Original Article

Association between implant surface roughness, smoking habits and implant site location on the occurrence of peri-implantitis: a pooled retrospective cohort study

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Background: Peri-implantitis is a multi-factorial disease that affects dental implants surrounding tissues. The identification of risk factors and risk indicators could contribute to explain the heterogeneity of the disease onset and progression. The aim of the present study is to investigate the influence of implant surface roughness and other initial conditions on the future development of peri-implantitis disease by means of a pooled individual data.

Methods: A total of 203 patients from four previous cohort studies were included. The patient included received a total of 630 dental implants between 1985 and 2013, with a mean follow-up time of 13 years.

Results: The multilevel regression analysis demonstrated that the smoking habit [odds ratio (OR) 2.939 with a 95% confidence interval (CI): 1.236–6.988], the presence of a rough surface implant (OR 4.877 with a 95% CI: 1.701–13.980) and the implant position in the mouth (anterior mandible OR 3.842 with a 95% CI: 1.080–13.671; posterior mandible OR 6.618 with a 95% CI: 2.437–17.975) were statistically associated with onset of peri-implantitis.

Conclusions: Within the limitation of the retrospective nature of this pooled analysis, it can be concluded that the peri-implantitis disease is correlated with many factors other than biofilm accumulation. The role of initial marginal bone loss (MBL) on the occurrence of peri-implantitis is uncertain.

Keywords: Pooled analysis; peri-implantitis; rough surface dental implant; regression model

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Introduction

Peri-implantitis is a disease involving the soft and hard tissues surrounding an osteointegrated dental implant, resulting in an inflammation of the peri-implant mucosa and a progressive breakdown of the implant supporting bone (1,2). The disease progression varies greatly from patient to patient and within the same patient from implant site to implant site. In a 9-year retrospective study, it has been observed that the mean onset time of radiographic bone loss is around three years after the completion of the implant-supported prosthetic rehabilitation (3). The development of symptoms, such as abscess, pain, implant mobility and implant loss, may require many years. Peri-implantitis shares with periodontitis the common features of non-linear and accelerating pattern over time, whereas it looks to differ for the rapidity of the hard tissue breakdown, which is faster in peri-implantitis (4).

An essential factor for the development of peri-

implantitis is over time plaque accumulation on the implant and the implant-supported restoration surfaces. Titanium rough surfaces (roughness parameter Sa >1 μm) might offer to the oral bacteria an optimal environment to organize themselves in pathogenic biofilm (5). However, the presence of biofilm is not enough on its own, as many clinical situations with uncontrolled plaque accumulation do not develop peri-implantitis, but only mucositis (that is inflammation of the peri-implant mucosa without progressive bone loss). Mucositis is supposed to precede peri-implantitis, but the etiopathogenetic mechanism of progression from mucositis to peri-implantitis (i.e., the extension of the inflammatory lesion from the soft tissue to the underlying bone along with the beginning of its destruction) is still elusive (6).

In this context, it is of great importance to investigate the initial risk factors/indicators related to the development of the peri-implantitis disease. The identification of such factors could contribute to explain the heterogeneity of the disease onset and progression.

The multifactorial nature of peri-implantitis disease has been deeply investigated. There is some evidence for the following aspect to have a the role in peri-implantitis: the macro and micro-design of the implant (7,8), the type of prosthetic restoration (9), the implant supportive therapy (10) and the susceptibility of the patient (11).

Moreover, the initial marginal bone loss (MBL) around implant seems to be related to future development of peri-implantitis (12).

Recently, three retrospective clinical trials suggested that the prevalence of peri-implantitis can vary a lot among different population of patients. In particular, the reported prevalence of peri-implantitis was 1.8% on machined implants placed in native bone after 13 to 32 years (13), 9.9% on machined implant placed in vertically regenerated bone with a follow-up ranged from 13 to 21 years (14) and 28.3% in moderately rough implant placed in native bone after a follow-up period of 5 to 17 years (15).

However, it is difficult to interpret altogether these results. In fact, the limitation of using the implant as statistical unit can mask the patient cluster effect on the outcome measurement, since each patient could participate to the sample with one implant or more.

For these reasons, it could be interesting to perform a pooled analysis of the data retrieved from the population of the three aforementioned studies (plus a fourth sample of patients that received rough implant in vertically regenerated bone, that will be described in a future publication).

The aim of the present study is to investigate the influence of implant surface roughness and other initial conditions on the future development of peri-implantitis disease by means of a pooled individual data. We present the following article in accordance with the STROBE reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-95/rc).

Methods

Study design

The study is designed as a retrospective cohort study.

Settings

Individual data used in this pooled analysis were derived from four previous cohort studies (13-16). In brief, each study analyzed retrospectively a cohort of patient characterized by a single surface of the dental implants (either rough or machined) and a single type of bone (either native or regenerated) where the implants were placed.

First cohort (14) comprised patients treated with machined surface implants placed in vertically regenerated bone between 1993 and 2000, with 13 to 21 years of follow-up. Second cohort (13) comprised patients treated with machined implants placed in native bone between 1985 and 2001, with 13 to 32 years of follow-up. Third cohort (15) comprised patients treated with rough implant in placed native bone between 2000 and 2013, with 5 to 17 years of follow-up. Finally, the last cohort (16) included patients who received rough implants in vertically regenerated bone between 2001 and 2013, with 4 to 15 years of follow-up.

Informed consent was obtained from each patient to use their clinical data in an anonymous way. The last publication obtained the approval from the Ethical Committee of the University of Milan (decision n. 47/18). The access to raw data was obtained from the corresponding authors of each paper.

Participants

The number of patients and implants included in the pooled analysis slightly differed from the published samples reported in the aforementioned articles due to different selection criteria. The following inclusion criteria were used for this retrospective analysis: (I) >18 years old

at time of implant surgery of both gender; (II) received at least one titanium dental implant by a single experienced operator (M.S.) in a single private practice located in Milan (Italy); (III) good general health (ASA status I or II); (IV) presence of an X-ray (peri-apical or panoramic) obtained approximately one year after implant loading; (V) presence of a follow-up visit where the presence/absence of peri-implantitis was clinically and radiographically assessed.

Exposure variable

The exposure variable was the type of implant surface measured as a dichotomous variable: "Machined" for dental implants with low surface roughness (Sa <1 µm, Brånemark System®; Nobel Biocare AB, Goteborg, Sweden) and "Rough" for dental implants with moderate surface roughness (Sa >1 µm, TiUnite®; Nobel Biocare AB, Goteborg, Sweden).

Outcome variable

The outcome variable was the diagnosis of peri-implantitis at the follow-up visit. It was measured as a dichotomous variable (presence/absence) following the last classification provided by the European Federation of Periodontology and the American Academy of Periodontology (4). In particular, peri-implantitis was defined as the contemporary presence of soft tissue inflammation and progressive bone loss.

Covariates

The following demographic, clinical and radiographic variables were recorded: (I) age at time of implant surgery; (II) gender; (III) smoking habits at time of surgery; (IV) baseline MBL defined as the vertical distance measured in mm from the implant shoulder to the first implant-bone contact (for extensive description of the method of measurement, see Ferrantino *et al.* 2019); (V) years of follow-up for each implant; (VI) type of bone (dental implant have been inserted either in augmented bone by means of vertical guided bone regeneration ("Regenerated") or in pristine bone ("Native"); (VII) implant location in the mouth. Implant location can be either in the upper jaw ("maxilla") or the lower jaw ("mandible"). Moreover, the implant could have replaced an "anterior" tooth (incisors and cuspids) or a "posterior" tooth (bicuspids and molars). Depending on the replaced tooth site, the implants were divided in the following four categories: (I) anterior maxilla; (II) anterior mandible; (III) posterior maxilla and (IV) posterior mandible.

Statistical analysis

Demographic, clinical and behavioral variables were reported for the entire sample and each cohort. Continuous variables were reported as mean and standard deviation (or median and interquartile range for non-normal data) and categorical variables as absolute and relative frequencies.

The adjusted association estimates [odds ratio (OR) and relative 95% confidence intervals (95% CIs)] between demographic, clinical and behavioral variables and the onset of peri-implantitis were fitted by generalized linear mixed-effect model (GLMM) to take into account the correlation in the outcome measurement of dental implants placed in the same patient (patient cluster effect). In fact, GLMM overcomes the patient cluster effect with a hierarchical structure, being the implant the lower level ("fixed effect") and the patient the higher level ("random effects").

Following the model building strategy (17), as first step, univariate analysis was used to explore the association between each variable and onset of peri-implantitis. Statistical significance in univariate analysis was set at $P<0.25$ (17).

The variables selected by the univariate analysis were entered in an initial multivariable model on which was applied the following backward approach: (I) the independent variables that do not present a statistically significant association ($P<0.05$) with the outcome in the multivariable logistic regression model were eliminated to build a parsimonious one; (II) the coefficients derived from the initial and the parsimonious multivariate models were compared to calculate the proportion of change. As a "rule of thumb", the parsimonious model was maintained if the change in all the coefficients was less than 20%. The process ended when each variable remaining in the equation was either statistically significant or made a significant (more than 20%) change in the other coefficients.

Statistical significance to build the final multivariate model was set at $P<0.05$.

All the analyses were performed using R statistical software V.3.3 (Foundation for Statistical Computing, Vienna, Austria).

Table 1 Clinical and demographic variables distribution of the pooled sample divided by source data

Variable	Cohort				Overall
	Simion *et al.* 2018	Ferrantino *et al.* 2019	Simion *et al.* 2016	Pieoni *et al.* 2021 (accepted)	
No. of patients	54	59	50	41	203[$]
No. implants	160	223	132	115	630
Age*, mean (SD)	48.19 (12.16)	53.57 (12.42)	46.19 (12.84)	44.19 (13.91)	48.52 (13.13)
Male (%)*	21 (38.9)	20 (33.9)	15 (30.0)	10 (24.4)	66 (32.5)
Smoking (%)*	10 (18.5)	22 (37.3)	11 (31.4)	12 (31.6)	55 (27.1)
Years of follow-up*, mean (SD)	17.52 (3.96)	10.43 (3.44)	15.14 (4.12)	9.66 (3.29)	13.03 (4.95)
Implant position (%)**					
Anterior mandible	14 (8.8)	30 (13.5)	2 (1.5)	3 (2.6)	49 (7.8)
Anterior maxilla	18 (11.2)	46 (20.6)	42 (31.8)	40 (34.8)	146 (23.2)
Posterior mandible	76 (47.5)	99 (44.4)	58 (43.9)	46 (40.0)	279 (44.3)
Posterior maxilla	52 (32.5)	48 (21.5)	30 (22.7)	26 (22.6)	156 (24.8)
Baseline marginal bone loss in mm, mean (SD)**	1.45 (0.62)	1.47 (0.30)	2.11 (1.17)	1.80 (0.88)	1.69 (0.80)
Peri-implantitis** (%)	4 (2.5)	63 (28.3)	(6.8)	31 (27.7)	107. (17.1)

*, referred to patients; **, referred to implants; [$], a patient appearing in both Ferrantino *et al.* 2019 and Simion *et al.* 2016 cohort, therefore the overall number of patients is 203 instead of 204. SD, standard deviation.

Table 2 Association estimates from univariate logistic regression model

Variable	OR	95% CI	P value
Age	1.012	1.003–1.020	0.005*
Smoking	3.862	1.301–11.463	0.015*
Implant surface	18.112	5.638–58.181	<0.001*
Type of bone	1.042	0.361–3.008	0.939
Years of follow-up	0.831	0.758–0.911	<0.001*
Implant position (reference = anterior maxilla)			
Anterior mandible	2.147	0.592–7.775	0.245
Posterior mandible	5.531	2.013–15.193	0.001*
Posterior maxilla	1.622	0.508–5.172	0.413
Baseline marginal bone loss	1.345	0.755–2.396	0.314

*, statistically significant. OR, odds ratio; CI, confidence interval.

Results

A total of 203 patients were included in this study. The mean age of the sample was 48.52 years. Sixty-six patients (32.5%) were male, and 55 (27.1%) patients were smokers. The patient included received a total of 630 dental implants. Three hundred thirty-eight implants were characterized by a rough surface and 292 by a smooth one. Two hundred forty-seven implants (39.2%) were placed in regenerated bone. The mean follow-up time was slightly more than 13 years. The most frequent implant site location was the posterior mandible (44.3% of the 630 included implants), followed by posterior maxilla (24.8%), anterior maxilla (23.2%) and anterior mandible (7.8%).

The mean T0 MBL was 1.69 with a standard deviation of 0.80.

Table 1 shows the patient and implant distributions in the pooled sample divided by cohort, and the analyzed variables.

Table 2 shows the results of the explorative univariate analysis. Age, smoking, implant surface, years of follow-up and implant position were statistically associated with onset of peri-implantitis.

The multivariate GLMM (*Table 3*) included all the statistically significant variables resulted at univariate explorative analyses.

From the multivariate GLMM, peri-implantitis was

Table 3 Multivariate GLMM

Variable	OR	95% CI	P value
Age	0.979	0.947–1.012	0.205
Smoking	2.939	1.236–6.988	0.015*
Implant surface	4.877	1.701–13.980	0.003*
Years of follow-up	0.915	0.832–1.006	0.066
Implant position (reference = anterior maxilla)			
Anterior mandible	3.842	1.080–13.671	0.038*
Posterior mandible	6.618	2.437–17.975	<0.001*
Posterior maxilla	1.974	0.641–6.076	0.236

*, statistically significant. GLMM, generalized linear mixed-effect model; OR, odds ratio; CI, confidence interval.

associated with the smoking habit (OR 2.939 with a 95% CI: 1.236–6.988), with the presence of a rough surface implant (OR 4.877 with a 95% CI: 1.701–13.980) and with the implant position in the mouth (anterior mandible OR 3.842 with a 95% CI: 1.080–13.671; posterior mandible OR 6.618 with a 95% CI: 2.437–17.975).

Discussion

The present pooled retrospective analysis aimed to find the correlation between the exposure variable implant surface roughness and the occurrence of peri-implantitis. Some putative risk-factors/indicators were added to the regression model to explore their association with the outcome and to control any possible confounding effect. For this reason, we forced the inclusion in the final model of "age" and "length of follow-up" beyond their statistically significance because of their importance as putative confounders.

The four sources of data (*Table 1*) were considered together for the homogeneity of their samples: all the patients included in the pooled analysis received a fixed implant-supported restoration by means of implant with similar morphology (bone level, cylindrical body, external hexagon, no platform switching). Moreover, they were treated in the same private dental practice and by the same operator, thus reducing uncontrolled confounding factors.

The implant surface demonstrated an important influence on the occurrence of peri-implantitis. The relationship between the surface characteristics and peri-implantitis (as a consequence of an easier and faster biofilm accumulation) has been hypothesized by the Authors in their previous publications (13-16); the presented comprehensive analysis strengthens this assumption.

The baseline MBL did not show in the univariate regression analysis any statistically significant correlation with the outcome. This is in contrast with previous published papers (12). However, initial MBL could be influenced by other factors: (I) the type of bone (dental implants placed in regenerated bone showed more MBL at baseline than those placed in native bone, as shown in *Table 1*); and (II) the prosthetic connection used (external hexagon), which can also influence the MBL (18). For these reasons, the relationship between baseline MBL and peri-implantitis in some clinical condition could be weak enough to be clinically irrelevant (*Figure 1*). The stability of vertical grafts around implants demonstrated to be similar to native bone, in accordance with previous publications (14,19).

The follow-up time appeared to have a strong statistically significant correlation with the outcome in the univariate analysis (P<0.001). An OR 0.831 suggests that a longer follow-up could be a protective factor against the development of peri-implantitis. This could be counterintuitive, as the common sense would suggest that the longer the follow-up the higher the probability to develop a peri-implantitis. The statistical significance disappear once this factor has been included in the multivariate GLMM (P=0.066). The confounding effect shown in the univariate analysis is due to the difference between the group of patients with machined surface implants, which have a very long follow-up and a low prevalence of peri-implantitis, and the group of patients with rough surface implants, which showed shorter follow-up and higher prevalence of peri-implantitis.

Figures 2,3 could better clarify that most of the implants with peri-implantitis had a follow-up ranged between 6 and 14 years and presented a rough surface.

In particular, the graphic showed in *Figure 3* report the pooled sample divided by the follow-up time (more than 15 years/less than 15 years) and surface (rough/machined). It is clearly shown that most of the peri-implantitis occurred on rough implants with a follow-up time less than 15 years.

Considering the statistically significant factors included in the multilevel GLMM, we can assume the following relationship with the outcome:

(I) Rough surface implants seem to be prone to develop peri-implantitis 4.9 times more than machined implants;
(II) Implant placed in smoking patients could suffer from peri-implantitis almost 3 times more than implants placed in non-smoking patients;

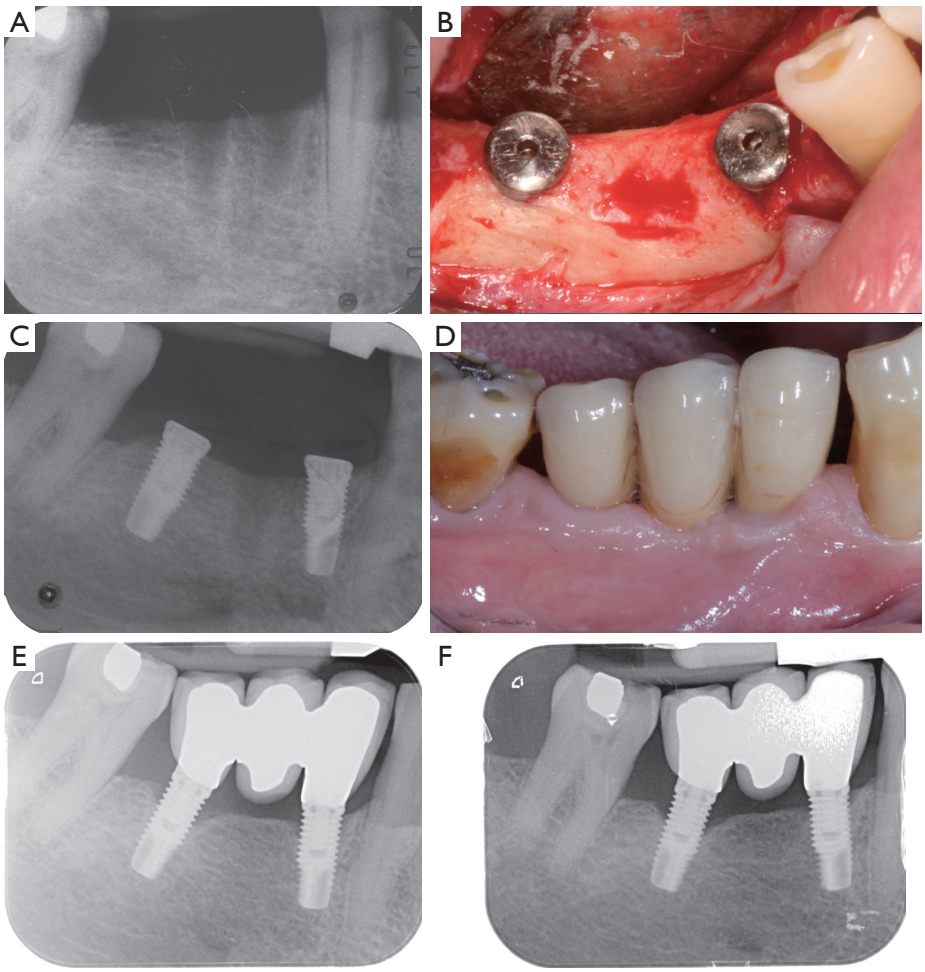

Figure 1 Initial marginal bone loss on different implants placed in the same patient. (A) A alveolar ridge 4 months after tooth extraction. (B) Intra-surgical image showing implant placed in native bone (A) [2009]. (C) Post-operative X-ray. (D) Final restoration delivery [2009]. (E) 1 year [2010] follow-up radiographs showing initial marginal bone loss. (F) 8 years follow-up showed [2017] stable bone loss despite the initial marginal bone loss.

(III) Implants placed in the posterior mandible are at greater risk of future peri-implantitis development (6.6 times more than implant placed in the anterior maxilla).

These findings are of great interest due to the extremely long follow-up of the sample, and the considerable sample size.

Even if the multivariate analysis reduces the impact of confounding factors, the follow-up difference between machined and rough surface implants should be considered as a limitation of the study. A balanced number of rough and machined surface implants with the same long follow-up period would probably give more robust information on the association between time and peri-implantitis.

Another limitation that is intrinsically related to the long follow-up, is the presence of many dropouts, as reported in the published articles used as source data. However, it is impossible to imagine such a long follow-up without having an important number of missing patients at recall visits.

Within the limitation of the retrospective nature of this pooled analysis, it can be concluded that the peri-implantitis disease is correlated with many factors other than biofilm accumulation. These factors can act reducing or increasing the risk of its occurrence on the long term. It is mandatory to interfere with the disease onset by providing to the

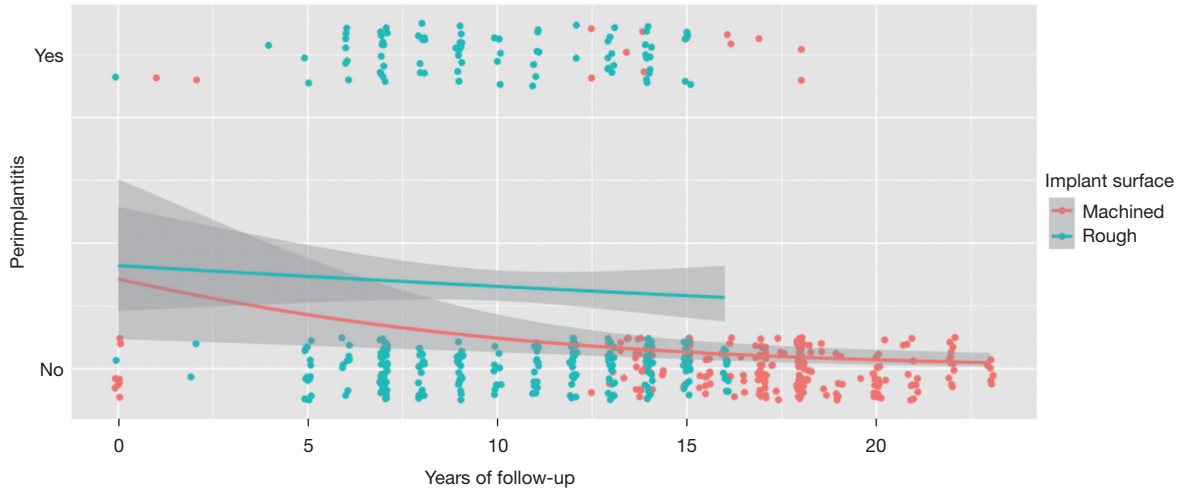

Figure 2 Scatter plot representing the number of years of follow-up on the x-axis and the occurrence of peri-implantitis on the y-axis, with each point representing an implant. The two regression lines are surrounded by their confidence intervals (dark gray shadows).

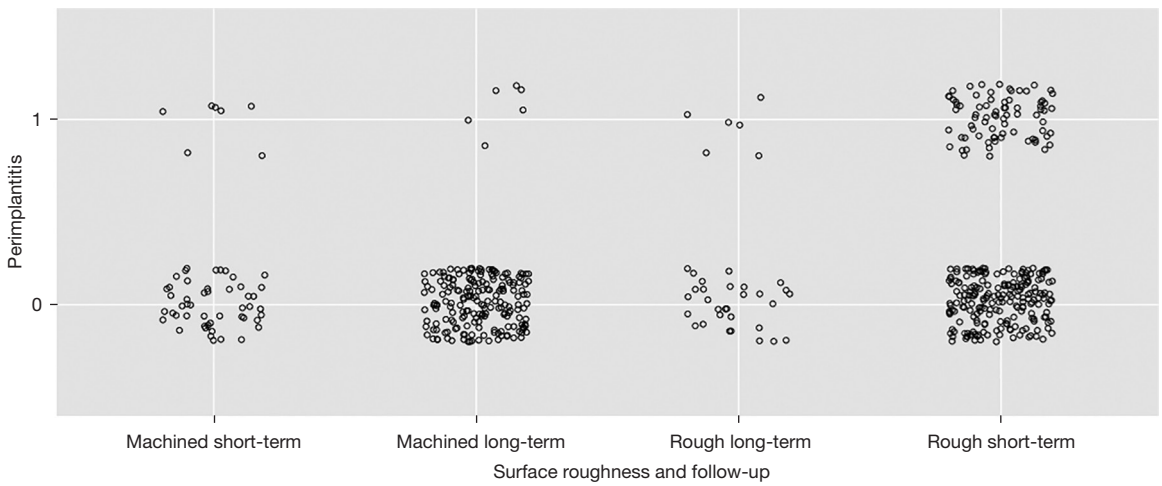

Figure 3 Scatterplot representing the subclassification of the pooled sample by the follow-up time (long-term = more than 15 years of follow-up; short-term = less than 15 years of follow-up) and the surface roughness (rough or machined). On the y-axis the occurrence of peri-implantitis is represented by 1, whereas no peri-implantitis is 0. Each point represents a dental implant.

patient a correct implant supportive care. Implants placed in the posterior mandibular area of smoking patients might need an additional attention and it could be favorable to use in such a situation an implant with a Sa <1 µm (e.g., machined surfaces). The role of initial MBL on the occurrence of peri-implantitis is uncertain.

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Footnote

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