ORIGINAL ARTICLE

Association between smoking and peri-implant diseases: A retrospective study

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Abstract

Objectives: To determine the association between tobacco and peri-implant diseases in a sample of patients who had received implant-supported restorations in a university dental clinic. Furthermore, the study aimed to investigate patient- and implant-related variables associated with peri-implant diseases.

Materials and Methods: The present retrospective study analyzed data from 117 patients treated with implant-supported restorations from 2001 to 2013. A total of 450 implants were evaluated. Patients were selected from an electronic database, and patient- and implant-related variables were evaluated. Detailed information regarding the smoking history (i.e., smoking status, lifetime cumulative dose, duration of exposure, intensity of the habit, and smoking cessation) was recorded. The primary study outcome was peri-implant status [i.e., health (H), peri-implant mucositis (PM) and peri-implantitis (PI)]. Univariate and multinomial regression models comparing PM and PI versus peri-implant health were conducted.

Results: A total of 117 subjects [55 (47%) females and 62 (53%) males] with a mean age at examination of 64.2 years (SD 11.6) and rehabilitated with 450 implants were included. The average number of implants per patient was 4.6 (SD 3.3) with a mean time in function of 8.0 years (SD 1.9). Fifty-six patients (47.9%) were non-smokers, 42 (35.9%) were former-smokers, and 19 (16.2%) were current-smokers. Thirty-nine subjects (33.4%) were H, whereas 41 (35%) and 37 (31.6%) exhibited PM and PI, respectively. At implant level, the corresponding values were 142 (31.6%), 230 (51.1%) and 78 (17.3%). In the multinomial regression model, significant associations for peri-implant diseases were observed for the mean number of implants per patient ($p=.016$), function time ($p=.048$), implants placed simultaneously with guided bone regeneration ($p=.016$), implant surface ($p=.020$), keratinized mucosa at the buccal aspect ($p=.032$), and access to interproximal hygiene ($p<.001$). In addition, ever smokers >23 pack-years exhibited a significantly higher risk for peri-implantitis ($p=.002$). Finally, the multinomial regression analysis revealed that subjects who had stopped smoking more than 21 years before the last examination presented a significantly lower risk of peri-implant diseases than a smoking cessation of ≤21 years ($p=.028$).

Conclusions: Smoke intensity was associated with an increased risk of the development of peri-implantitis. Moreover, the risk of peri-implant diseases might be similar in those subjects who had stopped smoking for more than 21 years with respect to never-smokers.

KEYWORDS
dental implants, implant-supported dental prosthesis, peri-implantitis, smoking

1 | INTRODUCTION

The use of dental implants has become a predictable therapy for the rehabilitation of partially and totally edentulous patients, resulting in high survival and success rates (Pjetursson et al., 2012); however, biologic complications may occur over time (Berglundh et al., 2002). Peri-implant mucositis (PM) has been described as the "presence of reversible inflammatory changes in the peri-implant mucosa without continuous marginal peri-implant bone loss" (Heitz-Mayfield & Salvi, 2018), while peri-implantitis (PI) is characterized by "inflammation of the peri-implant soft tissue and progressive loss of supporting bone" (Schwarz et al., 2018).

Derks and Tomasi (2015) showed, in a systematic review and meta-analysis, a prevalence of 43% for PM and 22% for PI. In addition, a cross-sectional study, conducted in Spain, revealed that, at the patient level, the prevalence of PM and PI was 27% and 24%, respectively (Rodrigo et al., 2018). All these data, and considering that the treatment of PI is not predictable, seem to indicate that prevention of peri-implant diseases is of key importance. According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, there is strong evidence that the risk of PI is higher in subjects with a history of periodontitis, poor plaque control, and a lack of regular maintenance after implant placement (Schwarz et al., 2018).

Regarding tobacco, the evidence supports that it is a risk factor for the onset and progression of periodontal disease and affects the composition of the biofilm (van Winkelhoff et al., 2001), the host response (Palmer et al., 2005), the wound healing (Frick & Seals Jr, 1994), and the success of periodontal therapy (Bunæs et al., 2015). Similarly, some studies concluded that the probability of suffering from PI was 2.7 to 31 times higher in smokers (Rinke et al., 2011; Roos-Jansåker, Lindahl, et al., 2006; Roos-Jansåker, Renvert, et al., 2006; Schwarz et al., 2017). Moreover, it has been reported, in a 10-year prospective cohort study, an incidence of peri-implant diseases of 6% in non-smokers vs. 17.9% in smokers (Karoussis et al., 2003). In this context, the biologic processes involved in osseointegration and maintenance of peri-implant bone levels could be affected by tobacco smoking and smokers showed significant worse clinical (i.e., bleeding on probing and probing depth) and radiographic parameters (i.e., marginal bone level) than non-smokers (ALHarthi et al., 2018). Furthermore, some studies demonstrated that tobacco contributes to the formation of dysbiotic biofilm (Ata-Ali et al., 2016; Sanz-Martin et al., 2017). Tsigarida et al. (2015) suggested that smoking shapes the peri-implant microbiome, characterized by a pathogen-rich community depleted of commensals even in a clinical health status.

Despite the results of these studies and considering that smoking was proposed as a risk factor/indicator for peri-implant diseases in the 6th European Workshop on Periodontology, there is no conclusive evidence supporting smoking as a risk factor/indicator for progressive loss of supportive bone (Schwarz et al., 2018).

Therefore, the objective of the present investigation was to determine the association between tobacco and peri-implant diseases in a sample of patients who had received implant-supported restorations in a university dental clinic. Furthermore, the study aimed to investigate patient- and implant-related variables associated with peri-implant diseases.

2 | MATERIALS AND METHODS

2.1 | Study design and patient selection

This research was designed as a retrospective cohort analysis of patients who were treated with implant-supported restorations at the Clínica Universitària d'Odontologia (CUO) of Universitat Internacional de Catalunya (UIC). The protocol was approved by the Ethical Committee of UIC (Ref. PER-ECL-2020-07) and the study was performed following the principles outlined in the Declaration of Helsinki of 1975 (revised in 2013). Prior to participation in the study, a written informed consent was obtained from each patient. This article followed the STROBE guidelines for reporting observational studies (von Elm et al., 2008).

Patients were recruited, from February 2021 until July 2021, on the basis of the following inclusion criteria: (1) men and women ≥18 years old; (2) partial or total edentulism subjected to rehabilitation with dental implants placed at CUO (UIC); (3) complete (fixed or removable), partial, or single tooth prosthesis; (4) cemented, screwed or mechanically retained prosthetic rehabilitation; and (5) adequate access for probing around dental implants. Moreover, implants placed between 2001 and 2013 were considered for the analysis and patients with incomplete records (i.e., when more than 10% of data was missing or incomplete) were excluded.

Subjects were selected from an electronic database collected at the CUO and composed of 1324 patients treated with at least one implant inserted during the above-mentioned period of time. This investigation used a stratified random sampling based on year of implant placement to select a representative sample of subjects

with implant-supported restorations conducted during the period 2001–2013 at the CUO. Then, one examiner (J.M.A) contacted patients by telephone in order to invite them to attend a clinical examination until the desired number of patients in each group was obtained.

In this context, the sample was divided into three groups: healthy patients (H), subjects with peri-implant mucositis (PM), and patients with peri-implantitis (PI).

2.2 | Data collection

Patient files were analyzed and the following subjects´ characteristics were registered: sex, age, referred medical conditions, type of edentulism, and supportive periodontal therapy (SPT). Quality of SPT was described in relation to the compliance with the maintenance therapy and participants were divided into three groups: fully compliers (i.e., subjects attending to the proposed SPT intervals during the observation period), erratic compliers (i.e., patients attending irregularly to the scheduled SPT intervals), and non-compliers (i.e., subjects not attending the SPT after the active periodontal therapy) (Amerio et al., 2020). The study variables were recorded in a case report form specially designed for the study.

2.2.1 | Periodontal and radiographic parameters

At patient level, full-mouth plaque score was assessed at four sites per tooth/implant (i.e., buccal, lingual, mesial, and distal) (O'Leary et al., 1972) and categorized as <20% and ≥20%.

At implant level, the following clinical parameters were evaluated at six sites per implant:

- Modified plaque index (mPI) (Mombelli et al., 1987).
- Modified bleeding index (mBI) (Mombelli et al., 1987).
- Suppuration on probing (SUP), assessed dichotomously within 30s after probing (i.e., presence/absence of suppuration).
- Probing pocket depth (PPD), recorded from the mucosal margin to the bottom of the peri-implant pocket.
- Mucosal recession (MR), measured from the implant neck to the mucosal margin.

Moreover, the width of keratinized mucosa (KM) was measured at the mid-buccal aspect of the implant site.

All clinical measurements were performed with an electronic pressure-calibrated probe (i.e., 0.20 N) (PA_ON Probe, Orange Dental®, Aspachstr, Biberach, Germany) by one examiner (J.M.A.).

Periapical x-rays were taken using the long-cone paralleling technique and a film holder. Digitally obtained radiographs were transferred into a software program (ImageJ; NIH, Bethesda, MA, USA) and calibrated according to the known dimensions of the implant. The distance between the implant shoulder and the first visible bone-to-implant contact (i.e., marginal bone level) was measured by a calibrated examiner (J.M.A), and the most apical level was registered.

2.2.2 | Periodontal diagnosis

Initial periodontal diagnosis was obtained from patient files. Since patients with implant-supported restorative therapy performed between 2001 and 2013 were selected, the periodontal status [periodontitis (mild, moderate, and severe) as well as no periodontitis] was based on the 1999 Consensus Classification of Periodontal Diseases (Armitage, 1999).

2.2.3 | Smoking habit

One examiner (J.M.A) collected data concerning the smoking habit at the clinical examination. Smoking status was classified into three categories: never smoker (i.e., <100 cigarettes per lifetime), former smoker, or current smoker. Moreover, current smokers were divided into light (<10 cigarettes/day), moderate (11–19 cigarettes/day), and heavy (≥20 cigarettes/day) smokers. Patients were asked about their tobacco smoke exposure in terms of consumption (i.e., number of cigarettes smoked per day), duration (i.e., number of smoking years), and age at starting smoking. Furthermore, lifetime exposure (i.e., pack-years) was calculated (Scott et al., 2001). In case of former smokers, patients were asked about the time since smoking cessation.

Smokers answered the Fagerström test for nicotine dependence (FTND) (Heatherton et al., 1991), which is a six-item questionnaire with a total score ranging between 0 (no dependence) and 10 (highest dependence level). Likewise, participants were asked about type of tobacco [cigarettes (factory-made, hand-rolled, and electronic), cigar, pipe]. Regarding cigarettes, the following information was registered: number of puffs per cigarette, nicotine yield on a pack, cigarette tar yield (regular, light, or ultralight), and flavor (unflavored or menthol).

Finally, information about the motivation to quit smoking was obtained: (1) Have you ever tried to quit smoking? (no/yes) (2) How many times have you ever tried to quit smoking? (3) How difficult is it for you to quit smoking? (very easy, easy, difficult, very difficult).

2.2.4 | Implants

Data regarding implant characteristics was collected from patient files [diameter, length, brand, function time, implant location, surface roughness (Albrektsson & Wennerberg, 2004), type of connection, timing of implant placement after tooth extraction, use of systemic antibiotics before and/or immediately following the surgical intervention, and bone augmentation].

In addition, the following prostheses' features were recorded: type of prosthesis, prosthetic loading protocol, and type of retention.

In addition, the access to oral hygiene around dental implants was evaluated and categorized as possible, difficult, and no accessibility (Takamoli et al., 2021).

2.3 | Case definitions

According to Berglundh et al. (2018), the following case definitions were considered:

- *Peri-implant health* was based on absence of clinical signs of inflammation, lack of bleeding and/or suppuration on gentle probing, and absence of bone loss following initial remodeling.
- *Peri-implant mucositis (PM)* was diagnosed in cases of presence of bleeding and/or suppuration on gentle probing and absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling.
- *Peri-implantitis (PI)*. Since baseline data was not always available, the following case definition was applied: presence of bleeding and/or suppuration on probing, marginal bone level ≥3 mm apical to the most coronal part of the intraosseous portion of the implant and/or probing depths ≥6 mm.

In case of more than one implant per patient, the implant with the worst clinical conditions was considered to classify subjects into one of these three categories.

2.4 | Sample size calculation

Sample size calculation was based on the main outcome variable: peri-implant diseases. Assuming an alpha risk of 5% and a beta risk of 20% in a bilateral contrast, a total of 120 subjects (40 patients in each group) were required to detect a minimum odd ratio (OR) of 4.6 of having peri-implant diseases (Roos-Jansåker, Renvert, et al., 2006). A replacement rate of 15% was anticipated.

2.5 | Calibration

The examiner (J.M.A) was calibrated in clinical (PPD) and radiographic (marginal bone level) parameters. Five non-study patients, with at least one loaded implant, were examined in two separate occasions, 1 week apart. The intra-examiner reliability resulted in intra-class correlation coefficients of 0.957 (SE = 0.079) and 0.997 (SE = 0.065) for PPD and marginal bone level, respectively.

2.6 | Statistical analysis

Categorical variables were expressed with absolute frequencies and percentages, whereas the description of continuous variables was performed using the mean and standard deviation (SD). The Kolmogorov–Smirnov test was used to assess whether data followed a normal distribution.

The analysis was performed at patient and implant level. Comparisons according to the study groups were carried out using the ANOVA test in case of continuous variables or Chi-squared test (Fisher test when expected frequencies <5) for categorical variables.

Smoke intensity was calculated combining smoking status (never, current and former smoker) and pack-years and transformed into a binary variable using the median value (>23 pack-years), obtaining an area under the curve (AUC) of 0.678.

A final model was developed using multinomial regression analysis including study groups as a dependent variable. A Generalized Estimation Equation model (GEE) with repeated measures was employed to include the patient effect. Healthy group was considered as reference category. Variables with a significance <.2 in the univariate analysis were included as independent variables. The results were described with odds ratio (OR) with a 95% confidence interval (CI) and *p*-values.

Additionally, with the objective to identify in former smokers the best predictive cut-off of smoking cessation years (>21 years) for peri-implant diseases, a multinomial regression model adjusted by age, gender, and number of implants was carried out.

For all the tests, *p*-values <.05 were considered statistically significant. The statistical analysis was performed with the statistical R package (V2.5).

3 | RESULTS

3.1 | Study population

Considering that 40 patients in each group were necessary, 250 subjects were randomly selected from all the 1324 patients (i.e., approximately 20%). Of these, 97 were not able or not willing to be examined, resulting in a response rate of 61.2%. The most common reasons for non-attendance included lack of interest (40%), general health (37%), geographical location (17%), and other reasons (6%). Hence, 153 patients were evaluated until the number of patients required per group was obtained. Moreover, 4 patients (i.e., one subject from the H group and 3 patients with PI) presented incomplete medical records and were excluded from the study.

A total of 117 subjects [55 (47%) females and 62 (53%) males] with a mean age at examination of 64.2 years (SD 11.6) and rehabilitated with 450 implants were included. The average number of implants per patient was 4.6 (SD 3.3) with a mean time in function of 8.0 years (SD 1.9) (Table S1).

Of these patients, 39 (33.4%) were H, whereas 41 (35%) and 37 (31.6%) exhibited PM and PI, respectively. Statistically significant differences in gender and educational level were observed between groups (*p* = .024 and *p* < .001, respectively). At implant level, the

TABLE 1 Description of studied patients ($n = 117$) and implants ($n = 450$).

Variable	Mean ± SD or n (%)	Health	PM	PI	p-Value
Patient-related variables	$n = 117$	$n = 39$	$n = 41$	$n = 37$	
Sex (men) (%)[a]	62 (53%)	22 (56.4%)	23 (56.1%)	17 (46%)	**.024**
Age (years)[b]	64.2 ± 11.6	62.7 ± 12.9	66.1 ± 11.2	63.6 ± 10.5	.399
Education Level (%)[a]					**<.001**
Low	45 (38.5%)	10 (25.6%)	20 (48.8%)	15 (40.5%)	
Medium	39 (33.3%)	14 (35.9%)	10 (24.4%)	15 (40.5%)	
High	33 (28.2%)	15 (38.5%)	11 (26.8%)	7 (18.9%)	
Systemic (%)[a]					
Healthy	37 (31.6%)	13 (33.3%)	14 (34.1%)	10 (27.0%)	.265
Cardiovascular disease	24 (20.5%)	7 (17.9%)	6 (14.6%)	11 (29.7%)	.052
Hypercholesterolemia	22 (18.8%)	4 (10.3%)	11 (26.8%)	7 (18.9%)	.061
Diabetes Mellitus	20 (17.1%)	2 (5.1%)	10 (24.4%)	8 (21.6%)	**.034**
Self-reported allergy to penicillin (%)[a]	8 (6.8%)	3 (7.7%)	1 (2.4%)	4 (10.8%)	.484
History of periodontitis (%)[a]	87 (74.4%)	23 (59.0%)	36 (87.8%)	28 (75.7%)	**<.001**
Periodontal status (%)[a]					**<.001**
Health	54 (46.2%)	26 (66.7%)	14 (34.1%)	14 (37.8%)	
Gingivitis	11 (9.4%)	3 (7.7%)	6 (14.6%)	2 (5.4%)	
Mild CP	20 (17.1%)	4 (10.3%)	10 (24.4%)	6 (16.2%)	
Moderate CP	21 (17.9%)	4 (10.3%)	8 (19.5%)	9 (24.3%)	
Severe CP	11 (9.4%)	2 (5.1%)	3 (7.3%)	6 (16.2%)	
Type of edentulism (partial) (%)[a]	107 (91.5%)	39 (100.0%)	37 (90.2%)	31 (83.8%)	**<.001**
Number of implants per patient [b]	4.6 ± 3.3	3.3 ± 2.8	5.3 ± 3.2	5.3 ± 3.4	**.007**
Full-mouth plaque score (<20%) (%)[a]	7 (6.0%)	0 (0%)	7 (17.1%)	0 (0%)	**.032**
SPT complier (%)[a]	47 (40.2%)	16 (41.0%)	14 (34.1%)	17 (46.0%)	**<.001**
Implant-related variables	$n = 450$	$n = 142$	$n = 230$	$n = 78$	
Width (mm)[b]	4.1 ± 0.5	4.1 ± 0.6	4.1 ± 0.5	4.1 ± 0.6	.581
Length (mm)[b]	11.1 ± 2.0	10.8 ± 2.3	11.2 ± 1.8	11.4 ± 2.1	.091
Function time (years)[b]	8.0 ± 1.9	7.45 ± 2.2	7.72 ± 1.8	8.55 ± 1.8	**<.001**
Jaw (maxilla) (%)[a]	260 (57.8%)	77 (54.2%)	137 (59.6%)	46 (59%)	.582
Position (posterior) (%)[a]	336 (74.7%)	109 (76.8%)	167 (72.6%)	60 (76.9%)	.590
Time of implant placement (delayed) (%)[a]	438 (97.3%)	140 (98.6%)	224 (97.4%)	74 (94.9%)	.261
Use of antibiotics (%)[a]	447 (99.3%)	142 (100.0%)	227 (98.7%)	78 (100.0%)	.236
Regeneration (yes) (%)[a]	110 (24.4%)	26 (18.3%)	67 (29.1%)	17 (21.8%)	.052
Surface roughness (%)[a]					**<.001**
Minimally rough	74 (17.0%)	8 (5.8%)	48 (21.4%)	18 (24.0%)	
Moderately rough	337 (77.3%)	128 (93.4%)	158 (70.5%)	51 (68.0%)	
Rough	25 (5.7%)	1 (0.7%)	18 (8.0%)	6 (8.0%)	
Type of prosthesis (%)[a]					.125
Single	91 (20.2%)	38 (26.8%)	41 (17.8%)	12 (15.4%)	
Partial	252 (56.0%)	77 (54.2%)	125 (54.4%)	50 (64.1%)	
Full arch	96 (21.3%)	23 (16.2%)	59 (25.7%)	14 (18.0%)	
Overdenture	11 (2.4%)	4 (2.8%)	5 (2.2%)	2 (2.6%)	

(Continues)

TABLE 1 (Continued)

Implant-related variables	n = 450	n = 142	n = 230	n = 78	
Type of connection (internal) (%)[a]	446 (99.1%)	142 (100.0%)	228 (99.1%)	76 (97.4%)	.153
Loading protocol (delayed) (%)[a]	438 (97.3%)	140 (98.6%)	224 (97.4%)	74 (94.9%)	.261
Type of retention (screwed) (%)[a]	387 (86.0%)	118 (83.1%)	198 (86.1%)	71 (91.0%)	.268
Access to interproximal hygiene (%)[a]					<.001
No accessibility	76 (16.9%)	15 (10.6%)	39 (17.0%)	22 (28.2%)	
Difficult	183 (40.7%)	33 (23.2%)	112 (48.7%)	38 (48.7%)	
Possible	191 (42.4%)	94 (66.2%)	79 (34.3%)	18 (23.1%)	

Note: Bold numbers are statistically significant, *p*-value <.05.

Abbreviations: CP, chronic periodontitis; PI, peri-implantitis; PM, peri-implant mucositis; SPT, supportive periodontal therapy.

[a]Chi-square or Fisher's test.

[b]ANOVA.

TABLE 2 Mean clinical and radiographic parameters at implant-level.

Variable	Mean ± SD n = 450	Health n = 142	PM n = 230	PI n = 78	*p*-Value
mPI	0.61 ± 0.57	0.25 ± 0.39	0.77 ± 0.57	0.79 ± 0.54	**<.001**
mBI	0.55 ± 0.64	0.00 ± 0.00	0.74 ± 0.57	1.01 ± 0.73	**<.001**
SUP	0.03 ± 0.14	0.00 ± 0.00	0.01 ± 0.09	0.11 ± 0.29	**<.001**
PPDm (mm)	3.50 ± 0.98	3.03 ± 0.48	3.48 ± 0.90	4.43 ± 1.20	**<.001**
PPDd (mm)	4.40 ± 1.05	3.53 ± 0.96	4.20 ± 0.98	5.31 ± 1.12	**<.001**
MR (mm)	0.20 ± 0.56	0.03 ± 0.13	0.22 ± 0.56	0.44 ± 0.87	**<.001**
KM (mm)	2.04 ± 1.42	2.17 ± 1.29	2.23 ± 1.48	1.72 ± 1.37	**.018**
BL (mm)	2.29 ± 1.10	0.24 ± 0.50	0.92 ± 0.91	4.40 ± 1.49	**<.001**

Note: Bold numbers are statistically significant, *p*-value <.05.

Abbreviations: BL, bone level measured at the deepest site per implant; KM, keratinized mucosa; mBI, Modified Bleeding Index; mPI, Modified Plaque Index; MR, mucosal recession; PPDd, probing pocket depth measured at the deepest site per implant; PPDm, probing pocket depth when average of the six sites per implant was used; SUP, suppuration on probing.

corresponding values were 142 (31.6%), 230 (51.1%) and 78 (17.3%). Patient and implant characteristics are detailed in Table 1.

3.2 | Peri-implant conditions

Table 2 provides descriptive statistics of the registered peri-implant parameters. According to the diagnosis of the peri-implant conditions, no sites of H implants showed bleeding, while the mean mBI scores for implants with PM and PI were 0.7 (SD 0.6) and 1.0 (SD 0.7), respectively (*p* <.001). This was in accordance with the mean values for PPD, which were statistically significant lower at H and PM groups in comparison with PI group (*p* <.001). With respect to marginal bone level, statistically significant differences were found between groups at the final examination [H: 0.2 mm (SD 0.5); PM: 0.9 mm (SD 0.9); PI: 4.4 mm (SD 1.5); *p* <.001] (Table 2).

Finally, regarding KM, statistically significant differences were also observed between groups (*p* = .018), being lower in the PI group compared with H and PM groups.

3.3 | Smoking habit

With regards to tobacco use, 56 patients (47.9%) were never-smokers, 42 (35.9%) former smokers, and 19 (16.2%) current smokers. In addition, the daily frequency of smoking was 15.7 cig/day (SD 11.2) and most patients were smokers of factory-made (82.4%) and ultralight (88.2%) cigarettes (Table 3).

In general, the mean FTND score was 4.0 (SD 1.0) and, concerning the smoking cessation, most patients (84.2%) had made an attempt to quit smoking [2.5 times (SD 4.4)], but they considered difficult/very difficult quitting (Table 3).

3.4 | Association of peri-implant diseases with smoking-related factors

The association between smoking-related variables and peri-implant diseases is shown in Table 3. Among the smokers, the

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TABLE 3 Description of smoking-related variables.

Smoking-related variables	Mean ± SD or n (%) n = 117	Health n = 39	PM n = 41	PI n = 37	p-Value
Smoking status (%)[a] (n = 117)					**<.001**
Never-smoker	56 (47.9%)	17 (43.6%)	24 (58.5%)	15 (40.5%)	
Former smoker	42 (35.9%)	16 (41.0%)	13 (31.7%)	13 (35.1%)	
Current smoker	19 (16.2%)	6 (15.4%)	4 (9.8%)	9 (24.3%)	
Age at initiation (years)[b] (n = 61)	18.6 ± 6.0	19.9 ± 6.8	18.8 ± 7.7	17.2 ± 2.7	.344
Smoking behaviour[a] (n = 19)					.536
Light smoker	6 (31.6%)	3 (50%)	2 (50%)	1 (11.1%)	
Moderate smoker	9 (47.4%)	3 (50%)	2 (50%)	4 (44.4%)	
Heavy smoker	4 (21%)	0 (0%)	0 (0%)	4 (44.4%)	
Duration of smoking (years)[b] (n = 61)	29.6 ± 14.1	20.2 ± 11.4	34.4 ± 12.6	35.4 ± 13.0	**<.001**
Number of cig/day (n = 61)	15.7 ± 11.2	16.0 ± 14.0	11.0 ± 5.9	18.9 ± 10.3	.087
Number of pack-years (n = 61)	26.1 ± 19.4	18.6 ± 17.7	23.3 ± 16.9	35.7 ± 19.6	**.009**
Smoke intensity (n = 117)					**.035**
Never-smoker	56 (47.9%)	17 (43.6%)	24 (58.5%)	15 (40.5%)	
≤23 pack-years	32 (27.3%)	14 (35.9%)	12 (29.3%)	6 (16.2%)	
>23 pack-years	29 (24.8%)	8 (20.5%)	5 (12.2%)	16 (43.2%)	
Type of tobacco (%)[a] (n = 19)					.061
Cigarettes	17 (89.5%)	6 (100%)	3 (75%)	8 (88.9%)	
Cigar	2 (10.5%)	0 (0%)	1 (25%)	1 (11.1%)	
Type of cigarettes (%)[a] (n = 17)					**.038**
Factory-made	14 (82.4%)	4 (66.7%)	3 (100%)	7 (87.5%)	
Hand-rolled	3 (17.6%)	2 (33.3%)	0 (0%)	1 (12.5%)	
Electronic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Cigarette tar yield (%)[a] (n = 17)					.125
Regular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Light	2 (11.8%)	0 (%)	0 (0%)	2 (25%)	
Ultralight	15 (88.2%)	6 (100%)	3 (100%)	6 (75%)	
Flavor (unflavored) (%)[a] (n = 17)	15 (88.2%)	5 (83.3%)	3 (100%)	7 (87.5%)	**.048**
Number of puffs per cigarette[b] (n = 17)	10.7 ± 3.8	12.8 ± 4.0	7.0 ± 2.4	10.9 ± 3.1	**.046**
FTND[b] (n = 19)	4 ± 1.0	4 ± 1.1	4 ± 1.0	4 ± 1.0	.852
Duration of smoking cessation (years)[b] (n = 42)	20.2 ± 12.6	26.7 ± 15.6	17.1 ± 6.6	15.2 ± 10.0	**.025**
Quitting attempt (yes) (%)[a] (n = 19)	16 (84.2%)	5 (83.3%)	3 (75%)	8 (88.9%)	.085
Number of quit attempts[b] (n = 19)	2.5 ± 4.4	1.5 ± 1.0	5.5 ± 9.7	1.8 ± 1.2	.315
Difficulty to quit smoking[a] (n = 19)					.075
Very easy	2 (10.5%)	0 (0%)	1 (25%)	1 (11.1%)	
Easy	1 (5.3%)	0 (0%)	1 (25%)	0 (0%)	
Difficult	10 (52.6%)	4 (66.7%)	2 (50%)	4 (44.4%)	
Very difficult	6 (31.6%)	2 (33.3%)	0 (0%)	4 (44.4%)	

Note: Bold numbers are statistically significant, *p*-value <.05.

Abbreviation: FTND, Fagerström test for nicotine dependence.

[a]Chi-square or Fisher's test.

[b]ANOVA.

frequency of PI was 24.3%, while 4 (9.8%) and 6 (15.4%) patients showed PM and peri-implant health, respectively. Nevertheless, although subjects with PI smoked a greater number of cigarettes per day [16.0 cig/day (SD 14.0), 11.0 cig/day (SD 5.9), and 18.9 cig/day (SD 10.3) for H, PM and PI patients, respectively], no statistically significant differences were observed between groups ($p = .087$). Moreover, subjects with peri-implant diseases started smoking earlier [PM: 18.8 years (SD 7.7); PI: 17.2 years (SD 2.7)] than H patients [19.9 years (SD 6.8)], without reaching statistical significance ($p = .344$).

Regarding the smoking duration, statistically significant differences were found between groups [H: 20.2 years (SD 11.4); PM: 34.4 years (SD 12.6); PI: 35.4 (SD 13); $p < .001$]. The same trend was found when lifetime cumulative dose was considered. The mean number of pack-years was 18.6 (SD 17.7), 23.3 (SD 16.9), and 35.7 (SD 19.6) for H, PM, and PI, respectively, being these differences statistically significant ($p = .009$).

Furthermore, when radiographs were analyzed, tobacco consumption seemed to be related to peri-implant bone resorption. Smokers showed a mean radiographic bone level of 2.30 mm (SD 2.06), while former smokers and never smokers exhibited a peri-implant marginal bone level of 1.30 mm (SD 1.87) and 0.96 mm (SD 1.28), respectively. The differences between groups were statistically significant ($p < .001$).

With respect to the number of years since smoking cessation, statistically significant differences were found between groups [H: 26.7 (SD 15.6) years; PM: 17.1 (SD 6.6) years; PI: 15.2 (SD 10.0) years; $p = .025$].

3.5 | Association of peri-implant disease with patient- and implant-related variables

Patient- and implant-related variables associated with peri-implant diseases are depicted in Table 1. At the patient level, peri-implant diseases were significantly associated with full-mouth plaque score ($p = .032$) as well as history of periodontitis, periodontitis status, SPT, and edentulism (all $p < .001$). In addition, the mean number of implants per patient was higher in individuals with PM and PI than those from the H group ($p = .007$).

Also, some aspects related to the implant characteristics and surgical approach resulted relevant. The mean time in function was significantly higher ($p < .001$) in those implants with PI as compared to those implants diagnosed with PM and H implants (Table 1). Moreover, when compared to moderately rough surface, minimally rough surfaces were more common in those implants affected with PM (21.4%) and PI (24%) than in H implants (5.8%) ($p < .001$). Additionally, peri-implant diseases were more frequent in those implants placed with guided bone regeneration (H: 18.3%; PM: 29.1%; PI: 21.8%); however, these differences were of borderline significance ($p = .052$).

In addition, prosthetic design seemed to be related to peri-implant diseases. While peri-implant diseases were less frequently observed in cement-retained rehabilitations than screw-retained prosthesis, implants rehabilitated with partial and complete fixed dentures presented more frequently peri-implant diseases than single restorations; however, these differences did not reach statistical significance ($p = .268$ and $p = .125$, respectively). Furthermore, those restorations that did not allow a proper access for oral hygiene were significantly more frequent in those implants with PM (no access: 17%; difficult: 48.7%) and PI (no access: 28.2%; difficult: 48.7%) ($p < .001$) (Table 1).

3.6 | Factors related to peri-implant diseases

Results of multinomial regression analysis are depicted in Table 4. At the patient-level, the final multinomial regression model indicated that the mean number of implants per patient was independently associated to peri-implant diseases (PM: OR = 1.29; 95% CI 1.07–1.57; PI: OR = 1.38; 95% CI 1.17–1.57; $p = .016$). In addition, ever smokers >23 pack-years exhibited a significantly higher risk for peri-implantitis (OR = 3.40; 95% CI 0.91–17.30; $p = .002$).

At the implant-level, those implants placed with guided bone regeneration appeared to be at higher risk for developing PM (OR = 2.22; 95% CI 1.30–5.29; $p = .016$). Moreover, implants with a moderately rough surface (PM: OR = 0.28; 95% CI 0.10–0.74; PI: OR = 0.29; 95% CI 0.11–0.80; $p = .020$) and good access to interproximal hygiene (PM: OR = 0.45; 95% CI 0.21–0.94; PI: OR = 0.19; 95% CI 0.07–0.46; $p < .001$) presented significantly lower risk of peri-implant diseases. Additionally, while a higher time of function was statistically significant associated with an increased risk of PI (OR = 1.11; 95% CI 1.01–1.55; $p = .048$), greater dimensions of KM at the buccal aspect decreased the risk of peri-implant bone loss (OR = 0.78; 95% CI 0.65–0.99; $p = .032$).

With respect to former smokers, the multinomial regression analysis after adjusting for age, gender, and number of implants revealed that subjects who had stopped smoking more than 21 years before the last examination presented a significantly lower risk of peri-implant diseases than a smoking cessation of ≤21 years (PM: OR = 0.12; 95% CI 0.02–0.78; PI: OR = 0.07; 95% CI 0.01–0.8; $p = .028$; Figure 1).

4 | DISCUSSION

The aim of this retrospective study was to determine the association between tobacco (i.e., smoking status, lifetime cumulative dose, duration of exposure, intensity of the habit, and smoking cessation) and peri-implant diseases in a sample of patients who had received implant-supported restorations in a university dental clinic. Furthermore, the study aimed to identify patient and implant characteristics associated with peri-implant diseases.

First, the results of this investigation showed that smoking status (i.e., never-smoker, smoker, former smoker) was not associated with an increased risk of development of peri-implant diseases when

TABLE 4 Random effects univariate and multinomial regression model comparing PM and PI versus peri-implant health.

| | Univariate OR (95% CI) | | | Multivariable OR (95% CI) | | |
| | Group | | | Group | | |
Variable	PM	PI	p-Value	PM	PI	p-Value
Patient-related variables						
Age	1.1 (0.98–1.3)	1.12 (0.96–1.06)	.399			
Sex (man)	1.05 (0.43–2.55)	0.63 (0.25–1.54)	.455			
Educational level			.120			
Low (ref)	1	1				
Medium vs. ref	0.33 (0.10–1.10)	0.68 (0.24–1.99)				
High vs. ref	0.34 (0.10–1.15)	0.38 (0.05–0.99)				
History of periodontitis	1.35 (0.36–3.90)	2.29 (0.40–8.51)	.489			
Periodontal status			.205			
Periodontal health (ref)	1	1				
Mild CP vs. ref	15.00 (1.34–167.64)	9.00 (0.76–108.00)				
Moderate CP vs. ref	12.00 (1.05–136.79)	13.50 (1.20–172.21)				
Severe CP vs. ref	9.00 (0.42–152.36)	17.00 (1.27–285.70)				
SPT	0.77 (0.31–1.92)	1.16 (0.47–2.87)	.587			
Number of implants	1.28 (1.06–1.56)*	1.27 (1.08–1.55)*	.010	1.29 (1.07–1.57)*	1.38 (1.17–1.57)*	.016
Smoking-related variables						
Smoking status			.436			
Never-smoker (ref)	1	1				
Smoker vs. ref	0.50 (0.12–2.10)	1.60 (0.48–6.50)				
Former smoker vs. ref	0.62 (0.23–1.77)	0.87 (0.32–2.85)				
Pack-years	1.02 (0.99–1.11)	1.16 (1.01–1.28)*	.032			
Duration of smoking	1.15 (1.02–1.27)*	1.10 (1.04–1.67)*	.004			
Smoke intensity			.030			.002
Never-smoker (ref)	1	1				
Yes (≤23 pack-years) vs. never-smoker	0.65 (0.24–1.95)	0.42 (0.21–1.50)		0.56 (0.19–1.69)	0.34 (0.05–1.62)	
Yes (>23 pack-years) vs. never-smoker	0.46 (0.13–1.66)	2.26 (1.77–6.68)*		0.25 (0.05–1.27)	3.40 (0.91–17.30)*	
Duration of smoking cessation	1.10 (0.98–1.22)	1.09 (0.95–1.28)	.060			
Implant-related variables						
Width	1.15 (0.61–2.45)	1.17 (0.72–3.00)	.856			
Length	1.08 (0.98–1.52)	1.14 (1.00–1.78)*	.040			
Jaw (mandible)	0.95 (0.44–1.69)	0.98 (0.48–1.50)	.721			
Position (posterior)	0.70 (0.36–1.44)	0.81 (0.44–1.88)	.288			
Regeneration (yes)	4.15 (2.14–15.12)*	3.47 (1.56–10.25)*	<.001	2.22 (1.30–5.29)*	1.73 (0.80–3.75)	.016
Buccal KM	0.95 (0.83–1.20)	0.76 (0.50–0.99)*	.040	0.90 (0.78–1.55)	0.78 (0.65–0.99)*	.032
Surface roughness (moderately rough)	0.35 (0.08–0.83)*	0.32 (0.09–0.85)*	.001	0.28 (0.10–0.74)*	0.29 (0.11–0.80)*	.020
Type of prosthesis			<.001			.090
Single (ref)	1	1				
Partial vs. single	2.01 (1.15–4.25)*	3.15 (1.98–7.58)*		1.18 (0.62–3.15)	1.23 (0.98–3.00)	
Complete vs. single	2.59 (1.14–5.87)*	6.25 (2.45–14.25)*		1.67 (0.98–4.85)	1.18 (0.90–4.21)	

(Continues)

TABLE 4 (Continued)

Variable	Univariate OR (95% CI) Group PM	PI	p-Value	Multivariable OR (95% CI) Group PM	PI	p-Value
Type of retention (cemented)	0.41 (0.17–1.10)	0.33 (0.22–0.75)*	.035			
Access to interproximal hygiene			**<.001**			**<.001**
No accessibility (ref)	1	1				
Limited vs.ref	5.25 (1.62–11.85)*	2.25 (1.00–7.58)*		1.90 (0.88–4.08)	1.26 (0.53–3.00)	
Possible vs. ref	0.56 (0.23–1.15)	0.21 (0.10–0.45)*		0.45 (0.21–0.94)*	0.19 (0.07–0.46)*	
Function time	1.10 (0.78–1.24)	1.22 (1.01–1.59)*	.03	1.01 (0.88–1.50)	1.11 (1.01–1.55)*	**.048**

*Statistically significant, *p*-value <.05.

Note: Bold numbers are statistically significant, *p*-value <.05.

Abbreviations: CP, chronic periodontitis; KM, keratinized mucosa; OR, odds ratio; SPT, supportive periodontal therapy.

comparisons were made between smokers vs. never-smokers and former smokers vs. never-smokers ($p = .436$). In this context, heterogeneous data have previously been reported.

Regarding PI, there are some investigations which did not find a relationship between tobacco and PI (Dalago et al., 2017; Daubert et al., 2015; de Araújo Nobre et al., 2015; Koldsland et al., 2011; Marrone et al., 2013; Renvert et al., 2014), whereas other studies supported this association (Rinke et al., 2011; Roos-Jansåker, Renvert, et al., 2006). In fact, although smoking has been associated to implant failure (Chen et al., 2013; Sánchez-Pérez et al., 2007; Strietzel et al., 2007; Takamoli et al., 2021), in the 2017 World Workshop Consensus Report on Periodontal and Peri-implant Conditions it was not considered a risk factor for peri-implantitis (Schwarz et al., 2018). These contradictory results might be partially explained by the different criteria used to define a smoker (i.e., number of cigarettes/day –continuous variable– or presence/absence of smoking –categorical variable–) and, strikingly, the minimum number of cigarettes per day to be included as a smoker was not reported in most of the investigations.

Moreover, the available data on the impact of the quantity of smoking on peri-implant diseases and late implant failure is scarce. In this context, Lindquist et al., (1997) observed, in a 10-year follow-up study, a significant higher bone resorption in patients who smoked >14 cig/day than those who reported smoking ≤14 cig/day and non-smokers. Recently, the results of a systematic review and meta-analysis showed a statistically significant higher risk of implant failure in subjects who smoked >10 cigarettes/day when compared to non-smokers (Naseri et al., 2020). Thus, these findings suggested a higher risk of peri-implant bone loss and, consequently, implant failure when the number of cigarettes smoked per day increases.

Nevertheless, the daily cigarette consumption is an imprecise indicator to provide information of smoking-related disease risk (Etter & Perneger, 2001). In this sense, pack-years (i.e., the product of smoking rate and duration of exposure) is used to estimate the lifetime cumulative dose (Peto, 2012). In the present investigation, a

significant association between pack-years and peri-implant diseases was found in the univariate analysis (PM: OR = 1.02; 95% CI 0.99–1.11; PI: OR = 1.16; 95% CI 1.01–1.28; $p = .032$). This is in line with previous studies in which the influence of tobacco smoking on periodontal disease progression was investigated and a dose–response association between pack-years and periodontal destruction was observed (Kibayashi et al., 2007). Likewise, Pleasants et al. (2020) demonstrated that an increased number of pack-years is associated with a higher risk of developing smoking-related diseases. Certainly, in the present study, the multinomial regression analysis revealed that ever-smokers with >23 pack-year history of smoking exhibited a significant higher risk of PI (OR = 3.40; 95% CI 0.91–17.30; $p = .002$) when compared to never-smokers. Similar findings were reported by Twito and Sade (2014) who observed, in a retrospective study, a significant higher risk of implant failure in those smokers with at least 10 pack-years of exposure (OR = 2.30) in comparison with non-smokers.

It is of importance to mention at this point that the pack-years product considers that the weight for both cigarettes/day and duration of smoking is equal. However, duration of smoking might be considered more significant than cigarettes smoked per day or cumulative dose (i.e., pack-years) in assessing risk of developing smoking-related alterations (Bhatt et al., 2018; Flanders et al., 2003; Inoue-Choi et al., 2017). Interestingly, the present study observed a significant association between the duration of exposure and peri-implant diseases (PM: OR = 1.15; 95% CI 1.02–1.27; PI: OR = 1.10; 95% CI 1.04–1.67; $p = .004$). These results are in accordance with those published in a retrospective study, with 10 years of follow-up, that demonstrated a higher risk of implant failure when the duration of tobacco exposure increases (Mundt et al., 2006). In this sense, recent studies suggested that smoking-related changes in DNA methylation are associated with the smoking duration (McCartney et al., 2018). Thus, tobacco smoking over an extended time period has substantial health consequences and early smoking initiation appears to be related to an increased risk of developing smoking-related diseases (Choi & Stommel, 2017).

(a) Peri-implant mucositis
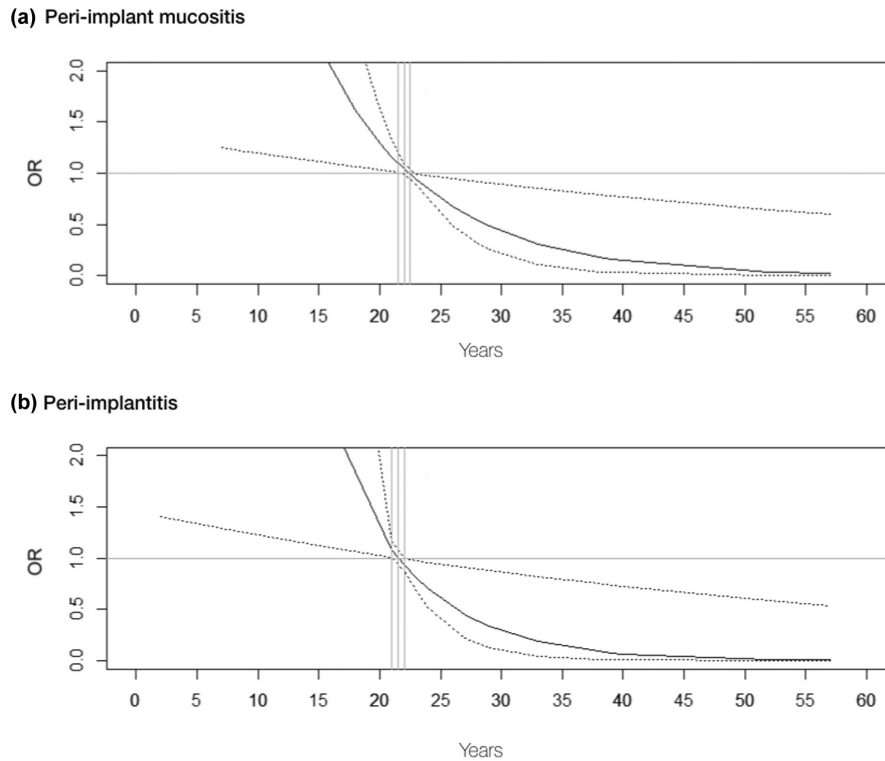
(b) Peri-implantitis

FIGURE 1 Regression logistic model in former smokers, adjusted by age, gender, and number of implants to identify the cut-off of duration of smoking cessation from which the risk of (a) peri-implant mucositis and (b) peri-implantitis decreases.

Hence, a comprehensive representation of tobacco exposure (intensity, duration, and age at initiation) is necessary in order to describe the risk of developing peri-implant diseases (Thomas, 2014).

Certainly, tobacco smoke increases the formation of advanced glycation end products (AGEs) (Katz et al., 2005) and induces an oxidative stress (Correa et al., 2019) as well as alterations in the immune system (i.e., levels and expression of inflammatory cytokines) (Palmer et al., 2005), which could be associated with the inflammation of peri-implant soft tissues and crestal bone loss (Alahmari et al., 2019). In the present investigation, smokers showed significantly higher marginal bone loss when compared to never- and former smokers (2.30, 0.96 and 1.30, respectively). These findings are in agreement with previous studies that investigated the impact of smoking on peri-implant bone tissue and observed a statistically significant higher marginal bone loss in smokers (i.e., cigarette or waterpipe) than former and non-smokers (Alahmari et al., 2019; Levin et al., 2008).

Interestingly, tobacco smoke contains more than 4000 toxic chemicals, including nicotine which contributes to addiction and, consequently, health alterations. In this context, different methods to assess tobacco smoke exposure have been described such as environmental measurements (i.e., air carbon monoxide levels), questionnaires/interviews and biomarkers (i.e., cotinine) (Florescu et al., 2009). In the present investigation, tobacco exposure was based on self-reported data and an accurate scale for the measurement of tobacco exposure (i.e., biomarkers) was not used. However,

it should be mentioned that questionnaires are the most commonly method for the assessment of long-term exposure to tobacco smoke and could be considered a reliable tool to collect data on smoking habits (Alqahtani et al., 2019).

With respect to peri-implant mucositis, the last consensus on peri-implant diseases suggested that biofilm accumulation, smoking, and radiation therapy could be considered as risk indicators (Heitz-Mayfield & Salvi, 2018). In contrast, in the present study, ever-smokers who had a smoking history of >23 pack-year presented a lower risk of PM (OR = 0.25; CI 95% 0.05–1.27). However, clinicians should consider that a decreased risk of tobacco consumption in the development of peri-implant mucositis may require careful interpretation. It should be taken into account that the main clinical sign to diagnose PM is bleeding on probing and it has been suggested that nicotine exerts a vasoconstrictive impact on gingival vasculature and, thereby, reduces the gingival blood flow (Clarke & Shephard, 1984). Ramseier et al. (2015) showed, in a retrospective analysis of patients enrolled in supportive periodontal therapy, a lower bleeding on probing scores in smokers when compared to non-smoker patients. Similar findings were reported by Alqahtani et al. (2019) and ArRejaie et al. (2019), who observed that bleeding on probing was significantly higher among non-smokers than smokers patients diagnosed with peri-implantitis.

Previous studies demonstrated that smoking cessation seems to have a positive impact on periodontal health (Rosa et al., 2011). In this context, some investigations showed that the risk of periodontitis

decreases after 10 years of cessation (Costa et al., 2013). In the present study, the multinomial regression analysis showed that the risk of peri-implant diseases might be comparable in those subjects who had stopped smoking for more than 21 years with respect to never-smokers. These findings are consistent with those obtained by Bergström et al. (2000), who observed a significant increase in probing depth in current smokers and a significant decrease in non-smokers and former smokers (i.e., subjects who had stopped smoking 19.4 years before the last clinical examination). Moreover, other investigations demonstrated that the risk of tooth loss in former smokers is comparable to that observed in never-smokers after 15 (Ravidà et al., 2020) and 20 years (Dietrich et al., 2007) following cessation. Then, dentists should advice to their patients to quit smoking and implement smoking cessation programs in dental clinics in order to reduce the risk of smoking-related diseases. However, it should be kept in mind that the process of smoking cessation is complex (i.e., 84% considered that is difficult/very difficult) and many smokers tray to quit smoking but failed (i.e., in the present study, a mean of 2.5 times).

The present investigation yields some limitations, inherent to the study design, that should be acknowledged. Firstly, the lack of baseline values of PPD and radiographs at prosthetic restoration delivery might have had an impact in the accuracy of disease diagnosis. Secondly, changes in smoking behavior could not be evaluated due to the retrospective collection of smoking history data. In addition, other factors such as the current periodontal status were not considered in this study and might also influence the diagnosis of peri-implant diseases. Furthermore, a larger sample size could yield a more precise estimation of the association between smoking habit and peri-implant diseases. Finally, the results of the present study could not be extrapolated to the general population since all implants were placed and restored in a university dental clinic.

Within the limitations of this study, it can be concluded that (a) smoke intensity is associated with an increased risk of peri-implantitis, (b) the risk of peri-implant diseases might be similar in those subjects who had stopped smoking for more than 21 years with respect to never-smokers, and (c) some implant- and patient-related variables are associated with peri-implant diseases (i.e., mean number of implants per patient, guided bone regeneration, rough surface, access to interproximal hygiene, and dimensions of buccal KM).

AUTHOR CONTRIBUTIONS

ACKNOWLEDGMENTS

CONFLICT OF INTEREST STATEMENT

DATA AVAILABILITY STATEMENT

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