

Diagnostic Accuracy of Clinical Parameters to Monitor Peri-Implant Conditions: A Matched Case-Control Study

Alberto Monje, DDS, MS^{*†¶}, Jordi Caballé-Serrano DDS, MS, PhD[§], Jose Nart, DDS, PhD[‡], David Peñarrocha, DDS, MS, PhD[¶], Hom-Lay Wang, DDS, MS, PhD^{*}, Mia Rakic, DDS, PhD[¶],

* Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA

† Department of Oral Surgery and Stomatology, ZMK School of Dentistry, Bern, CH

¶ Department of Periodontology, Universitat Internacional de Catalunya, Barcelona, Spain

§ Department of Oral and Maxillofacial Surgery, Universitat Internacional de Catalunya, Barcelona, Spain

¶ Department of Oral Surgery, Universitat de Valencia, Valencia, Spain

‡ INSERM UMR-1229 RMeS, Faculty of Dental Surgery, University of Nantes, Nantes, France.
Institute for Biological Research “Sinisa Stankovic,” University of Belgrade, Belgrade, Serbia

Corresponding author:

Alberto Monje, DDS, MS

Department of Periodontics and Oral Medicine

School of Dentistry, University of Michigan, Ann Arbor, MI, USA

1011 North University Avenue

Ann Arbor, Michigan, 48109-1078, USA

TEL: (734) 763-3383; FAX: (734) 936-0374

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E-mail: amonjec@umich.com

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One sentence summary: The combination of the clinical findings could accurately lead to the diagnosis of peri-implant diseases

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Abstract

Background: The aim of this case-control study was to estimate the diagnostic accuracy of the standard clinical parameters in diagnosing healthy peri-implant tissues, peri-implant mucositis, and peri-implantitis.

Methods: A case-control study was designed to compare the clinical parameters used in the diagnosis of peri-implant diseases such as: probing pocket depth (PPD), bleeding on probing (BOP), mucosal redness (MR), suppuration (SUP), and plaque index (PI). Furthermore, the influence of patient- (gender, age) and implant-related variables (implant neck configuration, time in function after loading) were evaluated to investigate the association with the clinical findings. The inferential analysis consisted of estimation by generalized estimating equations (GEE) of multilevel logistic regression models.

Results: In total, 1572 sites were evaluated around 262 implants from 141 patients. Sites with implant mucositis showed significant levels of BOP (OR=3.56), MR (OR=7.66) and PPD (OR=1.48) compared to healthy sites. The specificity was 90.3% while the sensitivity was only 43.6%. Likewise, Sites exhibiting peri-implantitis showed significant levels of BOP (OR=2.32), MR (OR=7.21), PPD (OR=2.43) and SUP (OR=6.81) compared to healthy sites. Again, the multiple logistic regressions showed high specificity (92.1%) but modest sensitivity (52.5%). PPD was the only diagnostic marker displaying significance comparing peri-implant mucositis and peri-implantitis sites (OR=1.76).

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Moreover, tissue-level compared to bone-level implants were less associated with SUP+ (OR=0.20), and PI (OR=0.36) and demonstrated statistical significance. In addition, age, gender and function time significantly influenced the tested clinical parameters.

Conclusion: The diagnosis of peri-implant diseases cannot rely solely upon individual clinical parameters but rather require a combination of criteria. The clinical parameters, particularly probing pocket depth, might accurately discern between diagnoses among peri-implant conditions. Nevertheless, the specificity of the clinical parameters surpasses the sensitivity in the detection of peri-implant diseases, validating its potential use as a diagnostic tool (NCT 03031392).

Introduction

Peri-implant diseases is becoming a more common condition, reaching a frequency of 30-40% determined at the implant-level.¹ Such a condition was first described in 1965 as soft tissue inflammation and concomitant bone destruction.² Later, as the fields of implantology and microbiology advanced, peri-implantitis was described as an imbalance in the bacterial load and host response.³ Subsequently, mucositis was paralleled with gingivitis and peri-implantitis to chronic periodontitis, and certain putative bacteria were capable of inducing the observed inflammatory response. Hence, mucositis and peri-implantitis were considered pathological counterparts of gingivitis and periodontitis on implants,⁴ while the keystone periopathogens were considered responsible for induction of the local immunological dysbiosis.⁵ However, recent research revealed that periodontal and peri-implant pathologies express different pathological characteristics since peri-implant lesions demonstrated more aggressive behavior and follow a progressive course⁶ In parallel, it was shown that treatment protocols adopted from periodontology provided unpredictable outcomes on implants with high recurrence rates.⁷ Hence, peri-implant diseases were defined as important pathological entities due to the increasing prevalence and lack of a standard treatment protocol.^{8,9}

Moreover, the high rate of inconsistency among case definitions was identified as an initial problem; thus, the *European Federation of Periodontology* (EFP) along with the *American Academy of Periodontology* (AAP) held a series of consensus meetings to define peri-implant diseases based on clinical and radiographic features.¹⁰⁻¹³ Hence, it was emphasized that there was a need for standardization of implant clinical parameters in order to provide accurate diagnostic values.¹⁰ As

such, it was agreed that the hemostatic biologic bone remodeling triggers up to a maximum acceptable threshold of 2mm bone loss.¹⁰⁻¹³ Pathologic bone loss was defined as progressive bone loss beyond this extent caused by biofilm-induced inflammatory conditions.¹⁰

It is important to acknowledge that peri-implant tissues histologically depict different anatomical structures when compared to the periodontium due to lack of two periodontal tissues, which compromises homeostatic potential to abrogate infective and biomechanical threats. While evolution has created a tight attachment to dentition surface via the long-junctional epithelium in the periodontium, peri-implant tissues are primarily supported with loose and parallel-oriented fibers, providing a compromised coronal seal.¹⁴ As such, the low diagnostic accuracy and sensitivity of probing pocket depth does not seem to accurately reflect disease/healthy condition per se when compared to natural dentition.^{15, 16} Moreover, the lack of standardization in dental implant macro- and micro-design leads to difficulty in reaching reproducible diagnostic tools.¹⁰ Nevertheless, probing pocket depth might still be a good diagnostic indicator but it is often suggested to combine the radiographic finding for the final diagnosis.^{10, 17}

Bleeding on probing is reported to have a high specificity and reasonable sensitivity to detect periodontitis.¹⁸⁻²⁰ Again, understanding the weak hemidesmosome attachment to the implant surface is imperative to discern appropriate probe penetration and bleeding. In the presence of inflammation, bleeding should be present indicating high sensitivity when probing deeper sites;²¹ however, the lack thereof in healthy condition does not seem to translate with high specificity.²² In this regard, it is noteworthy to mention that the mucogingival shift after implant placement often decreases the presence of keratinized mucosa, triggering a greater inflammatory status on the peri-implant tissues.²³ Thereupon, bleeding on probing, although it might reliably indicate presence of disease, does not seem to be a suitable single diagnostic parameter for peri-implantitis. On the other side, suppuration is caused by necrosis of peri-implant tissues, rich in polymorphonuclear cells. Thus, suppuration is logically and statistically a sensitive indicator of bone turnover.²⁴ In this scenario, it must be noted that, if detected in early stages where bone resorption has not occurred yet, it might be a consequence of a foreign body reaction (i.e., residual cement or dental floss remnants) or biofilm.^{25, 26}

Therefore, although the use of clinical parameters with radiological proof of bone changes represents a “gold standard”, the diagnostic value of clinical parameters of implants is still controversially reported and not well defined.¹⁰ Standardization of the diagnostic parameter implies well defined methodological approach intended to estimate the accuracy, precision, sensitivity and specificity of the parameter to distinguish different states of the target tissue or organ. The main pre-condition for reliable estimates is the use of a strict case definition and related criteria as well as use of appropriate analytical methods for data analysis. To the best of our knowledge, this is the first study to estimate diagnostic accuracy of the clinical parameters on implants using multiple analytical methods indicated for validation of diagnostic parameters. It is of the authors’ hypothesis that assessment of multiple clinical parameters will provide more accurate diagnostic information than independent parameters in evaluation of peri-implant tissues. Hence, the aim of this case-control study was to estimate the diagnostic accuracy of the standard clinical parameters to diagnose healthy peri-implant tissues, peri-implant mucositis, and peri-implantitis.

Material and methods

The present case-control study was conducted in accordance with the Helsinki declaration of human studies and received approval from the ethics committee from the University of Extremadura (Badajoz, Spain; approval # 18002909) as monitoring center. Moreover, this study was registered and approved by www.clinicaltrials.gov (NCT 03031392). The current study was reported according to the EQUATOR guidelines and followed the STARD statement on diagnostic accuracy.²⁷

Study population

All participants enrolled had to be consecutively evaluated in the routine peri-implant maintenance therapy with dental implants in function with fixed prosthesis for a minimum of 12 months after final prosthesis delivery from July 2016 up to April 2017. Patients were contacted and informed to participate in a cross-sectional assessment to identify the presence of peri-implant diseases or the evaluation was carried out during supportive periodontal/peri-implant therapy. Baseline periapical x-ray at the time of prosthesis delivery was retrospectively assessed to exclude implants with excessive early peri-implant bone loss before function that might lead to misdiagnosis (i.e., ≥ 2 mm from implant-abutment connection). If no baseline x-ray was available, the implant was automatically

excluded from the analysis. Two independent examiners conducted the clinical assessment. In order to compensate the possible variability of the data prior to the analysis, the Chi² test was applied to check for homogeneity. Additionally, to check the homogeneity of the variables provided by the examiners, the Kruskal-Wallis statistical method was applied.

A matched case-control study was conducted on 141 implant patients (62.4% males and 37.6% females with a mean age of 57.6±10.2 | range=23-79 years). Of these patients, 47 patients had implants with mucositis, 47 patients with peri-implantitis and remaining 47 patients with healthy implants. These made an overall of 262 implants where 90 were healthy, 76 with mucositis and 96 with peri-implantitis. In total, 1572 sites were evaluated. Table 1 presents the demographic data at patient-, implant- and site-specific levels.

Eligibility criteria

The following inclusion criteria were applied: patients within the age range of 18 to 80, non- or light-smokers (<10 cigarettes/day), no presence of infectious diseases at the time of implant placement or during the maintenance program, implants placed in pristine bone, no presence of systemic disease or condition or medication known to alter bone metabolism (i.e. bisphosphonates), partial edentulous patients without sign of active periodontal disease with or without history of chronic periodontitis. On the contrary, individuals were excluded for the following reasons: pregnancy, lactation, history of or current heavy smoking (≥10 cig/day), uncontrolled medical conditions such as diabetes mellitus, not adequate 3-dimensional implant position, implants placed in sites known to have received grafting procedures to augment the edentulous ridges, cement-retained restorations, not properly restored (i.e., overcontoured) impeding accurate probing depth recording or lack/minimal of keratinized mucosa.

Case definition of peri-implant mucositis

As suggested by the AAP academy statement¹¹ and the VIII EFP Workshop¹⁰ peri-implant mucositis was defined as an inflammatory condition that courses with swelling (tumor) and bleeding in the lack of radiographic peri-implant marginal bone loss beyond initial physiological bone remodeling. As such, implants with no bleeding, or only bleeding on probing at one surface assuming a point of bleeding as a consequence of trauma from probing, no suppuration, and bone loss <2.0 mm were

considered healthy. On the other side, overt bleeding (≥ 2 sites), tissue edema with minimal isolated or no suppuration and radiographic marginal bone loss $< 2\text{mm}$ was defined as mucositis.²⁸

Case definition of peri-implantitis

Definition peri-implantitis based was based upon clinical inflammation combined with radiographic bone loss. Accordingly, the presence of clinical inflammation in combination with radiographic bone loss $> 2\text{mm}$ as earlier proposed in the VIII *EFP* Workshop¹⁰ The landmark used to evaluate the peri-implant bone level was the neck in the case of rough full-bodied implants, or the rough-to-smooth interface in case of tissue level implants. As such, signs as presence of suppuration, bleeding on probing, mucosal redness, and probing depth were recorded at 6 sites per implant applying 0.15N/cm force as suggested by the *AAP* academy statement.¹¹

Alternative case definitions of peri-implantitis

Besides of the case definition proposed in the VIII *EFP* Workshop,¹⁰ alternative case definitions as proposed elsewhere²⁹ were further applied to assess the diagnostic accuracy. As such, peri-implant marginal bone loss of $\geq 0.5\text{mm}$, $\geq 1\text{mm}$, $\geq 3\text{mm}$ and $\geq 4\text{mm}$ in the presence of clinical inflammation were thresholds to study on the different case definitions for peri-implantitis.

Radiographic assessment

One calibrated (AM) examiner conducted the radiographic assessment. The peri-implant radiographic bone loss (RBL) was determined by taking linear measurements from the most mesial and distal point of the implant platform to the crestal bone on each peri-apical radiograph, corrected according to the known height and width of each implant using ImageJ (National Institute of Health). Moreover, a baseline x-ray (after prosthesis delivery) was obtained from the records to measure the initial physiological marginal bone loss to determine the progressed bone loss as consequence of an inflammatory condition (i.e. peri-implantitis).

Clinical assessment

The following clinical parameters were recorded: probing pocket depth (PPD), plaque index (PI), bleeding on probing (BOP), mucosal redness (MR) and suppuration (SUP). All these aforementioned

parameters were recorded at 6 sites per implant. In addition, the implant's neck design was subdivided in tissue-level or bone-level according to implant's manufacturer description to further investigate the impact of these on the peri-implant disease-related parameters.

Statistic analysis

The statistical package SPSS 15.0 was used to analyze the data. The three diagnosed groups were compared in pairs, aiming to identify the factors related to patient, implant and clinical parameters in the site able to distinguish between groups. The inferential analysis consisted of estimation by generalized estimating equations (GEE) of multilevel logistic regression models. Three levels of analyses were taken into consideration: patient, implant and site. The impact or degree of association between a predictive factor and the implant diagnose were estimated as odds ratio (OR) and confidence interval of 95% using a Chi² of Wald statistical test. The exactitude of the outcomes studied was evaluated by means of tables of classification of forecasts against real diagnoses. The statistical significance used in the analysis was set to 5% ($\alpha=0.05$).

A logistic model was described for the association between the outcome and an independent factor of 2 levels to reach a power of 80% to detect a significant OR of 2.0 within the sample, assuming a 95% confidence level. The power was calculated assuming an intra-class correlation (ICC) of 0.25 based on previous studies.^{20, 30, 31}

Results

Diagnostic accuracy of peri-implant mucositis-related parameters vs. health

The following parameters demonstrated significance:

- BOP: A site presenting as BOP+ significantly increased its diagnosis as mucositis (OR=3.56; $p<0.001$). The multiple logistic regression further demonstrated significance (OR=2.13; $p=0.013$).
- MR: A site presenting as MR+ significantly increased its diagnosis of mucositis (OR=7.66; $p<0.001$). The multiple logistic regression further demonstrated significance (OR=4.61; $p=0.001$).

- PPD: The mean PPD for healthy implants was 2.63±1.21mm and for mucositis was 3.26±1.57mm. For each 1mm of increased PPD, it significantly increased its diagnosis of mucositis by 48% (OR=1.48; p<0.001). The multiple logistic regression further demonstrated every 1mm increase of PPD (OR=1.39; p=0.001) was associated with a 39% greater likelihood of mucositis.

Accordingly, the following equation summarizes the findings to accurately diagnose peri-implant mucositis when compared to healthy sites based on the clinical parameters (Figure 1):

$$\frac{p}{1-p} = 0.12 \cdot 2.13^{BOP} \cdot 4.61^{MR} \cdot 1.39^{PD}$$

Therefore, 90.3% of the sites could be accurately diagnosed as healthy, showing high specificity, while only 43.6% could accurately diagnose mucositis, demonstrating low sensitivity. The positive and negative predictive values were 71.2% and 74.4%, respectively. As such, in total, 73.7% implants were accurately diagnosed using this diagnostic formula. The area under curve (AUC) of the ROC curve (Figure 2) associated to logistic model was 0.77 (95%CI: 0.74-0.89).

Diagnostic accuracy of peri-implantitis-related parameters vs. health

The following parameters demonstrated significance:

- BOP: A site presenting BOP+ significantly increased its diagnosis of peri-implantitis (OR=2.32; p=0.003). However, with adjustment via the multiple logistic regression model, no significance was observed.
- MR: A site presenting MR+ significantly increased its diagnosis of peri-implantitis (OR=7.21; p<0.001). The multiple logistic regression model further demonstrated significance (OR=3.28; p=0.003).
- PPD: The mean PPD for healthy implants was 2.63±1.21mm and for peri-implantitis was 4.58±1.71mm. For each 1mm of increased PPD, it significantly increased its diagnosis of peri-implantitis (OR=2.43; p<0.001). The multiple logistic regression model further

demonstrated significance for every 1mm increase of PPD (OR=2.03; p<0.001) a 200% greater the odds of peri-implantitis.

- SUP: A site presenting SUP+ significantly increased its diagnosis of peri-implantitis (OR=6.81; p<0.001). However, the multiple logistic regressions model did not display significance.

Moreover, PI was observed to play a dominant role in the peri-implantitis status, as PI was significantly higher at sites diagnosed with peri-implantitis (OR=2.32; p=0.003). Although not reaching statistical significance, the logistic regression model did verify its importance (OR=1.7; p=0.096)

Accordingly, the following equation summarizes the findings to accurately diagnose peri-implantitis when compared to healthy sites based on the described clinical parameters (Figure 3):

Applying the equation in Figure 3, the sensitivity to diagnose peri-implantitis was 52.5% with a specificity of 92.1%. The positive and negative predictive values were 72.7% and 82.8% respectively. As such, in total, 82.8% implants were accurately diagnosed using this model system. The area under curve (AUC) of the ROC curve (Figure 4) was 0.81 (95%CI: 0.78-0.84).

$$\frac{p}{1-p} = 0.023 \cdot 1.70^{PI} \cdot 3.28^{KM} \cdot 2.03^{PD}$$

Diagnostic accuracy of peri-implantitis-related parameters vs. mucositis

The following parameters demonstrated significance:

- PPD: For each 1mm of increased PPD, each site significantly increased its diagnosis of peri-implantitis (OR=1.76; p<0.001). The multiple logistic regression model demonstrated with statistical significance that every 1mm increase of PPD (OR=1.75; p<0.001) was associated with a 75% greater likelihood of peri-implantitis.

- SUP: Although statistical significance was not achieved, a site presenting SUP+ showed a positive trend associated with peri-implantitis compared to mucositis sites (OR=2.5; p=0.088).

Moreover, PI demonstrated to have a dominant role in peri-implantitis, as it was significantly more present in sites diagnosed with peri-implantitis (OR=3.46; p=0.001). Although not reaching statistical significance, the logistic regression model could verify its importance (OR=3.40; p=0.002)

Consequently, the following equation summarizes the findings to accurately diagnose peri-implantitis when compared to mucositis sites based on the clinical parameters:

Therefore, applying that equation, the sensitivity to diagnose peri-implantitis when compared to mucositis was 58.2% with a specificity of 81.3%. The positive and negative predictive values were 71.9% and 70.2%, respectively. The area under curve (AUC) of the ROC curve (see supplementary Figure 1 in online *Journal of Periodontology*) is 0.76 (95%CI: 0.72-0.79).

$$\frac{p}{1-p} = 0.060 \cdot 3.40^{PI} \cdot 1.75^{PD}$$

Association of implant's neck design and peri-implant disease-related parameters

Tissue-level compared to bone-level implants were less associated with SUP+ (OR=0.20; p=0.041), and PI (OR=0.36; p=0.002), representing a lower risk of 80% and 64% of being present in tissue-level implants, respectively. A linear regression was calculated for PPD and it was shown that tissue-level implants have an average reduction of 0.38mm compared to bone-level implants, showing a considerable trend towards significance (p=0.082). Conversely, neither BOP nor MR displayed significance (p=0.803 and p=0.554, respectively).

Association of patient-specific factors and function time

While neither gender nor age significantly influenced the odds of a health, mucositis or peri-implantitis diagnosis, the function time was associated on the diagnostic accuracy when health was compared to peri-implantitis (OR=2.44; $p<0.001$) and when mucositis was compared to peri-implantitis (OR=1.87; $p<0.001$).

In addition, the following parameters were statistically significantly associated to patient-specific factors:

- PI was associated solely with function time (OR=1.27; $p<0.001$)
- BOP+ was associated with gender (females OR=2.27; $p<0.001$) and age (each increased year of age OR=1.03; $p=0.010$)
- MR+ was associated with gender (females OR=2.17; $p=0.023$) and function time (OR=1.22; $p=0.002$)
- PPD+ was associated with gender and function time. As such, PPD in females was on average 0.69mm greater than in males ($p=0.001$) and each year in function was 0.22mm greater ($p<0.001$)
- SUP+ was associated only with gender (females OR=3.05; $p=0.006$)

Diagnostic accuracy for alternative peri-implantitis case definitions (Table 2)

- *RBL $\geq 0.5mm$* : To define peri-implantitis compared to health, BOP+ (OR=1.87; $p=0.040$), PPD (OR=1.99; $p<0.001$), MR+ (OR=4.67; $p=0.004$) and SUP+ (OR=4.68; $p=0.045$) demonstrated significance; and to define peri-implantitis compared to mucositis only PI (OR=1.94; $p=0.091$), and BOP+ (OR=1.04; $p=0.025$) reached significance.
- *RBL $\geq 1mm$* : To define peri-implantitis to health, BOP+ (OR=2.52; $p<0.001$), PPD (OR=2.04; $p<0.001$), MR+ (OR=45.28; $p<0.001$) and SUP+ (OR=3.89; $p=0.018$) demonstrated significance; and to define peri-implantitis compared to mucositis only PI (OR=2.62; $p=0.010$) reached significance.
- *RBL $\geq 3mm$* : To define peri-implantitis compared to health, PI (OR=2.27; $p=0.009$), BOP+ (OR=3.77; $p<0.001$), PPD (OR=2.92; $p<0.001$), MR+ (OR=6.01; $p<0.001$) and SUP+

(OR=5.45; p=0.010) demonstrated significance; and to define peri-implantitis compared to mucositis only PI (OR=2.44; p=0.017), and BOP+ (OR=1.71; p=0.001) reached significance.

- *RBL* $\geq 4\text{mm}$: To define peri-implantitis compared to health, BOP+ (OR=2.33; p=0.044), PPD (OR=3.03; p<0.001), and MR+ (OR=5.51; demonstrated significance; and to define peri-implantitis compared to mucositis only PPD (OR=1.33; p<0.024) reached significance.

Discussion

Peri-implant diseases are defined by inflammatory, clinical, and radiographic findings.¹³ While peri-implantitis was characterized as progressive bone pathology, according to the case definition, the clinical parameters have been a matter of discussion due to implication of a variety of biological and implant-related factors affecting their respective accuracy.^{1, 12, 32, 33} The present investigation estimated the diagnostic accuracy of the clinical parameters for diagnosis of peri-implant diseases using advanced analytical algorithms intended for validation and standardization of diagnostic parameters. Additionally, the study was carefully designed to constitute a representative study sample regarding qualitative and quantitative characteristics to ensure highly reliable outcomes. Our study agreed on the fact that the diagnosis of peri-implant conditions could be led by monitoring the clinical parameters, being PPD the most reliable prognostic indicator of disease progression followed by MR and BOP, particularly on the diagnosis of peri-implant mucositis compared to health. However, it is noteworthy that none of these parameters can be used alone for the diagnosis; rather a combination of them is required. While high specificity was presented in all the scenarios, sensitivity remained modest. Therefore, these findings are consistent with previous studies^{24, 34-37} suggesting that these clinical parameters must be cautiously interpreted for adequate diagnosis.

- Probing pocket depth (PPD)

The establishment of biological width around implants mandates the consistent PPD monitoring, which indicates a shift from a non-pathologic to pathologic status^{24, 36, 38, 39}. Indeed, the present study has shown that PPD significantly differs according to the peri-implant condition. Interestingly, it was demonstrated that these could vary based on the implant-neck design. An animal study found that healthy implants with a supra-crestal polished collar (i.e., tissue level) tends to have a roughly similar biological width to natural teeth in contrast with bone level implants⁴⁰. These findings can be explained, as there is an increase of laxity of the collagen fibers around the collar of the implant

restoration,^{22, 41} especially in the presence of inflammation.¹⁵ Other factors significantly influencing the PPD included patient gender and implant time in function. For example, PPD increased 0.22 mm every year the implant remained in function. This finding could be explained as ‘progressive bone loss’ increases over time in function and is supported by the previous study.¹ Also, greater the peri-implant bone loss was observed with more apical migration of the long junctional epithelium and connective tissue.¹⁷ Moreover, the increase of PPD, together with BOP+, was associated with the female gender, due to hormone fluctuation (i.e., estrogen).⁴²

- Bleeding on probing (BOP)

In the field of periodontology, the lack of BOP+ was proven to be a predictor for the periodontal tissue stability.^{19, 43} In contrast, Ericsson & Lindhe using beagle dogs reported that a deeper probe penetration with BOP+ does not necessarily reflect disease, as it was displayed around healthy implants as well.²² Interestingly, Lang et al. did not notice BOP+ around healthy implants, while it was significantly present in mucositis (67%) and peri-implantitis (91%) sites.¹⁷ Recent clinical studies seem to agree on the site-specific phenomenon positively correlated with PPD^{30, 44} and MBL.⁴⁵ For instance Merli et al. found the odds ratio of a site to be BOP+ by 1.81 for each 1mm increment in PPD.⁴⁴ Conversely, Fransson et al. showed that BOP+ occurred in more than 90% of implants with no progressive bone loss, indicating that such measurement cannot be used alone for the detection of peri-implantitis.²⁴ The multiple logistic regression conducted in the present study identified BOP+ to be sensitive in the diagnosis of peri-implant mucositis compared to healthy conditions (OR=2.13). Nevertheless, the generalized estimating equations indicated that BOP+ is significantly associated with peri-implantitis compared to health (OR=2.32).

Moreover, the present study is consistent with previous findings in regard to the manifestation of BOP+ in females.³⁰ Thus, there is speculation that the transient increase of gingival inflammation owing to hormonal variations might mislead the periodontal and peri-implant conditions. Additionally, age also reached significance, agreeing then previous findings when probing natural teeth.³¹ This fact is reasonable as with age increases the intake of anticoagulant medications. In contrast, none of the other factors analyzed in the present study yielded significance.

- *Mucosal redness (MR)*

The phenomenon of inflammation presents as a biological response to extrinsic or intrinsic insult. The Roman physician Cornelius Celsus (ca. 30 BC–38 AD) described four cardinal signs including *rubor*, *calor*, *tumor* and *dolor*.⁴⁶ *Rubor* (redness) is increased in the tissues as a result of the vasodilation during the onset and process of inflammation. The cause-effect relationship of plaque accumulation on soft tissue condition was demonstrated around natural dentition⁴⁷ and dental implants.⁴⁸ The present study found that MR is an accurate diagnostic tool to monitor the presence of pathology. Accordingly, when applied the multiple logistic regression, statistical significance was reached for the diagnosis of mucositis and peri-implantitis compared to health. Interestingly, a correlation between MR+ and female gender was observed. Unsurprisingly, this finding was concomitant with BOP+. Again, the hypothesis of the hormonal variations could explain this observation. These findings should be interpreted with caution as the patients evaluated presented with an adequate band of keratinized mucosa ($\geq 2\text{mm}$), which could positively impact on the gingival index.²³

- *Suppuration (SUP)*

Suppuration is defined as a pus formation followed by discharge within a natural aperture or fistula. Pus qualitatively represent the turbid viscous inflammatory exudate consisting of dead leukocytes, living or dead microorganisms, necrotic tissues, and protein-rich fluid called *liquor puris* rich in pro-inflammatory mediators and bacterial toxins. These components represent byproducts of the host reaction directed towards to persistent pathological irritants (e.g., infection or foreign body). Therefore, SUP is accepted as a highly specific clinical parameter of peri-implant inflammation since it reflects ongoing inflammatory processes in the tissues.³ For that reason, SUP was initially associated with the progressive forms of periodontal disease and recently has been proposed as an indicator for progressive bone loss on implants.^{24,34} In this regard, low predictability rate of SUP+ in peri-implant mucositis together with inversely high predictability in peri-implantitis confirms the SUP as an accurate clinical endpoint to disclose peri-implant bone loss³⁴. In agreement with those findings, the estimated predictability of SUP+ was compatible at both implant (OR=1.47) and site level (OR=6.81), thus supporting the accuracy of this parameter for dental implant diseases monitoring. Nevertheless, it is worth mentioning, that SUP did not reach significance for the logistic regression model, as it might have been masked by other more discriminative parameters (i.e. BOP or MR). Moreover, in line with findings related to other parameters investigated, SUP was more frequently associated with the female gender and bone level implants, as these had significantly

higher proportions of PI together with other signs of inflammation such as MR+ and BOP+. It is, therefore the authors' opinion that future research studies should aim to identify peri-implantitis patient clusters that discern SUP and related underlying factors.

Recommendations for future research

Peri-implant diseases represents a growing problem in the current field of dentistry due to increasing prevalence and lack of standard treatment protocols.⁹ Additionally, peri-implant diseases have a progressive and asymptomatic course. In that context, the reliable diagnostic protocol for the adequate monitoring of peri-implant tissues remains of essential importance. The results of the present study clearly demonstrate that the assessment of multiple clinical parameters provide more accurate diagnostic information simultaneously, suggesting the limitation of using isolated clinical parameters for the diagnosis of peri-implant diseases. When considering the results as a whole, investigation of the biological features of peri-implant tissues and better understanding of the underlying pathogenetical mechanisms will certainly contribute to improvement of the peri-implant diagnostics. This will continue to be a charge for future research. Furthermore, it seems that the personalized medicine approach proposed for multifactorial diseases and combines multiple clinical and biological markers might be a promising tool in monitoring peri-implant tissues.

Conclusion

The diagnosis of peri-implant diseases cannot rely on a single clinical parameter but rather requires a combination. This study showed that the clinical parameters, in particular probing pocket depth, might accurately discern between diagnoses among peri-implant conditions. Nevertheless, the specificity of the clinical parameters surpasses the sensitivity in the detection of peri-implant diseases. Therefore, progressive radiographic bone loss must be cautiously examined to reach the definitive diagnosis and avoid overtreatment.

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Table 1. Table of demographics at patient- implant- and site-levels

		Category	N	%	Mean ± SD	Total
Patient Level (N=141)	Group	Healthy	47	33.3		
		Mucositis	47	33.3		
		Peri-implantitis	47	33.3		
	Age (years)				57.6 ± 10.2	
	Gender	Men	88	62.4		
		Women	53	37.6		
	N. Implants				1.9 ± 1.3	262
	N. Healthy Implants				0.9 ± 1.2	127
	N. Mucositis Implants				0.5 ± 1.9	74
Num. Peri-implantitis Implants				0.4 ± 0.7	61	
Implant Level (N=262)	Group	Healthy	127	48.5		
		Mucositis	74	28.2		
		PI	61	23.3		
	Time in function (years)				3.17 ± 2.04	
	Position	MD ant.	26	9.9		
		MD post.	97	37.0		
		MX ant.	39	14.9		
		MX post.	100	38.2		
	System	NB	84	32.1		
		STR	67	25.6		
MG		52	19.8			

		BH	27	10.3		
		MIS	16	6.1		
		Other	16	6.1		
	Neck Design	BL	205	78.2		
		TL	57	21.8		
	Rx MBL (mm)				1.06 ± 1.42	
	N. Sites with plaque				2.14 ± 2.46	
	N. Sites with BOP				2.14 ± 2.28	
	PPD Average on Implants (mm)				3.26 ± 1.40	
	N. Sites with MR				1.40 ± 2.16	
N. Sites with SUP				0.61 ± 1.71		
Site Level (N=1572)	Plaque	Yes	560	64.4		
	BOP	Yes	1011	64.3		
	PPD (mm)				3.26 ± 1.57	
	MR	Yes	347	23.3		
	Suppuration	Yes	159	10.1		
MD= mandibular; MX= maxillary; ant=anterior; post=posterior; BL= bone level; TL= tissue level; Rx MBL=radiographic marginal bone loss; BH=Biohorizon (Birmingham, AL); MG=MozaGrau (Valadolid, Spain); NB=Nobel Biocare (Gothenburg, Sweden); STR=Straumann (Basel, Switzerland); MIS (Savion, Israel)						

Table 2. Diagnostic accuracy (%) of the decisive parameters according to the generalized estimating equations (GEE) of multilevel logistic regression on the alternative definitions of peri-implantitis based upon the different marginal bone loss (MBL) thresholds with signs of inflammation.

		Decisive parameters (GEE)	Diagnostic accuracy (%)		
			Site Level	S	SP
MBL ≥ 0.5 mm	Healthy vs. Mucositis	PPD	46.1	84.1	71.0
	Healthy vs. Peri-implantitis	PPD, MR	92.1	23.6	71.1
	Mucositis vs. Peri-implantitis	BOP, PI	100	0	81.2
MBL ≥ 1 mm	Healthy vs. Mucositis	PPD, MR, BOP	41.9	87.7	73.0
	Healthy vs. Peri-implantitis	PPD, MR	80.8	57.9	70.5

	Mucositis vs. Peri-implantitis	PI	100	0	72.2
MBL \geq 2 mm	Healthy vs. Mucositis	PPD, MR, BOP	43.6	90.3	73.7
	Healthy vs. Peri-implantitis	PPD, MR, PI	52.3	92.1	80.7
	Mucositis vs. Peri-implantitis	PPD, PI	58.2	81.3	70.9
MBL \geq 3 mm	Healthy vs. Mucositis	MR, BOP	41.4	91.5	72.2
	Healthy vs. Peri-implantitis	PPD, PI	43.8	96.4	87.3
	Mucositis vs. Peri-implantitis	PPD, PI	17.3	96.3	78.1
MBL \geq 4 mm	Healthy vs. Mucositis	PPD, MR, BOP	58.5	83.5	72.3
	Healthy vs. Peri-implantitis	PPD	14.1	98.3	90.6
	Mucositis vs. Peri-implantitis	PPD	0	100	88.9
S=sensitivity; SP=specificity					

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Figure 1. Graph of the predicted probability of peri-implant mucositis compared to healthy condition by different levels of significant predictors from generalized estimating equation (GEE) of multilevel logistic regression model.

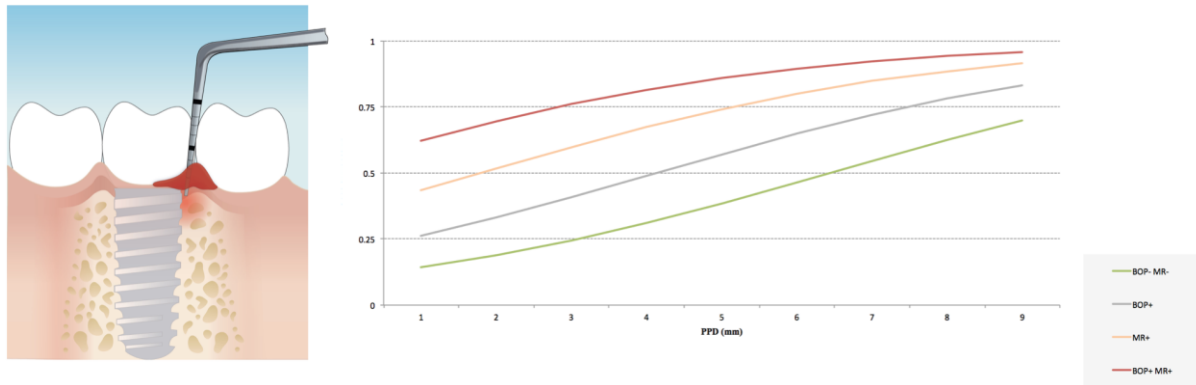


Figure 2. Receiving operating characteristics (ROC) curve graph on the sensitivity and specificity to detect peri-implant mucositis compared to health according to the generalized estimating equation (GEE)

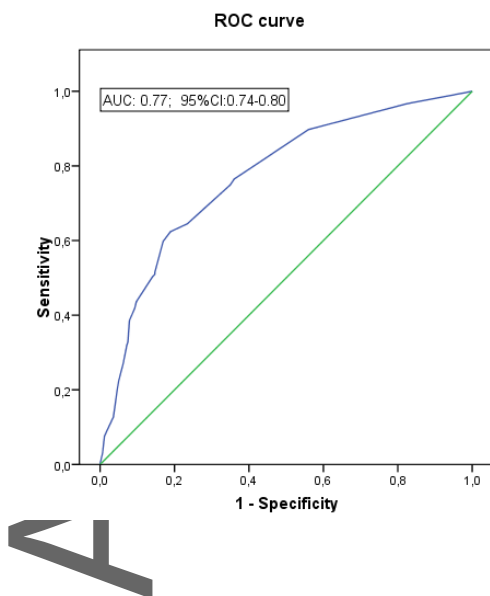


Figure 3. Graph of the predicted probability of peri-implantitis compared to healthy condition by different levels of significant predictors from generalized estimating equation (GEE) of multilevel logistic regression model.

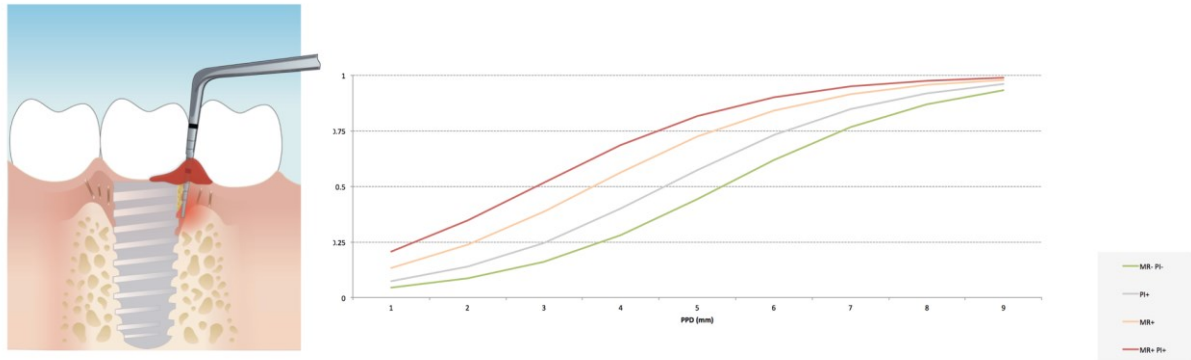
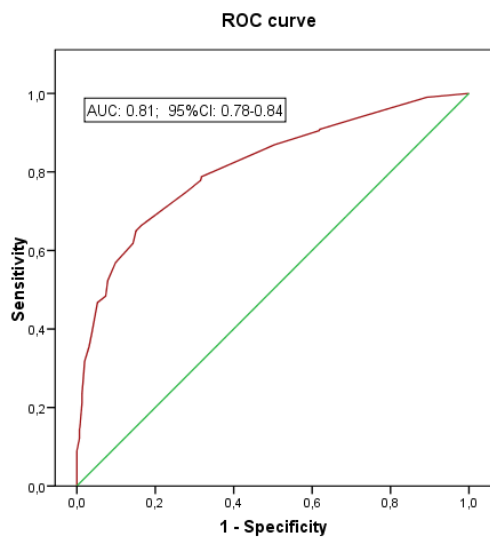


Figure 4. Receiving operating characteristics (ROC) on the sensitivity and specificity to detect peri-implantitis compared to health according to the generalized estimating equation (GEE)



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