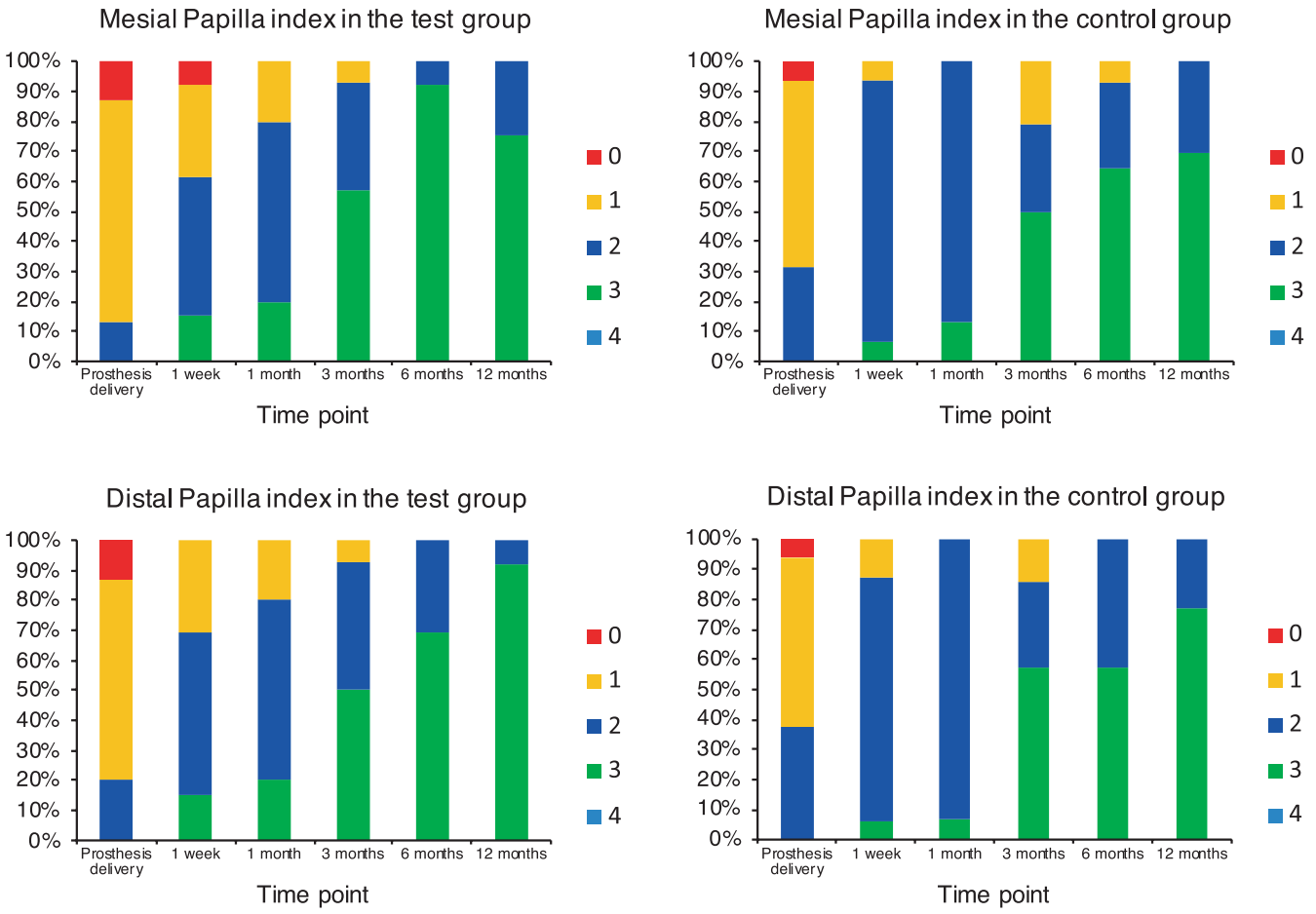

FIGURE 3 Mesial and distal papilla index for each group and time point

to reduce time for actual loading and to avoid damaging the bone on the adjacent teeth, which highly influences the bone around the implant (Galindo-Moreno, Padial-Molina, et al., 2017). In our study, marginal bone levels on adjacent teeth did not change significantly over time. Also related to this, the papilla index evaluated over time, clearly improved from loading to the 1-year follow-up, as the interproximal papilla mainly depends on the adjacent natural teeth (Roccuzzo et al., 2018). In our sample, this happened regardless of the inclusion of some smoker patients. We did not exclude these patients from our demanding loading protocol because previous clinical studies using the same surface used in the current study indicated that smokers were actually more benefited from having this implant surface than other (Esposito et al., 2013). A possible explanation for this might be that smoker patients might have their healing potential impaired. Thus, using an implant surface that stimulates bone healing, would benefit them specifically.

In our study, we have not found influence of any other variable on MBL, including the thickness of the peri-implant mucosa or the height of the transgingival Ti-base abutment. As mentioned, in our study, more 1.5 mm Ti-base abutments were used in the test group because the thickness of the tissue was lower at the time of impressions. This could be due to a lower maturation of the tissues after such short time, although our sample size is too small to support any conclusion in this sense. In any case, we have to keep in mind that several recent studies are highlighting that the effect of the thickness of the mucosa on MBL becomes irrelevant when the height of the transgingival abutment is high (Pico et al., 2019; Spinato et al., 2019). Our previous studies on this topic also refer to a cut-point of 2 mm of minimum transgingival abutment to prevent MBL (Galindo-Moreno et al., 2014). Finally, and maybe most importantly, we have to remember that not all transmucosal abutments behave in the same way, in terms of sealing the gap, being mechanically stable or allowing to separate the gap between the prosthesis and the implant far from the bone (Piattelli et al., 2003; Tallarico et al., 2018). In the current study, we used metal-ceramic crowns screwed over the implant. The crowns were cemented in the laboratory over a Ti-Base abutment in order to minimize the interface between the crown and the abutment. In contrast, the referenced studies used transmucosal abutments for multiple crowns in which the gap between the prosthesis and the abutment could be bigger, as this gap is not sealed extraorally. Thus, abutment height becomes particularly relevant in those situations but not so much in single-unit rehabilitations as those used in the current study.

Our study protocol was designed to be framed in the early loading range, with some important factors to be considered:

1. The drilling protocol was not modified by bone availability, and mechanical retention did not become a capital factor, as it is in immediate loading or very early loading protocols. So, we did not impose a minimum insertion torque as a criterion for inclusion or exclusion, unlike other studies already referenced (Grandi et al., 2015; Mitsias et al., 2018; Salvi et al., 2004).
2. The early loading concept (1 to 8 weeks after placement) actually encompasses the entire bone healing process around implants (Raghavendra et al., 2005), although the healed and functional bone will continue to remodel far beyond this time frame. However, we still subject our patients to long waiting times. We even defer loading processes for 6 months. This should only be used, in our opinion, in cases of concomitant bone regeneration, not so much because of the osteointegration of the implant but because of the maturation of the graft.
3. Finally, the use of modified surfaces, as the one used in the current study, to shorten the healing processes is recommended, although the definitive waiting time, as discussed above, cannot be clearly established. In this sense, there are implants available on the market with long-term studies on clinical success that were rehabilitated after relatively short times for osseointegration (Galindo-Moreno, Nilsson, et al., 2017; Marković et al., 2015). As consequence, this should invite us to shorten our daily clinical protocols.

The main limitation of the study is the sample size, particularly important to make within groups comparisons of the influence of other variables on the main outcome variable, MBL. Although no differences were found, which could be due to such limitation if they truly exist, our study is quite larger than all of the previous studies on similar topics. In fact, it is larger than the only previous report using the same coating treatment but different implant macrodesign and prosthetic connection. The novelty of our study in terms of loading protocol also has to be considered. Although most of our patients were younger than 50 and one would tend to think that young patients heal faster, this does not necessarily have to be the case. In addition, as discussed, we also have to keep in mind the time frame and the number of implants that did not support rotating forces at 4 weeks, which is approximately the most critical time. Thus, the patient must be properly informed of this potential complication when this kind of protocol is performed. Moreover, the follow-up period might be considered short-term for the analysis of MBL but we must also note that recent studies on this have been published with even shorter terms and, still more, our group has reported that early bone loss can be used as a predictor of future bone loss (Galindo-Moreno et al., 2015). Thus, one-year follow-up can be considered a short but adequate frame for the purpose of MBL analysis. In any case, the pilot nature of this study should serve to provide sufficient data for future studies on the particular surface and loading protocols evaluated in the current analysis.

5 | CONCLUSIONS

Within the mentioned limitations of this pilot study, it can be concluded that the marginal bone levels around implants with a modified surface based on a permanently adhering multi-phosphonate coating are not affected up to 1 year of follow-up by a loading protocol initiated 4 or 8 weeks after implant placement. Moreover, no

other clinical or radiographical variable has shown any influence on the final outcomes.

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Preliminary findings of the current study were presented at the 28th Annual Scientific Meeting of the European Association for Osseointegration (Padial-Molina et al., 2019).

CONFLICT OF INTEREST

Pablo Galindo-Moreno lectures regularly for MIS Implants Technologies, among other companies, although there is no commercial interest or royalties on any products mentioned in this manuscript. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Pablo Galindo-Moreno: Conceptualization (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Writing-original draft (lead). Lourdes Gutierrez-Garrido: Data curation (equal); Investigation (lead); Writing-review & editing (supporting). Lucia Lopez-Chaichio: Data curation (equal); Investigation (equal); Writing-review & editing (supporting). Claudia Guerra-Lorenzo: Investigation (equal); Writing-review & editing (supporting). Roque Rodriguez-Alvarez: Investigation (equal); Writing-review & editing (supporting). Miguel Padial-Molina: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Funding acquisition (supporting); Investigation (supporting); Methodology (equal); Project administration (lead); Resources (equal); Validation (lead); Writing-review & editing (lead).

ETHICAL ASPECTS

This prospective controlled randomized clinical trial was approved by the Ethical Committee for Research in Humans of the University of Granada, Spain (216/CEIH/2016). Moreover, this study was registered in clinicaltrial.gov with the protocol number NCT03059108. It was conducted in patients referred to the Oral Surgery and Implant Dentistry Clinic of the School of Dentistry, University of Granada, Spain. The protocol was developed in accordance with the Helsinki Declaration of the World Medical Association, the Clinical Research Guide to Medical Devices for Humans (ISO 14155:2011), and the General Guide to Good Clinical Practices (2001/20/EC).

CREDIT AUTHOR STATEMENT

PG-M, MP-M: Conceptualization; MP-M, PG-M: Methodology; MP-M: Validation; MP-M: Formal analysis; PG-M, LG-G, LL-C, CG-L, RR-A: Investigation; PG-M, MP-M: Resources; LG-G, LL-C, MP-M: Data Curation; PG-M: Writing - Original Draft; All: Writing - Review & Editing; LL-C: Visualization; PG-M: Supervision; PG-M, MP-M: Project administration; PG-M: Funding acquisition.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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