

Influence of abutment height and implant depth position on interproximal peri-implant bone in sites with thin mucosa: A 1-year randomized clinical trial

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Abstract

Objectives: The aim of this RCT was to assess radiographically the effect of abutment height and depth of placement of platform-switched implants on interproximal peri-implant bone loss (IPBL) in patients with thin peri-implant mucosa.

Material and Methods: Thirty-three patients received one prosthesis supported by two implants replacing at least two adjacent missing teeth (66 implants). Patients were randomly allocated and implant insertion depth adapted to abutment height groups (3 mm height group the implants were placed 2 mm subcrestally; 1 mm height group, equicrestally). Clinical and radiological measurements were performed at 3, 6 and 12 months after surgery. Interproximal bone-level changes were compared between treatment groups using repeated measures mixed ANOVA. The association between IPBL and categorical variables was also analyzed.

Results: The mean IPBL in 1 mm abutment group was 0.76 ± 0.79 mm at 3 months, 0.92 ± 0.88 mm at 6 months, and 0.95 ± 0.88 mm at 12 months, while in the 3 mm abutment group was 0.06 ± 0.21 , 0.07 ± 0.22 mm, and 0.12 ± 0.33 mm, respectively. Significant differences between both groups were observed at every time point. When the influence of patient characteristics and clinical variables was analyzed, no statistically significant differences were also observed.

Conclusions: The use of long abutments, in combination with subcrestal implant position in sites with thin mucosa, led to lower IPBL in comparison with the use of short abutments.

KEYWORDS

abutment height, implant-abutment connection, interproximal bone loss, platform switching, thin mucosa

1 | INTRODUCTION

The maintenance of the initially achieved peri-implant bone level is a key factor for long-term success and good aesthetic results in implant therapy, and therefore, the study of factors affecting marginal bone levels around implants has gained importance over the last

few years (Blanco et al., 2015, 2017; Molina, Sanz-Sánchez, Martín, Blanco, & Sanz, 2016; Nóvoa et al., 2017).

Implant placement in the vertical dimension in relation to the alveolar crest has been shown to be a key factor in marginal bone resorption. Different authors have demonstrated the influence of the microgap in the peri-implant bone loss when two-piece implants

(external connection) are placed. A greater amount of bone remodeling should be expected in those implants placed at the level or below the bone crest (Hermann, Cochran, Nummikoski, & Buser, 1997; Hartman et al., 2004). However, in bone-level implants when internal connection abutments are used, the microgap is present at abutment–restoration interface, therefore, far from the bone crest. A recent systematic review evaluated the effect of the apico-coronal implant position on crestal bone loss and recommended to place bone-level implants subcrestally or tissue-level ones equicrestally, in order to maintain the interproximal peri-implant bone (Saleh et al., 2018).

Initial mucosa tissue thickness (distance between the marginal mucosa and the bone) has shown to be one of the factors having an impact on bone stability. A minimum dimension of 3 mm between the marginal portion of the peri-implant mucosa and peri-implant bone has been reported (Abrahamsson, Berglundh, Wennstrom, & Lindhe, 1996; Berglundh & Lindhe, 1996). Therefore, a thin mucosa tissue is associated with bone loss, whereas a thick soft tissue maintains crestal bone level with minimal remodeling.

Recent retrospective studies have observed significant effects of the prosthetic abutment on the interproximal peri-implant bone level (Galindo-Moreno et al., 2015, 2014; Nóvoa et al., 2017). In a recently published randomized clinical trial was observed, when platform-switching implants were placed at bone level in locations with thick mucosa (at least 3 mm) and restored with different abutment height, a greater interproximal bone resorption when a short abutment was used at 6 months of follow-up (Blanco et al., 2017).

In clinical situations with thin mucosa, clinicians suggested performing soft tissue augmentation procedures to obtain a thicker mucosa in order to maintain crestal bone levels with minimal remodeling (Linkevicius, Puisys, Steigmann, Vindasiute, & Linkeviciene, 2015; Puisys & Linkevicius, 2015).

Recent studies have shown a reduction in interproximal peri-implant bone loss (IPBL) and implant threads exposure when bone-level implants are placed subcrestally in comparison with an equicrestal position (Aimetti, Ferrarotti, Mariani, Ghelardoni, & Romano, 2015; Koutouzis, Neiva, Nonhoff, & Lundgren, 2013). Vervaeke et al. (2018) have observed that is possible to prevent peri-implant bone remodeling if we adapt vertical implant position to soft tissue thickness.

The aim of this RCT was to assess radiographically the effect of abutment height and depth of placement of platform-switched implants on IPBL in patients with thin peri-implant mucosa.

2 | MATERIAL AND METHODS

2.1 | Study population

All subjects from this investigation were selected from patients of the Master of Periodontology in the University of Santiago de Compostela in need of implant restoration (bridge units/partially edentulous). All patients were included and treated between January and June 2017. The following inclusion criteria were established: (a) treatment site with a mucosa thickness ≤ 2 mm, (b) patients

age >18 years, (c) American Society of Anaesthesiologists (ASA) status I or II, (d) periodontal stability or enrolment in a periodontal maintenance program, and (e) adequate bone volume for implant installation. Individuals who took any medication or systemic disease that could affect bone metabolism, including patients with medical history of bisphosphonate therapy, pregnant or lactating women, poor oral hygiene (plaque index $> 20\%$), uncontrolled periodontal diseases, need of single implant restoration or simultaneous guided bone regeneration techniques, and sites with acute lesions were excluded. Lack of primary stability (≤ 20 N) also led to exclusion at surgery.

These patients signed an informed consent form for participation and were treated in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Investigation Committee of Galicia (2016-593). A similar design as in our previous publication reporting the results on the early healing of implants placed at bone level and restored with different abutments height in locations with thick mucosa was done (Blanco et al., 2017).

The patients were randomly assigned in two treatment groups: implants restored with 1 or 3 mm abutment height, in accordance with a randomization list generated by the statistic program Epidat vers 4.1 (Consellería de Sanidade, Xunta de Galicia). The allocation to the treatment was concealed by means of sealed envelopes until the time of the surgical procedure.

2.2 | Surgical and restorative procedures

Patients received a complete oral clinical examination and intra-oral radiograph and CBCT scan to assess bone dimensions for implant placement. An individualized film holder was also designed to have reproducible and comparable radiographs. Once enrolled in the study, a full-mouth professional prophylaxis was scheduled. At the time of surgery, and under local anesthesia (Artinibsa[®] Inibsa), the thickness of the mucosa (distance between the marginal mucosa and the bone in the edentulous site) was measured with a periodontal probe (15 mm, PCP-UNC 15; Hu-Friedy), a mid-crestal incision was performed, and the buccal and lingual flap elevated. Before implant osteotomy, sealed envelopes containing the allocation to treatment were opened. When short abutments had to be placed (1 mm), implant shoulder was installed equicrestally. When long abutments had to be used (3 mm), implant shoulder was placed two millimeters subcrestally in order to avoid abutment exposure due to the thin mucosa, trying to leave the abutment shoulder at the same level in both groups. Osteotomy procedure was performed according to the manufacturer's recommendations for 3.5- or 4-mm-diameter implants based on available bone and in a non-submerged technique (one abutment–one time protocol). Implants used in this study were bone level with platform-switching, straight, and tapered design (BioniQ implants[™]; LASAK) and an implant length ranging from 6.5 to 10 mm and diameters of 3.5 and 4 mm. The abutments were also commercially available, with conical design, internal connection, and two different heights (1 and 3 mm).

Implant stability was assessed using torque control with the hand-piece device. Immediately after implantation, screw-on definitive titanium abutments with internal connection and tightened at a torque always lower than the implant insertion torque (IT) were placed and protected with a titanium cover (one abutment—one time). Mucoperiosteal flaps were then sutured with Supramid 5/0 (Aragó, Barcelona, Spain) obtaining primary closure. A standardized intra-oral radiograph was made to check the implant position and abutment seating immediately after surgery (baseline data).

All patients were advised to have a soft diet and minimize the trauma in the implant area. Patients were instructed to rinse with 0.12% chlorhexidine/digluconate (Perio-aid; Dentaid) solution twice per day for 2 weeks. Systemic antibiotics (Amoxicillin 500/8 hr/7 day) and anti-inflammatories (Ibuprofen 600 mg/8 hr/3 day) were also prescribed. Sutures were removed 1 week after surgery, and patients received thorough dental hygiene instructions and were advised to clean the titanium cover with an extra soft toothbrush.

Eight weeks after surgery and after abutment retightened at 25 Ncm², the prosthetic phase was initiated. Custom impression trays, impression copings to the definitive abutments, and a full-arch polyether material were used (Impregum Penta Soft; 3M ESPE). One month later, after final impression was taken, the screw-retained metal ceramic prosthesis was positioned, the internal screws tightened at 15 Ncm² torque according to manufacturer guidelines, and screw access closed with light-cured composite. Occlusion was also checked to obtain an adequate distribution of occlusal contacts.

2.3 | Radiographic evaluation

To evaluate radiological variables around implants, a standardized intra-oral radiograph technique was used. A customized radiograph

film holder (Rinn holder/silicone) was made for each patient. It was used at each visit and fitted onto the antagonist jaw. The periapical radiographs were taken using the long-cone paralleling technique (Meijndert et al., 2004). A phosphor plate radiograph (Durr Dental), and a radiographic tube (Planmeca) with the same setting for each patient was used. For each implant, the radiological variables evaluated between implant placement (baseline), loading (3 months after surgery) 6-month and 12-month follow-up after surgery (Figure 1) were: (a) IPBL, defined as the distance from implant shoulder (S) to the mesial and distal first visible bone-implant contact (fBIC) and (b) bone over the implant platform. One independent and calibrated examiner (A.P.) measured these radiological variables to the nearest 0.1 mm using IMAGE J software (1.47 V Wayne Rasband; National Institutes of Health). The scale was set and calibrated by the height of the dental implant, which yielded a pixel/mm ratio.

2.4 | Clinical evaluation

Socio-demographical and clinical data were registered to evaluate the influence of these parameters on interproximal marginal bone level. Periodontal disease history was determined by assessment of attachment loss using a periodontal probe (15 mm, PCP-UNC 15; Hu-Friedy). Patients with presence of proximal attachment loss of ≥ 3 mm in ≥ 2 non-adjacent teeth were considered to have periodontitis (Tonnetti & Claffey, 2005). Smoking status was classified as non-smoker/smoker. Data relative to implant location (upper/lower), IT (≤ 35 Ncm²/ >35 Ncm²), width of keratinized tissue (<1 mm/ ≥ 1 mm), bone density (Lekholm & Zarb, 1985) categorized in type 1–2 (cortical) and type 3–4 (cancellous), biotype (thin/thick. De Rouck et al. 2009), and antagonist (no antagonist/natural tooth/dental prosthesis/implant prosthesis) were also registered.

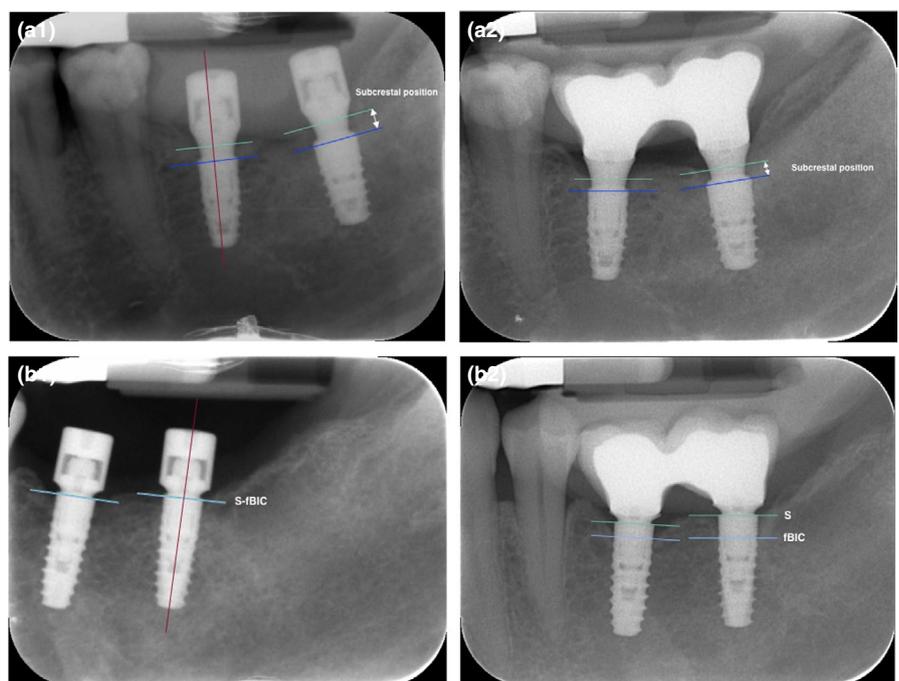


FIGURE 1 (a, b) Interproximal peri-implant bone loss measurement (S-fBIC) and subcrestal position after 12 months of follow-up at 3 mm group (a1, baseline; a2, 12 months post-surgery) and 1 mm group (b1, baseline; b2, 12 months post-surgery)

2.5 | Statistical analysis

The trial was designed to assess whether the average efficacy of both treatments can be considered different in interproximal crestal bone-level maintenance. In order to achieve 80% power at a significance level of 0.05, the sample size was computed considering to detect a difference of 0.5 mm (Blanco et al., 2017) in a design with four repeated measurements. Using PASS version 12 (NCSS, LCC), it was determined that 20 patients/20 bridges (10 per group) were required at least.

Demographical and clinical parameters were descriptively reported. For continuous variables, mean and standard deviations (*SD*) were calculated for each treatment group, and number and percentage were calculated for categorical variables. Interproximal peri-implant bone loss was measured at mesial and distal implant site and averaged to represent the IPBL over time. The IPBL in treatment groups were compared using repeated measures mixed ANOVA. Association between IPBL and variables measured over time was performed with repeated measures mixed ANOVA too. All analyses were performed using SPSS software, version 20.0 (SPSS Inc.). The level of significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Subjects and implants

Thirty-three consecutive subjects (aged between 40 and 76 years) and 66 implants (34 implants in the 1 mm and 32 in the 3 mm group) were included in this study. No clinical signs of inflammation, pain, or implant mobility were detected. All subjects completed the

follow-up evaluations, and all implants were available for the 12-month analysis, resulting in a survival rate of 100% (Figure 2).

Twenty-three implants were placed in non-smoker and 11 in smoker patients in 1 mm group, and 24 and 8 implants in the 3 mm group, respectively. Thirty-six patients had periodontitis, 19 in 1mm group and 17 in 3 mm group. The majority of implants (46) were 8 mm in length, 23 in each group. Thirty-eight implants were 3.5 mm in diameter and 28 were 4.0 mm. Twenty-eight implants were placed in the upper jaw. The majority of implants were placed in bone type III or type IV according to Lekholm and Zarb (1985). No significant difference was observed between groups. Natural teeth or dental prosthesis was the most frequent antagonist. Only 6% of implants had no antagonist (Table 1).

3.2 | Radiographic evaluation of interproximal peri-implant bone level

The mean IPBL was greater in the 1 mm abutment group from surgery to loading (0.76 ± 0.79 vs. 0.06 ± 0.21 mm), from surgery to 6 months (0.92 ± 0.88 vs. 0.07 ± 0.22 mm), and from surgery to 12 months of follow-up (0.95 ± 0.88 vs. 0.12 ± 0.33 mm) than in the 3 mm group. Figure 3 represents the mean IPBL changes during follow-up. The statistical analysis revealed significant differences between treatment groups. Greater bone preservation was observed in implants loaded with long abutments in comparison with short abutments (Table 2).

Table 3 exhibits demographical and clinical data obtained from the 33 patients (66 implants) included in the study. Greater IPBL was observed in smoker patients, no diagnosed or treated of periodontitis, in implants located in the upper jaw, and in type 1–2 bone quality

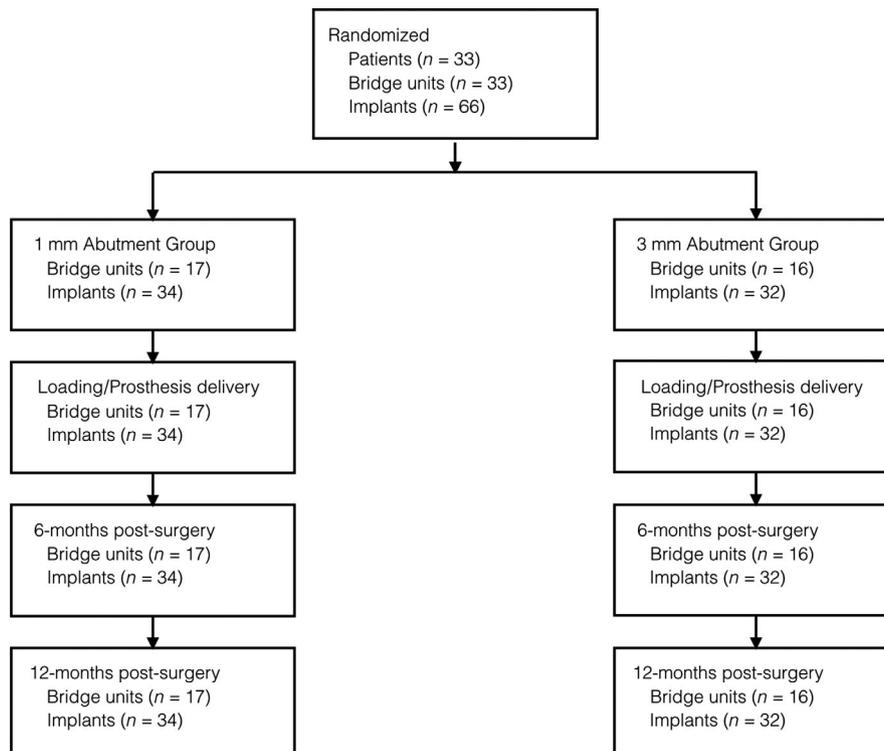


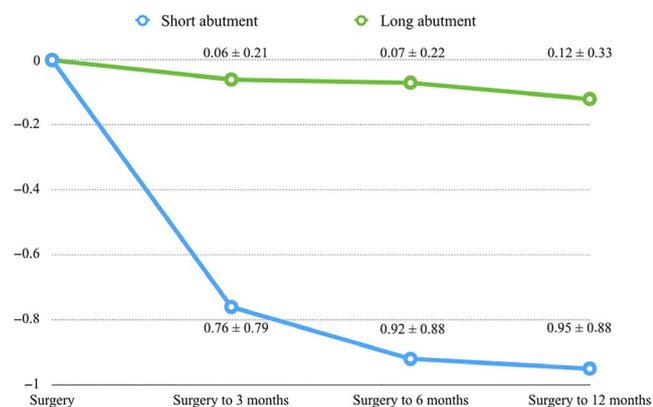
FIGURE 2 Flow chart of the study

TABLE 1 Demographical and clinical parameter of the study population and implant sites

Treatment groups (patients)	1 mm (n = 34)	3 mm (n = 32)
Age (years)	55.56 ± 7.73	52.27 ± 2.45
Smoking		
Non-smoker	22 (64.8%)	24 (75%)
Smoker	12 (35.3%)	8 (25%)
Periodontitis		
Yes	19 (55.9%)	17 (53.1%)
No	15 (44.1%)	15 (46.9%)
Implant length (mm)		
6.5	2 (5.9%)	1 (13.1%)
8	23 (67.6%)	23 (71.9%)
10	9 (26.5%)	8 (25%)
Implant diameter (mm)		
3.5	19 (55.9%)	19 (59.4%)
4.0	15 (44.1%)	13 (40.6%)
Implant position		
Upper	15 (44.1%)	13 (40.6%)
Lower	19 (55.9%)	19 (59.4%)
Antagonist		
No antagonist	1 (2.9%)	1 (3.1%)
Natural teeth	23 (67.6%)	22 (68.8%)
Dental prosthesis	2 (23.5%)	6 (18.8%)
Implant prosthesis	8 (5.9%)	3 (9.4%)
Bone quality		
1–2	13 (38.2%)	15 (46.9%)
3–4	21 (61.8%)	17 (53.1%)

but no statistically significant differences were observed at follow-up. Although the statistical analysis showed an absence of influence of all these factors, the effect of IT was almost significant ($p = 0.051$).

When the presence of bone over implant shoulder was analyzed, 15 implants (46.9%) in the long-abutment group showed this condition however no implant in short-abutment group did (Table 4).

**FIGURE 3** Graphic data presented with absolute values of IPBL at the 4 time points and changes of IPBL between the time points

4 | DISCUSSION

The results of the present randomized clinical trial showed greater interproximal peri-implant bone preservation during the first year, when platform-switching implants are placed in a subcrestal position and a long abutment is used in sites with thin mucosa, in comparison with short abutments. Adapt vertical implant position to soft tissue thickness in an attempt to reduce implant surface exposure was also investigated in a recent study by Vervaeke et al. (2018). They concluded that it is possible to anticipate biologic width re-establishment placing implants in a subcrestal position (Vervaeke et al., 2018). A recent systematic review also recommended placing bone-level implants subcrestally. At the same time, they claimed about the necessity of studies focussing on the effect of implant–abutment connection and soft tissue thickness around implants, on crestal bone level (Saleh et al., 2018).

If a minimum thickness of mucosa is not present, the establishment of the mucosal "attachment" implies bone resorption as demonstrated Berglundh and Lindhe (1996) in an animal study using two-piece implants. Recent studies have also demonstrated that platform switching did not prevent, by itself, peri-implant bone resorption when a thin mucosa is present (Linkevicius, Apse, Grybauskas, & Puisys, 2010; Puisys & Linkevicius, 2015).

A randomized clinical trial in humans analyzed crestal bone changes around bone- and tissue-level implants (van Eekeren, Elsas, Tahmaseb, & Wismeijer, 2016). After, at least, 1-year follow-up, they observed significantly greater bone resorption on bone-level implants when the initial mucosa thickness was 2 mm or less. This difference was not statistically significant when tissue-level implants were used (van Eekeren et al., 2016). The results of recent systematic reviews investigating the influence of soft tissue thickness on crestal bone levels presented similar results, demonstrating the influence of soft tissue thickness when bone-level implants are used (Suárez-López del Amo, Lin, Monje, Galindo-Moreno, & Wang, 2016).

As concluded in recently published retrospective (Galindo-Moreno et al., 2014; Nóvoa et al., 2017; Vervaeke, Dierens, Bessler, & Bruyn, 2014) and prospective studies (Spinato, Bernardello, Sassatelli, & Zaffe, 2017; Vervaeke, Collaert, Cosyn, & Bruyn, 2016), the selection of the abutment has also great importance. Our group has recently shown the necessity of using long abutments to restore bone-level implants to allow the establishment of the biologic width (Blanco et al., 2017; Nóvoa et al., 2017).

The prospective study recently published by our group aimed to compare the effect on the IPBL of two different abutment heights in sites with thick mucosa (≥ 3 mm). We observed a statistically significant crestal bone loss when short abutments were used in comparison with long abutments in bone-level implants placed equicrestally where a thick mucosa is present (Blanco et al., 2017). The positioning of the abutment–restoration interface close to the bone (using short abutments in platform-switching implants) could lead to peri-implant bone loss even in locations with thick mucosa due to the colonization of the microgap and the establishment of biologic width (Broggini et al., 2006).

TABLE 2 Mean interproximal peri-implant bone loss (S-fBIC) at 3-, 6-, and 12-month follow-up

	Abutment height 1 mm		Abutment height 3 mm		p-Value inter-groups	p-Value intra-groups $t \times ah^a$
	N	Mean \pm SD (mm)	N	Mean \pm SD (mm)		
Surgery to loading	34	0.76 \pm 0.79	32	0.06 \pm 0.21	<0.001	0.047
Surgery to 6 months	34	0.92 \pm 0.88	32	0.07 \pm 0.22		
Surgery to 12 months	34	0.95 \pm 0.88	32	0.12 \pm 0.33		

^aTime \times abutment height.

In cases with thin mucosa, is advisable to place the implant slightly deeper (subcrestally), in such a way the mucosa can hide the long abutment, avoiding aesthetic complications, and at the same time allowing the establishment of the biologic width. This concept was investigated by several authors (Aimetti et al., 2015; Koutouzis et al., 2013; Palaska, Tsaousoglou, Vouros, Konstantinidis, & Menexes, 2014; de Siqueira et al., 2016), and different results were obtained. While some authors observed better bone preservation placing bone-level implants in a subcrestal position (Aimetti et al., 2015; Koutouzis et al., 2013), Palaska et al. (2014) concluded that the connection pattern between fixture

and abutment, rather than vertical implant placement in relation to crestal bone level, seems to have more relevance. de Siqueira et al. observed no influence of different implant depths on crestal bone-level changes. In this investigation, they obtained higher crestal bone loss in both groups in comparison with Vervaeke et al. (2018) and the present study. This could be attributed to the high IT threshold ($>45 \text{ Ncm}^2$) used in this study (de Siqueira et al., 2016).

Vervaeke et al. (2018) have also recently evaluated the effect of soft tissue thickness on bone remodeling and if implant surface exposure can be avoided by adapting the vertical implant position

Variables	Mean interproximal peri-implant bone loss \pm SD				p-Value inter-groups
	N	3 months	6 months	12 months	
Smoking					
No smoker	46	0.31 \pm 0.55	0.40 \pm 0.66	0.47 \pm 0.70	0.092
Smoker	20	0.68 \pm 0.89	0.77 \pm 0.96	0.72 \pm 0.96	
Periodontitis					
Yes	36	0.31 \pm 0.57	0.40 \pm 0.67	0.38 \pm 0.59	0.117
No	30	0.56 \pm 0.79	0.64 \pm 0.88	0.75 \pm 0.95	
Location					
Upper	28	0.52 \pm 0.80	0.64 \pm 0.88	0.72 \pm 0.92	0.206
Lower	38	0.35 \pm 0.59	0.41 \pm 0.69	0.42 \pm 0.66	
Torque of insertion					
$\leq 35 \text{ Ncm}^2$	52	0.35 \pm 0.61	0.42 \pm 0.68	0.44 \pm 0.67	0.051
$> 35 \text{ Ncm}^2$	14	0.71 \pm 0.87	0.83 \pm 1.00	0.95 \pm 1.06	
Bone quality					
1–2	28	0.46 \pm 0.70	0.60 \pm 0.88	0.58 \pm 0.88	0.604
3–4	38	0.39 \pm 0.68	0.44 \pm 0.68	0.52 \pm 0.72	

TABLE 3 Mean interproximal peri-implant bone loss as a function of demographical and clinical factors

	Abutment height 1 mm			Abutment height 3 mm		
	n	%		n	%	
Surgery to loading	34	0	0	32	15	46.9
Surgery to 6 months	34	0	0	32	15	46.9
Surgery to 12 months	34	0	0	32	15	46.9

TABLE 4 Number and percentage (%) of implant sites with bone on the implant shoulder in the different treatment group at 3 months (loading), 6 and 12 months

in relation to the soft tissue thickness. They showed significantly better crestal bone-level preservation after 6-month and 2-year follow-up around implants placed in a subcrestal position (Vervaeke et al., 2018) with similar bone-level changes and differences between groups as we observed in the present study.

Different factors have also been related to crestal bone loss like the amount of keratinized tissue, position of the implant–abutment junction, implant design, history of periodontitis, or tobacco consumption (Galindo-Moreno et al., 2005, 2014; Hartman & Cochran, 2004; Hermann et al., 1997; Qian, Wennerberg, & Albrektsson, 2012).

In this study, we have observed the influence of the analyzed factors but did not reach statistical significance. 55.9% and 53.1% of the patients were diagnosed and treated of periodontitis and 35.3% and 25% smokers in 1 and 3 mm abutment group, respectively, but we were not able to identify the influence of these factors. The role of smoking and a history of periodontitis has been strongly studied and identified as predictors of implant failure and crestal bone loss. Galindo-Moreno et al. (2005) demonstrated, in a prospective study on 514 implants, that IPBL was significantly related to tobacco use or alcohol consumption, increased plaque levels, and gingival inflammation. A posterior retrospective study demonstrated lower survival rates and higher crestal bone loss in tobacco smokers with a history of treated and maintained periodontitis (Aglietta et al., 2011). A recent systematic review affirmed that the insertion of implants in smokers yielded to increased failure rates, postoperative infections and crestal bone loss (Chrcanovic, Albrektsson, & Wennerberg, 2015).

Although not reached a statistical significance, we observed a greater IPBL in implants placed with high IT. Barone et al. in a 12-month randomized clinical trial evaluated the influence of the IT with a threshold of 50 Ncm². They observed that implants placed with a high IT showed greater peri-implant bone remodeling and buccal soft tissue recession (Barone et al., 2015). A recent study of the same group with longer follow-up (3 years) has observed similar results in terms of bone resorption and a 98.2% success rate in implants placed with regular IT and 91.3% when high IT. These results demonstrated the importance of pay attention on implant placement protocols (Marconcini et al., 2018).

One limitation of our study might be that the results obtained in this research can only be considered when bone-level and platform-switching implants are used in combination with internal connection abutments, and installed with the one abutment–one time protocol. More studies are needed to understand the behaviour of other implant designs (platform-matching or external-connection implants).

Within the limitations of this study, it can be concluded that the use of long abutments (internal connection) placed at the time of surgery, in combination with subcrestal implant position, led to a greater interproximal peri-implant bone preservation in comparison with the use of short abutments to restore implants placed at bone level in clinical situations where thin mucosa is present.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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