The correlation between history of periodontitis according to staging and grading and the prevalence/severity of peri-implantitis in patients enrolled in maintenance therapy

Andrea Ravidà[1], Maria Vera Rodriguez[1], Muhammad H. A. Saleh[2], Matthew Galli[1], Musa Qazi[1], Giuseppe Troiano[3], Hom-Lay Wang[1], Pablo Galindo Moreno[4]

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

[2]*Department of Periodontics, University of Louisville School of Dentistry, Louisville, KY, USA*

[3]*Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy*

[4]*University of Granada, Oral Surgery and Implant Dentistry, Granada, Spain*

Corresponding authors:

Hom-Lay Wang, DDS, MS, PhD

Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry 1011 North University Avenue

Ann Arbor, Michigan 48109-1078, USA.

TEL: + 1 734 764-9148

FAX: (734) 936-0374

e-mail address: homlay@umich.edu

Abstract word count: 251

Total word count: 3781

Total number of tables and figures: 2 figures, 4 tables

Supplemental Material: 3 supplementary tables, 3 supplementary figures

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jper.10758.

Key Words: periodontitis, dental implants, periodontal diseases

Conflict of interest: The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

Abstract:

Background:

The aim of this study was to determine if a previous history of periodontitis according to the preset definitions of the 2017 World Workshop is correlated with increased implant failure, and occurrence and severity of peri-implantitis (PI).

Methods

A retrospective analysis of patients with a history of periodontitis who received nonsurgical and, if indicated, surgical corrective therapy prior to implant placement was performed. Periodontitis stage and grade were determined for each included patient based on data from the time of initiation of active periodontal therapy. Cox Proportional Hazard Frailty models were built to analyze the correlation between stage and grade of periodontitis at baseline with the implant failure, occurrence and severity of PI.

Results

99 patients with a history of periodontitis receiving 221 implants were followed for a mean duration of 10.6 ± 4.5 years after implant placement. Six implants (2.7%) failed and a higher rate of implant failure due to peri-implantitis was found for grade C patients ($p<0.05$), while only an increased trend was seen for stages III and IV compared to I and II. Grading significantly influenced the risk of marginal bone loss >25% of the implant length ($p=0.022$) in PI-affected implants. However, a direct correlation between higher-level stage and grade and PI prevalence was not recorded.

Conclusion

No statistically significant association between periodontitis stage or grade and the prevalence of PI was found. However, when PI was diagnosed, there was a relationship between periodontitis grade and severity of peri-implantitis or the occurrence of implant failure.

Introduction

Peri-implantitis (PI) is a highly prevalent and asymptomatic complex chronic inflammatory disease culminating in progressive loss of supporting bone around dental implants[1 2, 3]. The etiologies of both PI and periodontitis (PR) are believed to be microbially-mediated [4]. One of the principal articles of the recent 2017 World Workshop indicated that there is a strong level of evidence that patients with a previous history of PR, inadequate biofilm control, and a lack of regular maintenance care are at an increased risk for developing PI [1]. PI etiology, risk factors, and management are less well-understood compared to PR.

PR, much like PI, is a chronic inflammatory disease caused by a biologically destructive interaction between the host immunoinflammatory response and subgingival microbial biofilm which my lead to both oral (e.g tooth loss) and systemic sequelae [5-8]. Several studies included in a recent narrative review showed a greater risk (in between 2.2 and 19 times) of PI in patients with a history of treated PR [9]. A meta-analysis demonstrated that PR patients had a 2.3-fold greater risk of developing PI compared to periodontally healthy patients [10]. In addition, implants placed in patients with prior tooth loss due to PR were significantly more likely to develop PI and exhibited 0.5 mm more marginal bone loss (MBL) on average after 5 years [11]. Possible theories for a linkage between PR and PI include that PR patients might harbor more pathogenic bacterial species, a higher bacterial load, or an impaired host immune response[12].

Aoki and co-workers demonstrated that periodontal pathogens that reside in deeper pockets such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* can be transmitted from affected teeth to adjacent implants [13]. Pjetursson and co-workers also illustrated that PR patients with residual periodontal probing depths (PPD) ≥ 5 mm had a significant higher risk for the development of PI and implant loss [14]. Residual PPD ≥ 6 mm involving more than 10% of sites after treatment in severe periodontitis patients was shown to be a significant risk indicator for development of PI [15]. Daubert et al. (2015)[16] reported that severe PR was the strongest risk indicator for PI of all examined variables. In addition, Ong et al (2008)[17] found that PR patients had an overall higher percentage of biologic complications, including implant failures, than non-PR patients.

However, it should be noted that conflicting findings exist regarding the association of PR and subsequent development of PI, were an association with moderate and severe, but not mild,

periodontitis was found [18] [19, 20]. Different findings can possibly be attributed to the use of different case definitions in previous studies [9]. Adoptation of the 2017 World Workshop case definitions of PR and PI to investigate potential associations can lead to more accurate interstudy analyses and comparisons. Hence, the primary aim of this study was to determine if a previous history of periodontitis associated with higher-level stage (severity) and grade (rate of progression) increases the risk of implant failure or PI according to the 2017 World Workshop case definitions. Secondary aims were to investigate whether PR stage and grade have an influence on the severity of subsequent PI.

Materials and Methods

The present study was conducted in compliance with the Helsinki Declaration of 1975, as revised in 2013. The protocol of this study was approved by the University of Michigan, School of Dentistry, Institutional Review Board for Human Studies (HUM00157260).

Data was acquired from the physical and electronic charts of patients who received nonsurgical and, if indicated, surgical corrective therapy between January 1996 and January 2018 at the University of Michigan, School of Dentistry, Ann Arbor, MI, USA. Patients treated for periodontal disease (scaling and root planing (SRP) and/or surgical therapy) with a complete medical history, baseline periodontal charting, and full-mouth radiographs were included in the present study. All included patients were maintained after active periodontal therapy with at least one session of supportive periodontal therapy (SPT) per year at the University of Michigan, School of Dentistry. Furthermore, the following exclusion criteria were implemented: non-periodontal patients, patients receiving implant-related or periodontal care outside the School of Dentistry, periodontal patients that did not receive a dental implant or received an implant with a follow-up period of less than one year, and patients with incomplete or unclear data.

Staging and grading algorithms published by Tonetti and Sanz (2019)[21] were utilized to classify patient periodontal status. Determination of baseline periodontal staging and grading was conducted by a single investigator (MS) using clinical and radiographic data collected at the time of initial active periodontal therapy (T0) [22]. Data on pertinent patient characteristics, the number of SPT visits per year, and relevant medical history (history of diabetic status and self-reported smoking history at baseline) were collected. Radiographic bone loss (RBL, % of root length) at baseline was measured from periapical radiographs to assess PR stage and grade [23]. Tooth-specific data on clinical parameters including periodontal probing depth (PPD), clinical attachment level (CAL) calculated as the difference between PPD and the distance from the free gingival margin to the cemento-enamel junction, bleeding on probing (BOP), and furcation involvement were also recorded. Information about masticatory dysfunction, drifting, flaring, bite collapse, and plaque accumulation were retrieved from patient records where available. As part of the data collection process, additional information was gathered at the time of implant placement including: age, tobacco usage and diabetic history, the number of implants placed and their locations, implant characteristics (brand, length, diameter, soft tissue/bone level), mechanism of crown retention (screw or cement-retained),

number of follow-up visits and maintenance appointments, type of implant-abutment connection, as well timing of bone grafting (prior/during implant placement).

Survival Rate and PI Definition:

Based on the goal of conducting data analyses for both implant survival rates as well as PI prevalence/severity, two distinct follow-up periods were defined prior to data acquisition. These were (a) follow-up based on implant survival, and (b) follow-up based on the occurrence of PI. Follow-up based on implant survival was defined as the time occurring between implant placement and the last follow-up of the implant. At this date, each individual implant was classified as present or explanted [24]. Follow-up based on the occurrence of PI was defined as the duration of time between implant-supported prosthetic placement and the last radiograph in which peri-implant bone could clearly be visualized. The definition for PI proposed by the American Academy of Periodontology/European Federation of Periodontology 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions guidelines[25] was used to classify cases in a binary fashion as either positive or negative for PI (0 for peri-implant health, 1 for peri-implantitis). Since baseline data was available, peri-implantitis diagnosis was based on: 1) progressive bone loss beyond initial bone remodeling, 2) increased probing depth, and 3) presence of bleeding and/or suppuration on gentle probing.[25] The marginal bone level changes were radiographically examined by two authors (AR, MV) at the mesial and distal aspects of the affected implants using commercially available software (ImageJ, U. S. National Institutes of Health, Bethesda, MD, USA). If significant differences arose, a third reviewer (HLW) was included for reassessing the radiographs in a joint session and to give a final judgment. Interproximal marginal bone levels were radiographically calculated as a percentage of implant length, utilizing the most coronal bone-implant contact point to represent the marginal bone level, in order to classify implants based on the severity of bone loss (<25%; 25%–50%; or >50% of the implant length). For implants with a polished collar, the length was measured from the smooth-rough interface to the apex. For bone level implants, the platform level was used as the coronal demarcation point when evaluating implant length for calculation of radiographic peri-implant bone levels.

Statistical analysis

Descriptive statistics were employed for analysis of categorical (absolute and relative frequencies) and continuous (mean, standard deviation, range, and median) variables taking into account both implant failure events and PI diagnosis. At the implant-level, time-to-event 'implant failure' and time-to-event 'PI diagnosis' were analyzed using Kaplan-Meier survival methodology. Cumulative survival functions were plotted and compared between different patient profiles and clinical factors using a Log-rank test. In order to consider dependence between observations (implant-level data clustered by patients), univariate Cox regression frailty models were performed analyzing the influence of individual factors and covariates on failures and PI diagnosis. Hazard ratio estimations and corresponding 95% confidence intervals (CI) were obtained. Wald test was used to consider within-patient correlations. Then, multiple Cox regression frailty models were used to adjust for potential confounders. Schoenfeld's tests for proportional hazard and residual analysis were carried out to validate theoretical hypotheses.

For non-failed PI-afflicted implants, severity of bone loss (<25% or ≥25%) was related to stage and grade, adjusting by radiographic follow-up duration using logistic regression with generalized estimation equations (GEE). Odds ratios and 95% CIs were obtained using the Wald's Chi^2 statistic. The significance level for statistical analyses was set at 5% ($\alpha = 0.05$). Regarding the power analysis, a post-hoc estimation was obtained.

A sample size of 221 independent implants provided 96.5% power at 95% confidence to detect a relative risk (RR) of 3.0 as significant using a Cox multiple regression model to assess the influence of a two-level factor (e.g., maxillary or mandibular implant location), assuming that 80% of observations were censored (the proportion of no PI diagnosis was roughly 80%). In the power calculation, correction was performed to account for the two-level structure of the data. Each patient provided 2.23 implants on average and within-subject correlation CCI = 0.5 (moderate) was assumed, leading to a correcting coefficient D = 1.62. Therefore, 221 dependent implants provided the same power as 137 independent implants, calculated at 84% under the described conditions (RR=3.0; 95% confidence).

Results

Characteristics of the patient cohort:

In total, 99 patients composed of 49 males (49.5%) and 50 females (50.5%), with a mean age of 60.6 ± 10.2 years at the time of implant placement (range 38-86 years) were included in the present study. Overall, 221 implants were followed for a mean duration of 10.6 ± 4.5 years from implant placement, and 10.0 ± 4.5 years from prosthetic insertion. The loading protocol for all included implants followed a delayed approach (≥4 months after placement). Demographic characteristics of the included cohort are reported in Table 1.

Correlation between stage and grade and implant failure

Analysis at the patient-level revealed that five patients (5.1%) experienced implant failure at least at one site (one patient experienced two failures). At the implant-level, a mean survival rate of 97.3% was found at the end of the follow-up period, and six implants (2.7%) failed. The cumulative survival rate (Kaplan Mayer analysis) was 99% at 5-years, 98% at 10-years, 94% at 15-years, and 92% at 20-years follow-up (Sup. Figure 1A). In the present study, the only cause of implant failure found was PI (Sup. Figure 1B). Table 2A shows Kaplan Meier univariate implant survival analysis according to clinical variables related to the patient, implant position, characteristics, and surgery. Similarly, Table 2B illustrates Kaplan Meier survival analysis of time-to-event peri-implantitis diagnosis based upon above scenarios.

Regarding PR staging, four implant failures were recorded in patients with stage III PR at baseline, while the remaining two failures occurred in patients with a previous history of stage IV disease ($p>0.05$). Mean implant failure rates were 0% for stages I-II, 3% for stage III, and 6.5% for stage IV. Cumulative implant survival rates are shown in Figure 1A and Supplementary Table 1.

In terms of grading, one failure was recorded in a patient with a previous history of grade B PR, while the remaining five failures occurred in patients with a history of grade C disease. The mean failure rate was 0% for grade A, 0.8% for grade B, and 5.9% for grade C ($p<0.05$) (Figure 1B and Supplementary Table 2). Cox proportional hazard regression analysis showed that implants placed in grade C patients were associated with a trend towards a higher failure rate than those placed in grade A/B patients (HR=6.57; p=0.075) (Table 3). The same model demonstrated that implants placed in current high smokers were associated with a significantly higher failure rate compared to never-smokers (HR=4.71; p=0.04). Six implants were lost in patients with a history of stage III/IV PR, while no implants were lost in those with a history of stage I and II PR. Stage was not a significant predictor of implant failure (p=0.635) when stage IV was compared to stage III (Table 3). It should be noted that stages I-II were excluded from the model because of a lack of convergence since these categories were both associated with 0% implant failure rates.

Analysis of the association between stage and grade with the onset and severity of PI

A total of 45 implants (20.4%) were diagnosed with PI during the follow-up period. At the implant-level, the cumulative probability of PI occurrence (based on Kaplan Mayer analysis) was 5% at 5-years, 15% at 10-years, 35% at 15-years, and 54% at 20-years follow-up (Sup. Figure 2A). At the patient-level, the cumulative probability of PI occurrence is shown in Supplementary Figure 2B. Univariate survival analysis of peri-implantitis diagnosis according to clinical variables (implant position, implant characteristics, as well as patient-specific and surgical-related parameters) is shown in Table 2B. Overall, no correlation was found between increased staging and grading and increased prevalence of PI at both the implant- (Table 2B, Figures 1C and 1D) and patient-levels (Sup. Figures 3A and 3B). Cox proportional hazard regression analysis (Sup. Table 3) demonstrated a HR of 1.90 (p=0.027) based on implant diameter, such that each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis. Furthermore, external connections were

associated with a lower risk of PI compared to internal connections (HR=0.11; p=0.018). Distribution of implants diagnosed with PI (n=45) according to the severity of bone loss is shown in Figure 2A. Severity of MBL was associated with increased grading (A-B vs. C), but not with increased staging (Figure 2B). Results from the binary logistic regression model using GEE with fixed follow-up, showed that grading significantly influenced the risk of high MBL (>25%) (p=0.022). Risk of severe MBL increased roughly 7.6 times for patients with a previous history of grade C PR compared to the reference grades A/B. Furthermore, there was no significant difference in risk of severe MBL according to stage (p=0.399) (Table 4).

Discussion

Main findings

This study investigated the potential association between baseline PR stage and grade and future implant failure as well as PI prevalence and severity. Ninety-nine treated PR patients were subsequently rehabilitated with dental implants (n=221) and followed over a mean period of 10.6 years. Patients were classified according to periodontal stage and grade at the time of active periodontal therapy. Over the follow-up period, only 6 implants (2.7%) failed. Although the implant failure rate increased from stage I/II (0%) to stage IV (6.5%), this trend was not statistically significant. A statistically significant increase was seen from grade A (0%) to grade C (5.9%). Interestingly, our results showed no correlation between PR staging or grading and increased prevalence/incidence of PI at either implant- or patient-levels. Although the 2017 World Workshop proposed case definitions for PI, these definitions do not facilitate differentiation between severity levels of PI based on the magnitude of MBL [25, 26]. For the current analysis, a MBL severity threshold of 25% of the implant length was chosen to be correlated with PR stage and grade. The present study found that the severity of peri-implant MBL was directly associated with higher-level of grading. The periodontitis grade (C vs. A-B) significantly influenced risk of high MBL (>25%) (p=0.022). Risk of severe MBL increased 7.6 times for patients with a previous history of periodontal grade C compared to grades A/B.

Overall, these results suggest that staging and grading may not play a role in modulating probability of PI onset, but once PI pathogenesis is initiated, higher-level grading is associated with increased severity of MBL and higher probability of implant failure, whereas staging is not.

Agreement and disagreement with previous studies

There are conflicting results in the literature regarding the association between history of periodontitis and implant failure. Some of the previous studies utilizing the 1999 periodontal classification [27] reported higher long-term implant failure rates in patients who exhibited more severe forms of PR (survival rate range: 88% to 98.4%) compared to those who had moderate/mild PR (survival rate range: 92.8% to 100%) [28-32]. However, others did not confirm this correlation [33, 34]. In the present study, although a higher trend for implant failure was found in patients with a previous history of severe PR (stages III-IV), no statistically significant differences were found due to the small number of implants lost (only 6).

Grade is a risk assessment tool composed of a composite of systemic (smoking and diabetes mellites) and local parameters (radiographic bone loss/age). To allow for a more precise analysis of the effects of grading on implant failure, systemic risk factors were evaluated separately. Implants placed in current heavy smokers were associated with a significantly higher failure rate compared to never-smokers (HR=4.71; p=0.04). A recent systematic review showed that heavy smokers (> 20 cigarettes/day) were at a higher risk for implant failure (HR=4; $p < 0.001$) compared with non-smokers [35]. In addition, De Boever et al. (2009)[36] reported a 17% increased implant failure rate in current smokers with a history of aggressive periodontitis, and a 2% increase in former smokers. In spite of these findings, the 2017 World Workshop recently referred to smoking and diabetes as "inconclusive" risk indicators [1] for peri-implantitis development due to a lack of conclusive evidence [9].

Our findings also did not show a significant correlation between PR severity and PI prevalence. It is important to note that the present study population was entirely composed of PR patients with varying levels of severity. Most existing studies investigating the association between PR and PI compared PR patients to those with no previous history of PR [10, 36-38]. However, very few correlated different levels of PR severity with prevalence and severity of PI [28, 31, 39]. Utilizing stage to categorize patients based on PR severity, results of the present investigation were similar to those from previously published studies which utilized other systems for diagnosing PR severity. Roccuzzo and co-workers reported a PI prevalence of 27% in patients with moderate PR, and 47.2% in patients with severe PR [39]. In a subsequent study, they reported a PI prevalence of 52.2% in patients with moderate PR, and 66.7% in patients with severe PR. In the current study, patients with mild and moderate severity PR (stage I and II) had a PI prevalence of 33.3%, while patients with severe PR

(stage III and IV) had a PI prevalence of 52.7%. In spite of this, the present study did not find any statistically significant association between PI prevalence and PR severity (stage).

The prevalence of PI at both the implant- and patient-levels in the present study can be compared to the results of Romandini et al, since this study also utilized the 2017 World Workshop definition of PI in a PR population [3]. Over a mean follow-up of 7.8 years at the patient-level, the authors reported a PI prevalence of 23.2% in healthy versus 56.6% in PR patients. At the implant-level, they found PI prevalence in healthy and PR patients was 12.4% and 27.9%, respectively. In comparison, the prevalence of PI in the present study was lower at a rate of 20.4% at the patient-level, and 15% at the implant-level after 10-years follow-up.

Additional factors which influenced incidence of PI

Implant diameter and type of abutment-fixture connection were significantly associated with risk of PI development. Each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis (HR=1.90; p=0.027) (Sup. Table 3). Previous studies reported contradictory findings regarding implant diameter and PI risk. The majority of studies reported a higher rate of peri-implantitis for narrow diameter implants [40-42]. Others agreed with our study and showed that wider implants were associated with a higher marginal bone loss and risk of peri-implantitis [43,44]. Overall, the evidence regarding implant diameter as a contributing factor towards PI pathogenesis is limited.

Additionally, implants with external connections were associated with significantly lower prevalence of PI when compared to internal connections (HR=0.11; p=0.018). Further investigation revealed that 100% of the implants with external connection in the current study had a machined surface, which have been associated with lower PI rates [45, 46]. Previous meta-analyses have reported reduced marginal bone loss in conical internal connection implants, suggesting that the stability of the abutment-fixture connection is an important determinant of peri-implant bone levels [47, 48]. Prior clinical studies have also demonstrated better bone preservation associated with internal connection implants relative to external connection implants [49, 50]. The low number of external

connection implants in our sample (18 fixtures), in conjunction with a machined surface for all of them, can potentially explain this controversial result.

Limitations

The present study is not exempt from limitations. First of all, severe forms of PR may have reduced available bone quality and quantity, which in turn may potentially influence PI prevalence and severity [15]. Although this statement cannot be validated from our findings, our results did not show any significant difference in PI rates between different levels of PR staging or grading. Secondly, the small sample size in lower severity classes (stage I and grade A), which was dictated by their lower prevalence in the population [26] and by the exclusion of non-compliant patients (<1 maintenance/year) could have influenced the strength of the relationships evaluated during statistical analysis. For instance, grade C PR patients were associated with a much higher implant failure rate (HR=6.57; p=0.075), but the difference did not reach a level of statistical significance. The same can be seen for the stage; although all failed implants were found in patients with a history of stage III and IV PR, the comparison with stage I and II did not reach the significance. Finally, factors contributing to PI were not totally accounted for, including but not limited to: implant (mal)positioning, residual cement, and prosthetic considerations (emergence profile and abutment height). Future studies should consider these factors to have a better understanding of how they may interact with a previous history of periodontitis in order to influence PI prevalence and severity.

Conclusions

In a well-maintained compliant population with a history of periodontitis, no statistically significant association between staging or grading and prevalence of peri-implantitis was found. However, when peri-implantitis was diagnosed, increased severity of marginal bone loss and probability of implant failure were associated with a previous history of grade C periodontitis. Further studies are needed to confirm these preliminary findings.

Acknowledgements

This manuscript was partially supported by the University of Michigan Periodontal Graduate Student Research Fund. The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

Author Contributions

Andrea Ravidà: Contributed to the conception and design of the study, acquisition of the data and drafting of the article

Musa Qazi: Contributed to the acquisition of data

Maria Vera: Contributed to the acquisition of data

Matthew Galli: Contributed to the acquisition of data and drafting of the article

Muhammad H. A. Saleh: Contributed to the drafting of the article

Giuseppe Troiano: Contributed to the conception and design of the study, data analysis and interpretation

Hom-Lay Wang: Contributed to the conception, critical revision of the article and final approval of the version to be published

Pablo Galindo Moreno: Contributed to the conception, critical revision of the article and final approval of the version to be published

Table and Figure Legends

Figure 1 (A-D): (A) Implant failure survival analysis by stage; (B) Implant failure survival analysis by grade; (C) Peri-implantitis prevalence survival analysis by stage; The drop of the blue curve (represents stages I/II) at 23 years follow-up is due to the reduced sample size at that time (D) Peri-implantitis prevalence survival analysis by grade. The drop of the blue curve (represents grades A/B) at 23 years follow-up is due to the small sample size at that time.

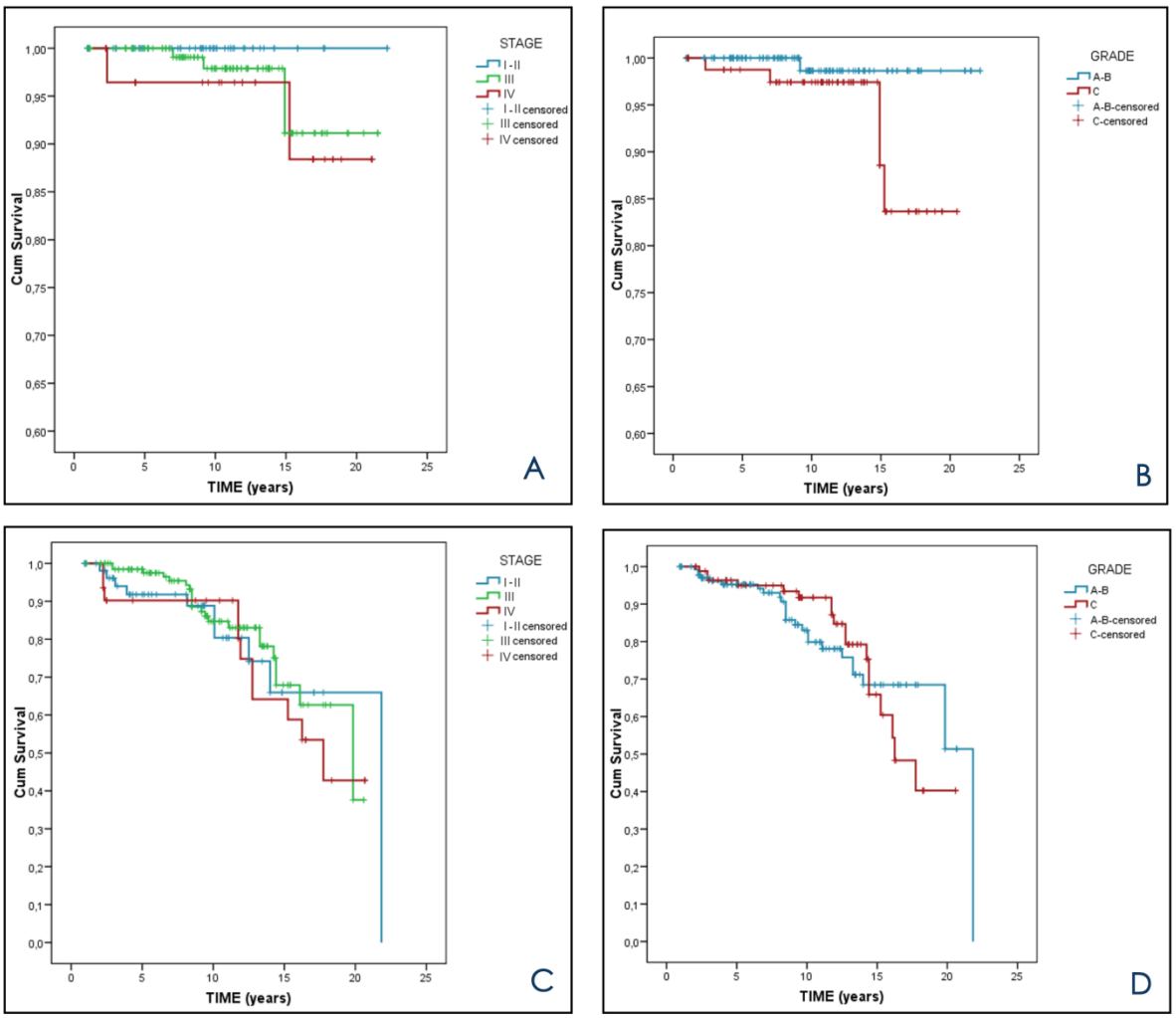

Figure 2 (A-B): (A) Distribution of implants diagnosed with peri-implantitis (n=45) according to marginal bone loss severity (<25%/25-50%/>50% of implant length); (B) Categorization of implants diagnosed with peri-implantitis according to baseline staging/grading and severity of marginal bone loss

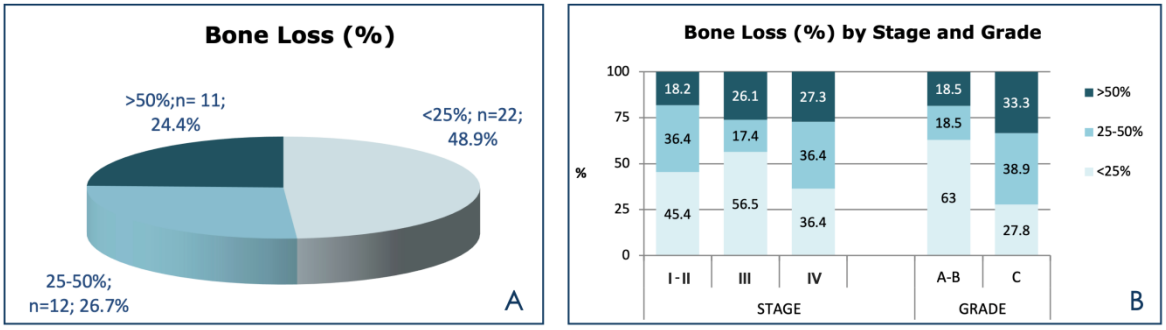

Table 1: Demographic characteristics of the sample and periodontitis status at baseline, as well as results of Kruskal-Wallis test (KW) for comparison between different levels of stage and grade.

		N. of maintenances per year	p-value (KW)	Follow-up since IP (years)	Follow-up since CP (years)
NUMBER OF PATIENTS	99	2.2 ± 1.0		10.6 ± 4.5	10.0 ± 4.5
MEAN AGE (years)	60.6 ± 10.2				
GENDER					
Male	49 (49.5)				
Female	50 (50.5)				
SMOKING					
No	63 (63.6)				
Former smoker	20 (20.2)				
Yes (<10c/d)	8 (8.1)				
Yes (>10c/d)	8 (8.1)				
DIABETES					
No	90 (90.9)				
Yes	9 (9.1)				
STAGE					
1	7 (7.1)	2.7 ± 2.0	0.515	6.8 ± 3.4	6.1 ± 3.5
2	27 (27.3)	1.9 ± 0.8		9.8 ± 4.8	9.2 ± 4.8
3	56 (56.6)	2.2 ± 0.9		11.3 ± 4.0	10.7 ± 4.0
4	9 (9.1)	2.2 ± 1.3		12.1 ± 5.5	11.1 ± 5.7
GRADE					
A	5 (5.1)	2.2 ± 1.0	0.526	10.0 ± 2.9	9.4 ± 3.0
B	68 (66.7)	2.2 ± 1.0		10.1 ± 4.6	9.5 ± 4.6
C	26 (26.3)	2.2 ± 1.0		12.2 ± 4.1	11.5 ± 4.2
EXTENSION					
Localized	78 (78.8)				
Generalized	21 (21.2)				

*p<0.05; †p<0.01; ‡p<0.001

Table 2: Results of Kaplan Meier survival analysis of time-to-event data implant survival and peri-implantitis diagnosis

2A: Kaplan Meier survival analysis of time-to-event data based on clinical variables related to the patient, implant position, characteristics, and surgery.

	Total (%)	**Failure rate (%)**	**p-value**
NUMBER OF IMPLANTS	221	6 (2.7)	
MEAN AGE (years)	60.3 ± 9.3		
GENDER			0.516
Male	110 (49.8)	2 (1.8)	
Female	111 (50.2)	4 (3.6)	
SMOKING			0.141
No	121 (54.8)	2 (1.7)	
Former smoker	48 (21.7)	0 (0.0)	
Yes (<10c/d)	18 (8.1)	1 (5.6)	
Yes (>10c/d)	34 (15.4)	3 (8.8)	
DIABETES			0.104
No	204 (92.3)	5 (2.5)	
Yes	17 (7.7)	1 (5.9)	
STAGE			p=0.411 (STAGE 1+2 vs. 3 vs. 4)
1	8 (3.6)	0 (0.0)	p=0.226 (STAGE 1+2 vs. 3+4)
2	48 (21.7)	0 (0.0)	p=0.267 (STAGE 1+2 vs. 3)
3	134 (60.6)	4 (3.0)	p=0.131 (STAGE 1+2 vs. 4)
4	31 (14.0)	2 (6.5)	
GRADE			**0.048***
A	5 (2.3)	0 (0.0)	(GRADE A+B vs. C)
B	131 (59.3)	1 (0.8)	
C	85 (38.5)	5 (5.9)	
EXTENSION			0.465
Localized	171 (77.4)	4 (2.3)	

Generalized	50 (22.6)	2 (4.0)	
ARCH			0.172
Maxilla	122 (55.2)	5 (4.1)	
Mandible	99 (44.8)	1 (1.0)	
POSITION			0.223
Anterior	37 (16.7)	0 (0.0)	
Posterior	184 (83.3)	6 (3.3)	
PROSTHESIS TYPE			0.956
Single	153 (69.2)	3 (2.0)	(Single vs. Splinted)
Splinted	59 (26.7)	2 (3.4)	
Overdenture	9 (4.1)	1 (11.1)	--
LEVEL			0.806
Soft	48 (21.7)	1 (2.1)	
Bone	173 (78.3)	5 (2.9)	
CONNECTION			0.769
Internal	200 (90.5)	5 (2.5)	(Internal vs. External)
External	18 (8.1)	1 (5.6)	
Locator	3 (1.4)	0 (0.0)	--
RETENTION			**<0.001‡**
Cemented	204 (92.3)	4 (2.0)	(Cemented vs. Screw)
Screwed	14 (6.3)	1 (7.1)	
Ball atachment	3 (1.4)	1 (33.3)	--
IMPLANT LENGTH			0.110
<=11mm	66 (29.9)	1 (1.5)	
11.5mm	45 (20.4)	3 (6.7)	
12mm	34 (15.4)	1 (2.9)	
>=13mm	76 (34.4)	1 (1.3)	
IMPLANT DIAMETER			0.183
<4mm	52 (23.5)	0 (0.0)	
4-4.5mm	90 (40.7)	3 (3.3)	
>4.5mm	79 (35.7)	3 (3.8)	

BONE GRAFT			0.755
No	149 (68.3)	4 (2.7)	
Yes	69 (31.7)	2 (2.9)	
FAILURE			
No	215 (97.3)		
Yes	6 (2.7)		
PERI-IMPLANTITIS			**<0.001‡**
No	176 (79.6)	0 (0.0)	
Yes	45 (20.4)	6 (13.3)	

*p<0.05; †p<0.01; ‡p<0.001

2B: Kaplan Meier survival analysis of time-to-event peri-implantitis diagnosis according to clinical variables related to the patient, implant position, characteristics, and surgery.

	Total (%)	**PI rate (%)**	**p-value**
NUMBER OF IMPLANTS	221	45 (20.4)	
AGE (years)	60.3 ± 9.3		
GENDER			0.825
Male	110 (49.8)	21 (19.1)	
Female	111 (50.2)	24 (21.6)	
SMOKING			0.723
No	121 (54.8)	23 (19.0)	
Former smoker	48 (21.7)	11 (22.9)	
Yes (<10c/d)	18 (8.1)	6 (33.3)	
Yes (>10c/d)	34 (15.4)	5 (14.7)	
DIABETES			0.094
No	204 (92.3)	40 (19.6)	
Yes	17 (7.7)	5 (29.4)	
STAGE			0.411

1	8 (3.6)	1 (12.5)	(STAGE 1+2 vs. 3 vs. 4)
2	48 (21.7)	10 (20.8)	
3	134 (60.6)	23 (17.2)	
4	31 (14.0)	11 (35.5)	
GRADE			0.990
A	5 (2.3)	2 (40.0)	(GRADE A+B vs. C)
B	131 (59.3)	25 (19.1)	
C	85 (38.5)	18 (21.2)	
EXTENSION			0.650
Localized	171 (77.4)	33 (19.3)	
Generalized	50 (22.6)	12 (24.0)	
Time since 1st SRP to IP (years)	12.9 ± 8.1		
Total follow up (years)	10.7 ± 5.1		
RX follow up (years)	9.6 ± 5.1		
Number of maintenances per year	2.3 ± 1.0		
ARCH			0.546
Maxilla	122 (55.2)	22 (18.0)	
Mandible	99 (44.8)	23 (23.2)	
POSITION			0.110
Anterior	37 (16.7)	8 (21.6)	
Posterior	184 (83.3)	37 (20.1)	
PROSTHESIS TYPE			0.409 (Single vs. splinted)
Single	153 (69.2)	20 (13.1)	
Splinted	59 (26.7)	18 (30.5)	
Overdenture	9 (4.1)	7 (77.8)	--
LEVEL			0.120
Soft	48 (21.7)	5 (10.4)	
Bone	173 (78.3)	40 (23.1)	
CONNECTION			**0.008**† (Internal vs. External)
Internal	200 (90.5)	41 (20.5)	
External	18 (8.1)	3 (16.7)	

Locator	3 (1.4)	1 (33.3)	--
RETENTION			**0.002‡** (Cemented vs. Screw)
Cemented	204 (92.3)	39 (19.1)	
Screwed	14 (6.3)	3 (21.4)	
Ball atachment	3 (1.4)	3 (100)	--
IMPLANT LENGTH			**0.009†**
<=11mm	66 (29.9)	10 (15.2)	
11.5mm	45 (20.4)	12 (26.7)	
12mm	34 (15.4)	2 (5.9)	
>=13mm	76 (34.4)	21 (27.6)	
IMPLANT DIAMETER			**0.009†**
<4mm	52 (23.5)	7 (13.5)	
4-4.5mm	90 (40.7)	22 (24.4)	
>4.5mm	79 (35.7)	16 (20.3)	
BONE GRAFT			0.551
No	149 (68.3)	29 (19.5)	
Yes	69 (31.7)	14 (20.3)	
FAILURE			
No	215 (97.3)	39 (18.1)	
Yes	6 (2.7)	6 (100.0)	
PERI-IMPLANTITIS			
No	176 (79.6)		
Yes	45 (20.4)		

*p<0.05; †p<0.01; ‡p<0.001

Table 3. Cox proportional hazard regression model illustrating time-to-event failure by clinical variables related to the patient, implant position, characteristics, and surgery.

	HR	95% CI	p-value
AGE (years)	1.02	0.95 – 1.10	0.538
GENDER			
Male	1		
Female	1.75	0.36 – 8.60	0.491
SMOKING			0.102
No	1		
Former smoker	--	--	--
Yes (<10c/d)	1.82	0.21 – 15.6	0.578
Yes (>10c/d)	4.71	1.08 – 20.6	**0.040***
DIABETES			
No	1		
Yes	5.79	0.63 – 53.5	0.122
STAGE			
1-2	--	--	--
3	1		
4	1.54	0.26 – 9.17	0.635
GRADE			
A-B	1		
C	6.57	0.82 – 52.4	0.075
EXTENSION			
Localized	1		
Generalized	1.86	0.40 – 8.58	0.429
ARCH			
Maxilla	1		
Mandible	0.25	0.03 – 2.18	0.209
PROSTHESIS TYPE			

Single	1		
Splinted	1.04	0.10 – 10.5	0.971
Overdenture	--	--	--
LEVEL			
Soft	1		
Bone	1.31	0.16 – 10.9	0.801
CONNECTION			
Internal	1		
External	0.72	0.07 – 7.29	0.777
Locator	--	--	--
RETENTION			
Cemented	1		
Screwed	51.9	4.89 – 550.4	**0.001**†
Ball atachment	--	--	--
IMPLANT LENGTH	1.05	0.79 – 1.39	0.743
IMPLANT DIAMETER	2.23	0.79 – 6.26	0.128
BONE GRAFT			
No	1		
Yes	1.30	0.25 – 6.94	0.756

*p<0.05; †p<0.01; ‡p<0.001

Table 4: Risk of ≥ 25% bone loss according to periodontal diagnosis (stage and grade) adjusted by time since crown placement to radiographic analysis (RX). The results of the binary logistic regression model were evaluated using GEE, adjusted odds ratio (OR), and 95% CI.

	OR	95% CI	p-value
STAGE			0.399
1-2	1		
3	0.26	0.04 – 1.93	0.186
4	0.25	0.03 – 2.16	0.209
GRADE			
A-B	1		
C	7.61	1.35 – 43.1	**0.022***
RX follow up (years)	1.11	0.97 – 1.28	0.127

*p<0.05; †p<0.01; ‡p<0.001

Supplementary Table 1: Survival analysis of time-to-event failure by stage: cumulative survival probability at different time-point (years)

Supplementary Table 2: Survival analysis of time-to-event failure by grade: Cumulative survival probability at different time-point (years)

Supplementary Table 3: Time-to-event PI by clinical variables related to patient, implant position, characteristics, and surgery. Results of Cox proportional hazard regression model, non-adjusted hazard ratio (HR), 95% CI and p-value of Wald test.

Supplementary Figure 1 (A-B): (A) Overall implant survival rate cumulative function estimated by Kaplan Meier's method; (B) Implant survival rate cumulative function estimated by Kaplan Meier's method by binary peri-implantitis status (yes/no)

Supplementary Figure 2 (A-B): (A) Cumulative survival function estimated by Kaplan Meier's method illustrating implant level time-to-PI diagnosis events throughout the follow-up ("Cum Survival" on the y-axis denotes PI diagnosis events) **(B)** Cumulative survival function estimated by Kaplan Meier's method illustrating patient level time-to-PI diagnosis events ("Cum Survival" on the y-axis denotes PI diagnosis events)

Supplementary Figure 3 (A-B): (A) Cumulative survival function estimated by Kaplan Meier's method illustrating implant level time-to-PI diagnosis events by stage ("Cum Survival" on the y-axis denotes PI diagnosis events) (B) Cumulative survival function estimated by Kaplan Meier's method illustrating implant level time-to-PI diagnosis event by grade ("Cum Survival" on the y-axis denotes PI diagnosis events)

References

1. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Periodontol* 2018;89 Suppl 1:S267-S290.

2. Romandini M, Cordaro M, Donno S, Cordaro L. Discrepancy between patient satisfaction and biologic complication rate in patients rehabilitated with overdentures and not participating in a structured maintenance program after 7 to 12 years of loading. *Int J Oral Maxillofac Implants* 2019;34:1143-1151.

3. Romandini M, Lima C, Pedrinaci I, Araoz A, Soldini MC, Sanz M. Prevalence and risk/protective indicators of peri-implant diseases: A university-representative cross-sectional study. *Clin Oral Implants Res* 2021;32:112-122.

4. Lafaurie GI, Sabogal MA, Castillo DM, et al. Microbiome and Microbial Biofilm Profiles of Peri-Implantitis: A Systematic Review. *J Periodontol* 2017;88:1066-1089.

5. Romandini M, Lafori A, Romandini P, Baima G, Cordaro M. Periodontitis and platelet count: A new potential link with cardiovascular and other systemic inflammatory diseases. *J Clin Periodontol* 2018;45:1299-1310.

6. Lindhe J, Berglundh T, Ericsson I, Liljenberg B, Marinello C. Experimental breakdown of peri-implant and periodontal tissues. A study in the beagle dog. *Clin Oral Implants Res* 1992;3:9-16.

7. Carcuac O, Berglundh T. Composition of human peri-implantitis and periodontitis lesions. *J Dent Res* 2014;93:1083-1088.

8. Heitz-Mayfield LJA, Heitz F, Lang NP. Implant Disease Risk Assessment IDRA-a tool for preventing peri-implant disease. *Clin Oral Implants Res* 2020;31:397-403.

9. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Clin Periodontol* 2018;45 Suppl 20:S246-S266.

10. Ferreira SD, Martins CC, Amaral SA, et al. Periodontitis as a risk factor for peri-implantitis: Systematic review and meta-analysis of observational studies. *J Dent* 2018;79:1-10.

11. Schou S, Holmstrup P, Worthington HV, Esposito M. Outcome of implant therapy in patients with previous tooth loss due to periodontitis. *Clin Oral Implants Res* 2006;17 Suppl 2:104-123.

12. Kornman KS. Mapping the pathogenesis of periodontitis: a new look. *J Periodontol* 2008;79:1560-1568.

13. Aoki M, Takanashi K, Matsukubo T, et al. Transmission of periodontopathic bacteria from natural teeth to implants. *Clin Implant Dent Relat Res* 2012;14:406-411.

14. Pjetursson BE, Helbling C, Weber HP, et al. Peri-implantitis susceptibility as it relates to periodontal therapy and supportive care. *Clin Oral Implants Res* 2012;23:888-894.

15. Zhang H, Li W, Zhang L, Yan X, Shi D, Meng H. A nomogram prediction of peri-implantitis in treated severe periodontitis patients: A 1-5-year prospective cohort study. *Clin Implant Dent Relat Res* 2018;20:962-968.

16. Daubert DM, Weinstein BF, Bordin S, Leroux BG, Flemming TF. Prevalence and predictive factors for peri-implant disease and implant failure: a cross-sectional analysis. *J Periodontol* 2015;86:337-347.

17. Ong CT, Ivanovski S, Needleman IG, et al. Systematic review of implant outcomes in treated periodontitis subjects. *J Clin Periodontol* 2008;35:438-462.

18. Dvorak G, Arnhart C, Heuberer S, Huber CD, Watzek G, Gruber R. Peri-implantitis and late implant failures in postmenopausal women: a cross-sectional study. *J Clin Periodontol* 2011;38:950-955.

19. Derks J, Schaller D, Hakansson J, Wennstrom JL, Tomasi C, Berglundh T. Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-implantitis. *J Dent Res* 2016;95:43-49.

20. Kordbacheh Changi K, Finkelstein J, Papapanou PN. Peri-implantitis prevalence, incidence rate, and risk factors: A study of electronic health records at a U.S. dental school. *Clin Oral Implants Res* 2019;30:306-314.

21. Tonetti MS, Sanz M. Implementation of the new classification of periodontal diseases: Decision-making algorithms for clinical practice and education. *J Clin Periodontol* 2019;46:398-405.

22. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Clin Periodontol* 2018;45 Suppl 20:S149-S161.

23. Pepelassi EA, Tsiklakis K, Diamanti-Kipioti A. Radiographic detection and assessment of the periodontal endosseous defects. *J Clin Periodontol* 2000;27:224-230.

24. Chrcanovic BR, Albrektsson T, Wennerberg A. Periodontally compromised vs. periodontally healthy patients and dental implants: a systematic review and meta-analysis. *J Dent* 2014;42:1509-1527.

25. Berglundh T, Armitage G, Araujo MG, et al. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol* 2018;89 Suppl 1:S313-S318.

26. Ravida A, Galli M, Siqueira R, Saleh MHA, Galindo-Moreno P, Wang HL. Diagnosis of peri-implant status after peri-implantitis surgical treatment: Proposal of a new classification. *J Periodontol* 2020;91:1553-1561.

27. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol* 1999;4:1-6.

28. Gatti C, Gatti F, Chiapasco M, Esposito M. Outcome of dental implants in partially edentulous patients with and without a history of periodontitis: a 5-year interim analysis of a cohort study. *Eur J Oral Implantol* 2008;1:45-51.

29. Gianserra R, Cavalcanti R, Oreglia F, Manfredonia MF, Esposito M. Outcome of dental implants in patients with and without a history of periodontitis: a 5-year pragmatic multicentre retrospective cohort study of 1727 patients. *Eur J Oral Implantol* 2010;3:307-314.

30. Roccuzzo M, De Angelis N, Bonino L, Aglietta M. Ten-year results of a three-arm prospective cohort study on implants in periodontally compromised patients. Part 1: implant loss and radiographic bone loss. *Clin Oral Implants Res* 2010;21:490-496.

31. Roccuzzo M, Bonino L, Dalmasso P, Aglietta M. Long-term results of a three arms prospective cohort study on implants in periodontally compromised patients: 10-year data around sandblasted and acid-etched (SLA) surface. *Clin Oral Implants Res* 2014;25:1105-1112.

32. Levin L, Ofec R, Grossmann Y, Anner R. Periodontal disease as a risk for dental implant failure over time: a long-term historical cohort study. *J Clin Periodontol* 2011;38:732-737.

33. Kim KK, Sung HM. Outcomes of dental implant treatment in patients with generalized aggressive periodontitis: a systematic review. *J Adv Prosthodont* 2012;4:210-217.

34. Ramanauskaite A, Baseviciene N, Wang HL, Tozum TF. Effect of history of periodontitis on implant success: meta-analysis and systematic review. *Implant Dent* 2014;23:687-696.

35. Naseri R, Yaghini J, Feizi A. Levels of smoking and dental implants failure: A systematic review and meta-analysis. *J Clin Periodontol* 2020;47:518-528.

36. De Boever AL, Quirynen M, Coucke W, Theuniers G, De Boever JA. Clinical and radiographic study of implant treatment outcome in periodontally susceptible and non-susceptible patients: a prospective long-term study. *Clin Oral Implants Res* 2009;20:1341-1350.

37. Aglietta M, Siciliano VI, Rasperini G, Cafiero C, Lang NP, Salvi GE. A 10-year retrospective analysis of marginal bone-level changes around implants in periodontally healthy and periodontally compromised tobacco smokers. *Clin Oral Implants Res* 2011;22:47-53.

38. Lee J, Mattheos N, Nixon KC, Ivanovski S. Residual periodontal pockets are a risk indicator for peri-implantitis in patients treated for periodontitis. *Clin Oral Implants Res* 2012;23:325-333.

39. Roccuzzo M, Bonino F, Aglietta M, Dalmasso P. Ten-year results of a three arms prospective cohort study on implants in periodontally compromised patients. Part 2: clinical results. *Clin Oral Implants Res* 2012;23:389-395.

40. French D, Larjava H, Tallarico M. Retrospective Study of 1087 Anodized Implants Placed in Private Practice: Risk Indicators Associated With Implant Failure and Relationship Between Bone Levels and Soft Tissue Health. *Implant Dent* 2018;27:177-187.

41. Rodrigo D, Sanz-Sanchez I, Figuero E, et al. Prevalence and risk indicators of peri-implant diseases in Spain. *J Clin Periodontol* 2018;45:1510-1520.

42. Sordi MB, Perrotti V, Iaculli F, et al. Multivariate analysis of the influence of peri-implant clinical parameters and local factors on radiographic bone loss in the posterior maxilla: a retrospective study on 277 dental implants. *Clin Oral Investig* 2020 Nov 5. doi: 10.1007/s00784-020-03666-x. Online ahead of print.

43. Shatta A, Bissada NF, Ricchetti P, Paes A, Demko C. Impact of Implant and Site Characteristics on the Pattern of Bone Loss in Peri-implantitis. *Int J Oral Maxillofac Implants* 2019;34:1475-1481.

44. Ibanez C, Catena A, Galindo-Moreno P, Noguerol B, Magan-Fernandez A, Mesa F. Relationship Between Long-Term Marginal Bone Loss and Bone Quality, Implant Width, and Surface. *Int J Oral Maxillofac Implants* 2016;31:398-405.

45. Gallego L, Sicilia A, Sicilia P, Mallo C, Cuesta S, Sanz M. A retrospective study on the crestal bone loss associated with different implant surfaces in chronic periodontitis patients under maintenance. *Clin Oral Implants Res* 2018;29:557-567.

46. Simion M, Nevins M, Rasperini G, Tironi F. A 13- to 32-Year Retrospective Study of Bone Stability for Machined Dental Implants. *Int J Periodontics Restorative Dent* 2018;38:489-493.

47. Laurell L, Lundgren D. Marginal bone level changes at dental implants after 5 years in function: a meta-analysis. *Clin Implant Dent Relat Res* 2011;13:19-28.

48. Schmitt CM, Nogueira-Filho G, Tenenbaum HC, et al. Performance of conical abutment (Morse Taper) connection implants: a systematic review. *J Biomed Mater Res A* 2014;102:552-574.

49. Galindo-Moreno P, Fernandez-Jimenez A, O'Valle F, et al. Influence of the crown-implant connection on the preservation of peri-implant bone: a retrospective multifactorial analysis. *Int J Oral Maxillofac Implants* 2015;30:384-390.

50. Penarrocha-Diago MA, Flichy-Fernandez AJ, Alonso-Gonzalez R, Penarrocha-Oltra D, Balaguer-Martinez J, Penarrocha-Diago M. Influence of implant neck design and implant-abutment connection type on peri-implant health. Radiological study. *Clin Oral Implants Res* 2013;24:1192-1200.