Suppuration as diagnostic criterium of peri-implantitis

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Abstract

Background: Suppuration (SUP) as a diagnostic parameter for monitoring dental implants is not yet well understood. The retrospective clinical and radiographic study was therefore carried out to investigate the patient, implant and site characteristics among individuals exhibiting SUP.

Material and methods: Demographic characteristics and clinical parameters were recorded. Radiographic features were analyzed using cone-beam computed tomography (CBCT). Peri-implantitis was defined based on the consensus report of Workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions: probing pocket depth (PPD) ≥ 6 mm, presence of bleeding on probing (BOP) and/or SUP on gentle probing, and radiographic bone loss (MBL) ≥3mm. SUP was graded according to profuseness (dot vs. line/drop) and time after probing (≥15 seconds vs. <15 seconds after probing vs. spontaneous). Simple binary logistic regression models were estimated using generalized estimation equations (GEE) in order to explain the probability of SUP based on demographic, clinical and radiographic variables.

Results: A total of 111 eligible patients ($n_{implants}$= 501) were assessed. Of them, 57 ($n_{implants}$= 334) were diagnosed with peri-implantitis according to the established case definition, and of these individuals, 31 ($n_{implants}$= 96) presented SUP. Therefore, the prevalence of SUP was 27.92% in the total sample size and 54.38% in peri-implantitis patients. Overall, 28.74% implants displayed SUP within peri-implantitis

patients. SUP was more frequently found at buccal sites (51%) and proved less prevalent at mesio-lingual sites (16.7%). Defect morphology (OR=6.59; p=0.004), PPD (OR=1.63; p=0.024) and MBL (OR=1.35; p=0.010) were significantly associated with the presence of SUP. Likewise, defect morphology (p=0.02), PPD (p=0.003) and MBL (p=0.01) were significantly correlated with the grade of SUP.

Conclusion: The presence and grade of suppuration are associated with peri-implant bone loss, probing pocket depth and defect morphology in peri-implantitis patients.

Introduction

Peri-implantitis is characterized by progressive bone loss and inflammation of the peri-implant soft tissues.[1] Unlike the majority forms of periodontitis, the progression of peri-implantitis has been shown to follow an accelerating non-linear pattern.[2-4] In fact, despite the shared etiologic factors, marked differences have been suggested to exist between the pathogenesis of peri-implantitis and periodontitis.[5] Peri-implantitis lesions are commonly larger in size as those noted at periodontitis sites.[5, 6] In addition, they exhibit greater numbers and densities of plasma cells, macrophages and neutrophils, and a higher density of vascular structures outside and lateral to the cellular infiltrate, compared to periodontitis sites.[5] When compared to peri-implant mucositis, peri-implantitis lesions are considerably larger and contain significantly greater proportions of B cells (CD19+) and elastase-positive cells.[7]

Clinical studies on the clinical manifestations of peri-implantitis have shown suppuration (SUP) to be a likely event in scenarios of progressive bone loss and peri-implant pathology.[8-10] Fransson et al. found SUP to occur in 19% of all peri-implantitis

implants, versus in only 5% of the implants with stable bone levels.[8] Likewise, Ramanauskaite et al. identified SUP in 17.39% of the implants of 30.16% of all peri-implantitis patients.[9] French et al. reported SUP in a significantly increased number of scenarios characterized by peri-implant bone loss over 8.5 years.[10] Interestingly, sites exhibiting peri-implantitis showed significant levels of SUP (odds ratio [OR] = 6.81) compared to healthy sites.[11] More recently, Bhavsar et al. demonstrated a frequency of 16.7% SUP implants.[12] Preclinical findings have further evidenced the increase in the frequency of SUP as bone loss progresses in a ligature-induced peri-implantitis model.[13]

SUP as a diagnostic parameter for monitoring dental implants is therefore not yet well understood. The present clinical and radiographic study was thus carried out to investigate the patient, implant and site characteristics among individuals exhibiting SUP.

Material and Methods

A retrospective study was conducted in accordance with the Declaration of Helsinki on human studies, following approval from the Ethics Committee of the University of Extremadura. Patients received and signed a written inform consent. Patient data was anonymized. The study is reported according to the STROBE statement.[14]

Study population

All enrolled patients had been consecutively evaluated with dental implants in function for at least 36 months after final prosthesis delivery from February to October 2019. The clinical analyses were carried out by a single experienced periodontist (AM), and the radiographic assessments were made by a previously trained post-doctoral student (MV).

Eligibility criteria

The following inclusion criteria were applied: partially or completely edentulous patients aged 18-80 years and rehabilitated with implant-supported, single-crown fixed prostheses or implant-supported overdentures; smokers or non-smokers; absence of infectious disease at the time of implant placement; and absence of systemic disorders or medications known to alter bone metabolism. Subjects were excluded if they were pregnant; presented uncontrolled medical conditions or diseases (i.e., diabetes mellitus with HbA1c level >8*)*; or exhibited inadequate bucco-lingual implant positioning outside of the bony contour that could have predisposed disease.[15] Moreover, zygomatic or pterygoid implants were excluded. Patients with treated peri-implantitis/mucositis were likewise excluded to the effects of analysis.

Peri-implantitis case definition

The following diagnostic definition of peri-implantitis was applied, based on the consensus report of Workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions:[16]

- Presence of bleeding and/or SUP on gentle probing.
- Probing depth ≥ 6 mm.
- Bone level ≥ 3 mm apical to the most coronal portion of the implant or at the rough-smooth interface in tissue-level implants.

Clinical assessment

- Probing pocket depth (PPD) was recorded in mm using a North Carolina probe.

- The modified sulcular bleeding index (mSBI) was scored from 0-3 according to the extent and severity of bleeding on probing (BOP).[17]
- The plaque index (PqI) was scored from 0-3 according to the visibility and severity of plaque accumulation.[18]
- Keratinized mucosa (KM) around the dental implants was measured from the free mucosal margin to the mucogingival junction at the mid-buccal position and recorded to the nearest mm using a North Carolina probe.

Assessment of suppuration

The presence/absence of SUP was recorded at 6 sites per implant with a light vertical probe.[10] The following index was applied according to the grade of SUP: grade 0 = no SUP or non-suppurative exudate; grade 1 = SUP manifesting ≥ 15 seconds after gentle probing or SUP at a single spot (dot); grade 2 = SUP manifesting < 15 seconds after gentle probing or profuse SUP (drop or line) forming a confluent line; grade 3 = spontaneous SUP manifesting through the peri-implant sulcus upon palpation/compression of the peri-implant soft tissues. The variables "profuseness" and "time after probing" were adopted from previously published indices/classifications to categorize peri-implant bleeding and mucosal condition.[10, 19, 20]

Assessment of peri-implantitis confounders

Patient- and implant-related variables were recorded, including age, gender, total number of implants, type of edentulism (complete/partial), implant position (mandibular anterior [ma], mandibular posterior [mp], maxillary anterior [MA], maxillary posterior [MP]), type of prosthesis (single crown [SC], fixed denture [FD],

overdenture [R]) accessibility with the 0.5 mm interproximal brush (yes/no), and smoking habit (yes/no),

Radiographic assessment

Cone-beam computed tomography (CBCT) images were obtained by an experienced radiologist (VC). Images from eligible patients were acquired with a CBCT*. The imaging parameters were set at a width and depth of 16x13 mm, 120 kVp, 20.27 mAs, scan time 14.7 s, resolution 0.25 voxel and a field of view (FOV) that varied according to the scanned region. Defect morphology and severity (at four sites per implant) were determined using† by a previously calibrated examiner (MV). The examiner reached an intra-examiner Cohen kappa index of > 85% after analyzing 10% of the sample calculated *a priori* in the statistical power analysis. Peri-implantitis defects morphology was characterized in agreement with the principal investigator (AM).

Peri-implantitis bone morphological and severity classification

Characterization of the peri-implantitis defects was based on defect morphology (classes I-III) and severity (grades S-M-A), as proposed elsewhere.[21] Briefly, according to the morphology was classified as follows: class I: infraosseous defect (class Ia: buccal dehiscence, class Ib: 2-3 walls defect, class Ic: circumferential defect), class II: supracrestal/horizontal defect and class III: combined defect (class IIIa: buccal dehiscence + horizontal bone loss, class IIIb: 2-3 walls defect + horizontal bone loss, class IIIc: circumferential defect + horizontal bone loss. Regarding severity, implants were graded as: Slight (S): 3-4mm/<25% of the implant length, moderate (M): 4-

* i-CAT Model 17–19 system (Imaging Sciences International LLC, Hatfield, PA, USA)

† Osirix DICOM viewer (Pixmeo, CH-1233 Bernex, Switzerland)

5mm/≥25%-50% of the implant length and advanced (A): >6mm/>50% of the implant length.[21]

Statistical analysis

For the inferential analysis at patient level, the Kruskal-Wallis test was used to assess the homogeneity of distribution of the averages of the clinical and radiographic variables in the three independent groups defined by the maximum grade of SUP. At implant level, simple binary logistic regression models were estimated using generalized estimation equations (GEE) in order to explain the probability of SUP implants within patients exhibiting SUP based on patient demographic, clinical and radiographic variables. The models provided estimations of odds ratios (OR) from Wald's chi-statistic. Linear regression models were also estimated under the GEE approach. The same statistical method was used at site level. The Kruskal-Wallis test had to detect a power of 50% to identify differences in the distribution of a clinical variable in these groups of maximum SUP grade compatible with a large size, assuming a level of 95%. A logit regression model like the one described for the association between outcome SUP (yes/no) and a two-level factor reached a power of 86.7% in detecting OR=4 as significant in a sample of 96 totally independent implants, assuming a level of confidence of 95%. Due to the multi-level data design (several implants per patient), the statistical power had to be corrected, assuming a moderate intra-subject reciprocity (p = 0.5), obtaining a power of 56.9% under the aforementioned conditions.

Results

Demographic characteristics

A total of 111 eligible patients (72.1% females and 27.9% males; mean age 57.3 ±12.2 years) with 501 implants were assessed. The vast majority were non-smokers (88.3%). Most of the patients contributed with one or two implants, representing 40.5% of the total sample size. The mean number of implants per patient was 4.5±3.4.

Prevalence of suppuration

Fifty-seven patients ($n_{implants}$=334) were diagnosed with peri-implantitis according to the established case definition, while 54 ($n_{implants}$=167) were either healthy or presented mucositis. Of the former patients, 31 presented SUP, while 26 did not. Hence, the prevalence of SUP patients in the total sample was 27.92%. Among the peri-implantitis patients, the prevalence of SUP was found to be 54.38% ($n_{patients}$=31) at patient level and 28.74% ($n_{implants}$=96) at implant level. At patient level, 35.5% presented SUP grade 1, 38.7% grade 2 and 25.8% grade 3. Likewise, at implant level, 23% presented SUP grade 1, 28.1% grade 2 and 18.8% grade 3, while no SUP was present in 30.2% of the implants in patients with SUP (Figure 1). SUP was more often found at buccal sites (51%) and was less prevalent at mesio-lingual sites (16.7%) (Figure 2).

Association of suppuration grade to patient characteristics

The Kruskal-Wallis test found no patient-related variables to be significantly correlated to SUP grade. Nevertheless, a tendency towards significance was observed for Pql (p=0.06), PPD (p=0.13) and smoking (p=0.14) (Figure 3).

Association of suppuration to peri-implantitis characteristics

Defect morphology (class Ib) was associated to the presence of SUP (OR=6.59; p=0.004). Moreover, PPD proved significant (OR=1.63; p=0.024) on comparing SUP versus no SUP. Each additional 1 mm of PPD was associated with a 63% increase in the risk of SUP (OR=1.63; p=0.024). Likewise, MBL proved significant (OR=1.35; p=0.010) on comparing SUP versus no SUP (Table 1). Therefore, each additional 1 mm of MBL was associated with a 35% increase in the risk of SUP (Figure 4-5).

Association of suppuration grade to peri-implantitis characteristics

Defect morphology (p=0.02), PPD (p=0.003) and MBL (p=0.01) showed statistical significance with grade of SUP. In peri-implantitis exhibiting class Ib defect morphology, SUP increased the likelihood to be displayed 0.92 points out of 3. Any additional 1 mm in PPD represented an increased likelihood to display SUP of 0.29 points out of 3. Likewise, any additional increase of 1mm in MBL resulted in an increase of the odds to display SUP of 0.13 points out of 3.

Discussion

"*Ubi pus ibi incisum*" or "*ubi pus ibi evacua*" are Latin aphorisms used in the medical sciences in relation to the management of infectious processes that means "where there is pus, evacuate it".[22] The rationale is that the successful resolution of disorders exhibiting *liquor puris* depends on adequate drainage of the lesion. Peri-implantitis is regarded as a chronic inflammatory disease secondary to infection dominated by plasma cells, neutrophils and macrophages.[5] Thus, the manifestation of SUP through the peri-implant sulcus should not be an extraordinary finding in infected implants.

SUP was not identified in any healthy implant or exhibiting mucositis. This finding supports previous observations.[9, 12] In contrast, recent data suggested that SUP can be present in mucositis that display a higher pathogenicity of microbiome

compared to non-SUP mucositis implants.[23] Findings from the present study demonstrate that SUP is an indicator of peri-implantitis, since it correlates with clinical (PPD) and radiographic (MBL) features of the disease. In this regard, the different grades of SUP exhibited statistically significant associations to other indicators of disease severity, such as PPD and MBL. Hence, the proposed grading index seems suitable to distinguish advanced peri-implant MBL and deep PPD associated with peri-implantitis. As such, implants displaying spontaneous SUP (grade 3) through the peri-implant sulcus are generally associated with more supporting bone loss as consequence of peri-implantitis compared to scenarios where the stimulus of peri-implant probing is associated with SUP (grade 1 – grade 2). Along these lines, it is worth mentioning that the features defining the grading system applied were adopted from previous bleeding/mucosal indices/classifications.[10, 19, 20]

Few studies have addressed the prevalence of suppuration.[8-10, 12] From a historical perspective, Fransson et al. showed SUP to occur in 19% of peri-implantitis implants, versus in only 5% of implants with stable bone levels.[8] Hence, SUP was seen to be an indicator of progressive MBL (OR=2.3; p=0.002). Moreover, concurring with our findings, Fransson et al. showed that smokers are significantly more prone to exhibit SUP ($p<0.05$).[8] More recently, Ramanauskaite et al. identified SUP in 17.39% all implants among 30.16% of their peri-implantitis patients.[9] In this sense, our prevalence of SUP in peri-implantitis patients was significantly higher compared to the two aforementioned studies.[8, 9] One potential explanation for the uneven distribution of SUP might be the different case definition of peri-implantitis adopted. While peri-implantitis was previously defined as progressive bone loss[8] and ≥2mm of MBL[9] together with soft tissue inflammation, respectively, data from the present study was assessed in accordance to the case definition proposed the 2017 World Workshop on the classification of periodontal and peri-Implant diseases and conditions for

scenarios without baseline records.[16] In this sense, the vast majority peri-implantitis cases included in the present study (61.4%) presented >6mm of MBL. Moreover, their analyses were based on data retrieved from Northern European University settings, while the present study was performed in private practice in the Southwest of Spain. Hence, these numerical differences may be explained by multifactorial cultural/social discrepancies between the different cohorts analyzed such as the distinct levels of oral hygiene education and habits.[24] Moreover, French et al. in turn found that in implants with over 8 years in function, SUP was present in 5.3% and 6.5% of the cases at implant and patient level, respectively. In fact, it was estimated the event of suppuration significantly increased in scenarios of peri-implant bone loss over 8.5 years.[10] Recently, Ravidà et al. showed that in patients with peri-implantitis, SUP was present in 84.6% of the implants with < 2 mm of KM, versus in 59.5% of the implants with > 2 mm of KM.[25] Findings from our study are consistent with those of the aforementioned article, since the prevalence of SUP in our patients with peri-implantitis was 54.3%. The high prevalence of peri-implantitis and SUP in the present study may be due to the fact that our investigation involved consecutive patients in a private practice of reference with expertise in the management of peri-implant diseases. In this context, the mean PPD in the current study and in that published by Ravidà et al. in relation to SUP implants was approximately 6 mm, while other studies have found the mean PPD to be <5 mm in implants exhibiting progressive MBL.[9, 10] This can further explain the higher frequency of SUP found in the present study.

Peri-implantitis is regarded as a chronic inflammatory disease caused by pathogenic bacteria.[16] In fact, the severity of human peri-implantitis lesions correlates with the level of submucosal microbial dysbiosis.[26] In this context, it is known that in periodontitis, SUP results from the generation of chemotaxins by bacteria and the accumulation of neutrophils and macrophages that undergo autolysis mediated by

their own lysosomal enzymes.[27] In addition, recent findings have demonstrated that SUP implants are significantly associated with a distinct microbiome compared to non-SUP implants.[23] As such, mucositis sites exhibiting SUP are characterized by more pathogenic bacteria with a proteolytic metabolism such as *Fusobacterium* and *Tannerella*.[23] It was further shown that SUP sites presented with higher relative abundance of *Peptostreptococcaceae*.[23] This symbiotic family of bacteria has been associated to abscesses and necrotizing soft tissue infections in humans.[28] Moreover, the generation of antibodies by the humoral immune system contributes to phagocyte bacteria and confront the infectious process, thereby facilitating the resolution of SUP.[29] Nevertheless, in advances forms of peri-implantitis the inflammatory process persists due to the features of the microflora.[26, 30] Indeed, Fretwurst et al. has recently shown peri-implantitis lesions to have increased numbers of macrophages displaying a distinct macrophage M1 polarization signature compared to periodontitis lesions.[31] Considering that M1 macrophages express high levels of proinflammatory cytokines as compared to M2 macrophages, it is conceivable that in established and advanced lesions there is a failure to return to homeostasis.[32] This could explain the correlation of SUP and its grade with PPD and MBL found in our study.

Findings from the present study must be interpreted with cautiousness in light of shortcomings inherent to the study design. Further, it must be noted that the clinical examinations were recorded by one examiner, which could lead to bias. Moreover, the present study was carried out in a specialty practice of regional reference with expertise in the management of peri-implant diseases. This is critical to understand the higher prevalence and severity of peri-implantitis patients and the frequency of SUP compared to other cohorts reported elsewhere in Spanish population.[33] In addition, it is important to note that the proposed grading system for SUP is

subjected to variations such as probing force or probing direction. Therefore, it is the authors´ though that future studies should be larger sample size to assess SUP under calibrated conditions using the Florida probe applying 17 grams.[10] It is further encouraged to be addressed in the future the significance of SUP on the prognosis of dental implants.

Conclusions

The presence and grade of suppuration are associated with peri-implant bone loss, probing pocket depth and defect morphology in peri-implantitis patients.

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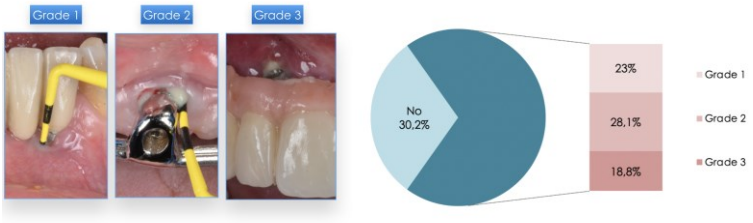

Figure 1. Presence and grades of suppuration in patients exhibiting suppuration.

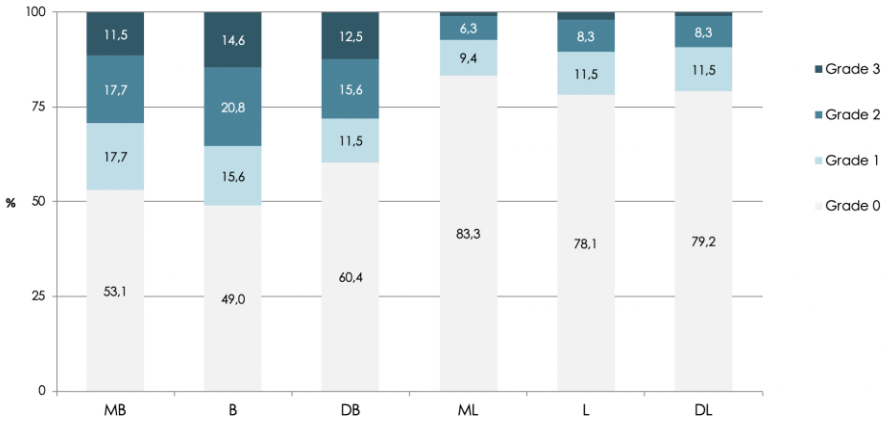

Figure 2. Presence and grade of suppuration per measured site.

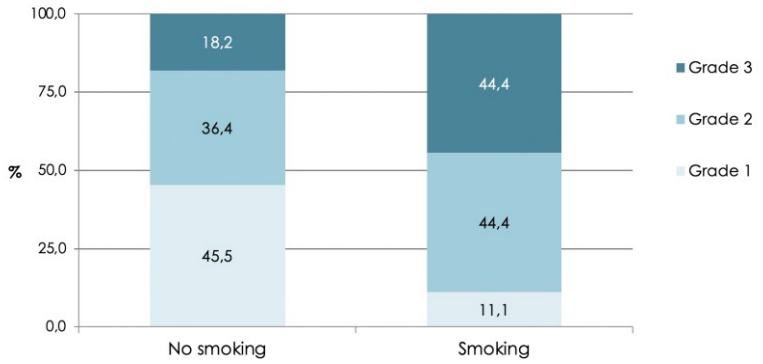

Figure 3. Grades of suppuration according to smoking habit.

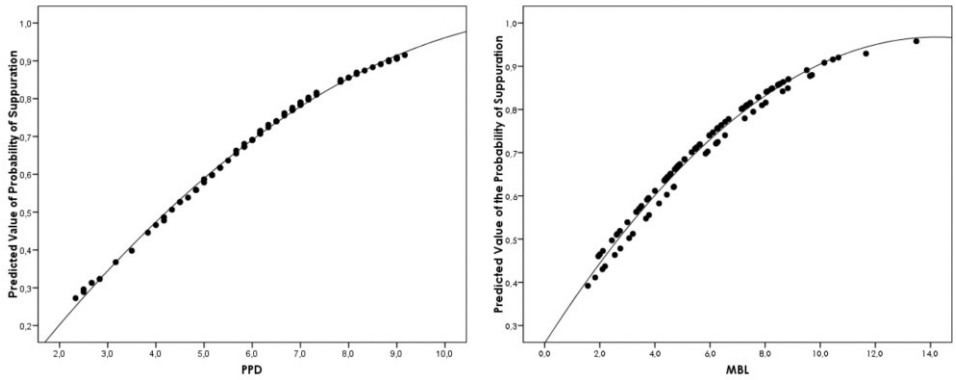

Figure 4. Plots showing the association between suppuration and probing pocket depth (A) and marginal bone loss (B).

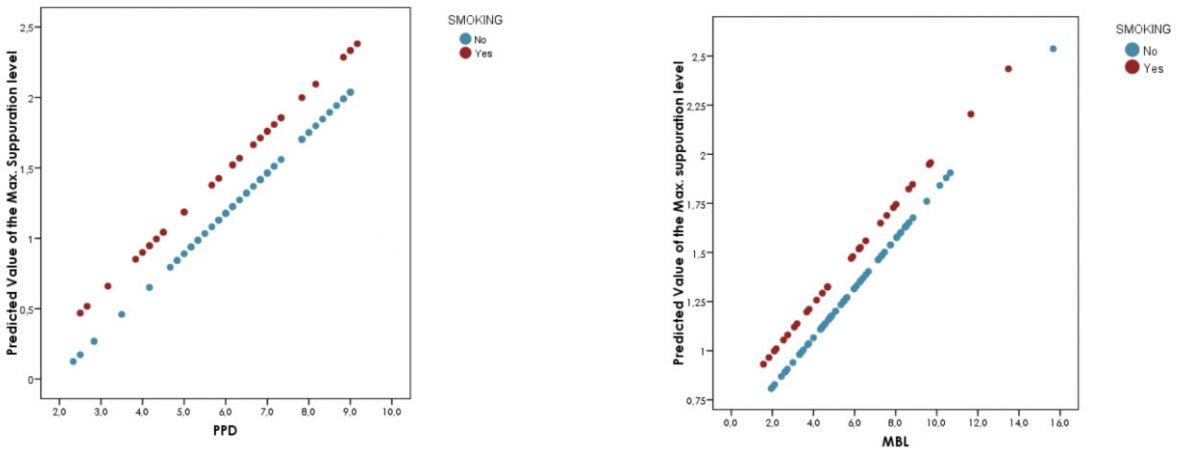

Figure 5. Association between grade of suppuration and (A) probing pocket depth and (B) marginal bone loss among smokers and non-smokers.

Table 1. Association between suppuration and the clinical and radiographic parameters at implant level of patients presenting suppuration (GEE model adjusted for smoking).

	Suppuration		OR	95%CI	p-value
	No	**Yes**			
n (implants)	29	67			
Position					**0.800**
Ma	2 (6.9)	5 (7.5)	1		
Mp	13 (44.8)	37 (55.2)	1.07	0.14-8.02	**0.946**
ma	4 (13.8)	6 (9.0)	0.60	0.06-6.07	**0.668**
mp	10 (34.5)	19 (28.4)	0.68	0.08-5.87	**0.729**
Accessibility					
No	14 (48.3)	44 (65.7)	1		
Yes	15 (51.7)	23 (34.3)	0.49	0.18-1.30	**0.151**
Type of prosthesis					**0.659**
FD	21 (72.4)	51 (76.1)	1		
R	6 (20.7)	9 (13.4)	0.63	0.19-2.14	**0.459**
SC	2 (6.9)	7 (10.4)	1.40	0.31-6.37	**0.660**
Defect morphology					**0.034***
Ia	3 (10.3)	2 (3.0)	1		
Ib	6 (20.7)	26 (38.8)	6.59	1.86-23.4	**0.004****
2	11 (37.9)	16 (23.9)	2.22	0.60-8.18	**0.233**
IIIb	9 (31.0)	19 (28.4)	3.28	0.89-12.1	**0.075**
Others (Ic, Ib, IIc)	0 (0.0)	4 (6.0)	--	--	**--**
PPD (mm)	5.36 ± 1.82	6.70 ± 1.55	1.63	1.07-2.48	**0.024***
mSBI	1.17 ± 1.02	1.41 ± 0.78	1.38	0.67-2.85	**0.387**
MR (mm)	0.83 ± 1.26	0.68 ± 1.10	0.87	0.58-1.29	**0.486**
PqI	1.32 ± 0.88	1.21 ± 0.77	0.86	0.42-1.75	**0.673**
KM (mm)	1.85 ± 2.13	2.31 ± 2.02	1.12	0.87-1.43	**0.381**
MBL (mm)	4.68 ± 2.10	6.37 ± 2.72	1.35	1.08-1.69	**0.010***
Severity					**0.069**

Slight	7 (24.1)	10 (14.9)	1		
Moderate	10 (34.5)	10 (14.9)	0.67	0.12-3.66	**0.646**
Advanced	**12 (41.4)**	**47 (70.1)**	**2.68**	**0.69-10.4**	**0.154**

*p<0.05; **p<0.01; ***p<0.001