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ORIGINAL ARTICLE

Periodontitis predicts HbA1c levels and glucose variability in type 1 diabetic patients: the PARODIA Florence Project study

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Abstract

Objective The aim of the present study was to assess the extent and severity of periodontal disease among type 1 diabetic patients (T1DM) and to investigate the possible association with systemic markers of glucose control and variability.

Material and methods Patients were consecutively enrolled in a Diabetic Unit. A full-mouth periodontal evaluation was performed, and data on systemic markers of diabetes were collected. Descriptive statistics and logistic and linear models were performed.

Results A total of 136 T1DM patients (mean age: 45.5 ± 14.6 years) were examined. Periodontitis was detected in 62% of cases (mean CAL: 3.0 ± 0.9 mm): stage III periodontitis was diagnosed in 32% of patients while stage IV in 8%. Mean level of glycated hemoglobin (HbA1c) was 7.5% ± 1.4. Among the investigated factors, mean CAL (p=0.040) was associated with HbA1c ≥ 7%; 93% of patients with mean CAL > 6 mm showed HbA1c ≥ 7%. Mean CAL (p=0.004), mean PPD (p=0.005), mean FMPS (p=0.030), and stage III/IV periodontitis (p=0.018) predict glucose coefficient of variation (CV).

Conclusions Periodontitis showed a relevant prevalence in the present, well-controlled T1DM population and predicts poor glycemic control (HbA1c ≥7%) and higher glucose variability. The present findings suggest that periodontal infection may have systemic effects also in T1DM patients.

Clinical relevance The extent and severity of periodontitis and its possible systemic effects in T1DM patients could be underestimated.

Keywords Periodontitis · Type 1 diabetes · Glycated hemoglobin · Glucose variability

Introduction

Periodontal disease (PD) is a chronic inflammation, caused by specific pathogens contained in the dental plaque, leading to host imbalance and destruction of connective tissue, bone resorption, and tooth loss [1]. PD shows a high prevalence (over than 40%) among individuals living in industrialized countries, while severe forms affect more than 10% of the global population [2].

A significant body of evidence demonstrated that PD interacts with several systemic diseases, including cardiovascular diseases and diabetes [3, 4]. Hypothetical mechanisms of interaction imply the possible induction of systemic inflammation from periodontal tissues, increasing the level of circulating inflammatory markers leading to the imbalance of chronic inflammatory processes [5–7]. Conversely, less agreement exits on the hypothesis of transient bacteremia caused by periodontal pathogens, reaching the blood stream and interacting with vascular surfaces [8].

A bidirectional association between PD and type 2 diabetes mellitus (T2DM) is supported by current evidence [9, 10]. Poorly controlled T2DM is considered a risk factor for PD [11], leading to the alteration of periodontal tissues via advanced glycation end products (AGEs) deposition and reduction of fibroblastic activity [12, 13], selecting

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periodontal pathogens [14] and reducing the chemotaxis and diapedesis of polymorphonuclear leukocyte cells (PMN) [15]. Additionally, T2DM could impair oral wound healing process [16].

Conversely, severe PD increases glycated hemoglobin levels (HbA1C) in T2DM patients, and it is associated with a higher prevalence of diabetic complications [17, 18]. A recent consensus concluded that PD is significantly associated with poor glycemic control, measured by HbA1C, in T2DM patients and that the risk is more elevated in patients with poorer HbA1C at baseline [17]. Hypothetical mechanisms of interaction may be related to the increasing levels of pro-inflammatory mediators (tumor necrosis factor-alfa; C-reactive protein and mediators of oxidative stress) and to the associated dyslipidemia in case of PD that may complicate glycemic control [19]. Initial evidence suggested that periodontal treatment may improve glycemic control [20]. Recently, a large, multicenter randomized trial demonstrated that periodontal treatment improves HbA1C levels in T2DM patients compared with controls, after 1 year of follow-up [21].

The association between PD and T1DM is more controversial. A consistent heterogeneity exits among studies in terms of periodontal diagnosis/collected variables, population samplings, and number of enrolled individuals [21]. The overall assessment of studies suggested that there is a higher incidence of PD among T1DM patients compared with healthy individuals, even if the consistency of the association between periodontal variables and diabetic systemic markers was not definitively addressed [21]. A recent consensus report concluded that there is insufficient evidence on the possible association between PD and poor glycemic control among people with T1DM [17].

The aim of the present cohort study was to assess the extent and severity of PD among type 1 diabetic patients and to investigate its possible association with diabetic systemic markers.

Material and methods

Source of data and study participants

The PARODIA (*PAROdontite and DIAbete*) Project is an observational study aimed at investigating the extent and severity of periodontal disease (PD) in patients with type 1 diabetes (T1DM) and the possible association between PD and systemic markers of glucose control and variability. The present manuscript conforms to STROBE guidelines for human observational studies. The study protocol was approved by the Ethical Board (PARODIA Project, approval number: CEAVC 30952/2019). Informed consent was obtained from all subjects included in the study. The present manuscript is a companion paper of a recently published short communication [22].

Patients were recruited at the Diabetes Unit, Azienda Ospedaliera Universitaria Careggi, Firenze (Italy). The following entry criteria were considered:

i) Patients aged ≥ 18 years
ii) Diagnosed with type 1 diabetes and currently treated with multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII)
iii) Flash glucose monitoring (FGM) device (FreeStyle Libre FGM, Abbott Diabetes Care, IL) usage for the last 3 months.

Subjects with a history of other systemic diseases such as cancer, HIV, and bone metabolic diseases and history of radiation or immunosuppressive/modulating therapy were excluded, as well as those who had taken antibiotics, corticosteroids, or non-steroidal anti-inflammatory drugs in the last 3 months.

At baseline, all included patients underwent HbA1c, glucose coefficient of variability (CV), height, weight, and blood pressure measurements. Data on comorbidities were retrieved from medical records, and a screening for complications (fundus examination, measurement of serum creatinine, albumin/creatinine ratio, vibratory perception threshold with biothesiometer, and electrocardiogram) was performed. Furthermore, data on total cholesterol, triglycerides, and high-density lipoprotein (HDL) levels were collected.

Periodontal examination implied a full-mouth clinical examination performed with an NCP-15 periodontal probe, collecting data (six sites per tooth of each subject) on:

- Plaque index (PI)
- Bleeding on probing (BoP)
- Probing pocket depth (PPD), measured from the gingival margin to the sulcus/pocket deepest point
- Gingival recession (REC), measured from the cemento-enamel junction (CEJ) to the gingival margin (GM)
- Furcation involvements
- Tooth mobility

The clinical attachment level (CAL) of each site was estimated as the sum of PD + REC.

Information regarding hygiene habits, frequency of dental appointments, smoking habits, and previous dental treatments were also collected during the patient interview. Periodontitis was defined according to the *2017 Classification of Periodontal and Peri-implant Disease and Conditions* [23].

All periodontal variables were collected by a single experienced operator (LB) that attended a preliminary calibration

session, reporting an intraclass correlation coefficient of 0.87 (95% CI 0.82; 0.91).

Sample size and statistical analysis

The sample size was estimated using the sample size tables for logistic regression [24], with α=0.05, a power of 80%, a percentage of patients with HbA1c ≥ 7% of 70%, and an odds ratio of 1.7, referred to one standard deviation above the mean of the quantitative variables (for example mean CAL or mean PPD). Considering these parameters, a sample size of at least 130 patients was necessary.

Descriptive statistics using mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables, were used. Outcome variables were HbA1c ≥ 7% and glucose CV. Bivariate analyses were conducted, considering every single variable as a predictor variable. For HbA1c ≥ 7%, logistic regression models were used for quantitative variables and the Fischer exact test for qualitative variables. For glucose CV, linear regression models were used for quantitative variables and ANOVA test for qualitative variables. Stepwise backward analyses were performed using significant variables in the bivariate analyses. The level of significance ($p > .05$) was considered exclusion criteria for the stepwise backward analysis. A sensitive analysis was performed considering only patients with at least 12 teeth.

Table 1. Descriptive statistics. Patient characteristics and systemic markers.

Variable	
Females n (%)	73 (55%)
Mean age (years)	45.5 ± 14.6 (19–81)
Smokers n (%)	22 (17%)
BMI (Kg/m^2)	24.9 ± 4.3
Systolic blood pressure (mmHg)	124.2 ± 12.6
Diastolic blood pressure (mmHg)	72.7 ± 8.8
Total cholesterol (mg/dl)	187 ± 29.3
HDL (mg/dl)	63.5 ± 14.9
Triglycerides (mg/dl)	74.8 ± 31.3
Diabetes duration (years)	19.3 ± 13.4 [1-59]
Patients with diabetic complications n (%)	46 (35%)
Cardiovascular complications n° (%)	4 (3%)
Peripheral arteriopathy n (%)	4 (3%)
Retinopathy n (%)	39 (29%)
Neuropathy n (%)	14 (11%)
Renal complications n (%)	8 (6%)
HbA1c (mmol/mol)	7.5% ± 1.4
Patients with Hba1c > 7% n (%)	92 (69%)
Average glucose level (mg/dl)	162.7 ± 30.8
Glucose coefficient of variation (%)	38.9 ± 7.2
Time in range (%)	58.7 ± 16.4
Time in hypoglycemia (%)	6.5 ± 8.2
Time in hyperglycemia (%)	34.8 ± 18.1

BMI body mass index, *HDL* high-density lipoprotein, *HbA1c* glycated hemoglobin

Results

Of the 150 enrolled patients, 136 attended the scheduled periodontal visit. Finally, a total of 133 patients were available for the present analysis (data on FMPS and FMBS were not available for 3 patients).

The mean age was 45.5 ± 14.6 years (19–81). Seventy-three patients (55%) were female, and 22 (17%) were current smokers. The mean value of glycated hemoglobin was 7.5% ± 1.4. Out of the 133 patients, a total of 46 (35%) reported at least one diabetic complication. Data on descriptive statistics regarding systemic markers are reported in Table 1. In the assessed sample, a total of 83 patients (65%) showed periodontitis, while 3% was completely edentulous. The mean CAL was 3.0 ± 0.9 mm. Stage III periodontitis was detected in 32% of patients while stage IV in 8%. Details of periodontal variables are reported in Table 2.

A bivariate analysis considering all possible predictive periodontal and systemic variables and HbA1c ≥ 7% as outcome variable was performed (Table 3). Among all investigated factors, mean CAL (p=0.040) was associated with HbA1c ≥ 7%. Interestingly, the increase in CAL for each mm showed an OR = 1.79 [1.03; 3.12] for HbA1c ≥7%; 93% of patients with mean CAL > 6 mm showed HbA1c ≥7%. Mean CAL was significantly associated to HbA1c ≥ 7%, also in patients with at least 12 teeth (p=0.045).

Similarly, a bivariate analysis considering all possible predictive variables and glucose CV as outcome was performed (Table 4). Among all investigated factors, mean CAL (p=0.004), mean PPD (p=0.005), FMPS (p=0.030), and stage III/IV periodontitis (p=0.018) were associated with glucose CV.

Stepwise backward analyses with glucose CV as outcome variable were also performed, showing that mean PPD (2.87 ± 0.99 [0.90–4.84]; p=0.005) predicts glucose CV (Table 5). Finally, stage III and IV periodontitis were significantly associated with glucose CV (p=0.018) compared to stage I and II (Table 6).

Discussion

Over 30% of adults in the USA and Northern Europe showed periodontal disease; in 13% of these individuals, the condition was severe [2, 25]. A meta-regression assessing the global burden of PD in the last two decades showed that

Table 2. Descriptive statistics. Periodontal variables.

Mean CAL (mm)	3.0 ±0.9		
Mean PPD (mm)	2.7 ± 0.6		
FMPS (%)	32.9 ± 23.6		
FMBS (%)	36.2 ± 23.8		
Mean tooth loss	4.8 ± 6.5		
Completely edentulous patients n (%)	4 (3%)		
Patients with no periodontitis n (%)	46 (35%)		
Patients affected by periodontitis n (%)	83(62%)		
Stage I periodontitis n (%)	13 (10%)	Grade B 5	Localized 11
		Grade C 8	Generalized 2
Stage II periodontitis n (%)	20 (15%)	Grade A 2	Localized 17
		Grade B 5	Generalized 3
		Grade C 13	
Stage III periodontitis n (%)	42 (32%)	Grade A 1	Localized 25
		Grade B 14	Generalized 17
		Grade C 27	
Stage IV periodontitis n (%)	8 (6%)	Grade C 8	Generalized 8

CAL clinical attachment level, *PPD* periodontal probing depth, *FMPS* full-mouth plaque score, *FMBS* full-mouth bleeding score

the prevalence of more severe forms was stable around 11% worldwide [2]. The progression of untreated PD leads to tooth loss, impaired quality of life, and significant systemic inflammation [26]. A significant body of evidence has shown that PD interplays with several important chronic diseases, including diabetes mellitus. Data on T2DM showed a significant, bidirectional association between the two diseases, but current data on the systemic impact of PD in T1DM are inconclusive [17]. The aim of the present study was to explore the possible association between PD and type 1 diabetes in a sample of Italian patients.

In the present analysis, 62% of T1DM patients showed signs of PD. In details, 32% was diagnosed with stage III and 8% with stage IV PD. Interestingly, the reported prevalence of PD in type 1 diabetic patients is significantly higher than that described in a recent systematic review [21]. Possible reasons may be related with great heterogeneity in periodontal diagnosis, mainly using screening methods or partial-mouth probing evaluation. On the other hand, a standard full-mouth periodontal charting was performed in the present cohort of patients, according to the recent classification presented at the World Workshop in Periodontology 2017 [23]. Our findings suggested a high prevalence of PD among type 1 diabetic patients, thus supporting the role of T1DM as a significant risk factor for PD. A large body of evidence showed that type 2 diabetes mellitus is a significant risk factor for PD [27] and this seems to be related to a number of factors including impairment of immune response, selection of periodontal pathogens, and alteration of periodontal connective tissues due to AGEs deposition [9]. Data regarding the possible association between T1DM and PD are lacking and controversial, even if a large study on diabetic children showed a greater incidence of periodontal destruction in these individuals compared with healthy controls [27]. Findings from our study suggest that early periodontal diagnosis and treatment are critical in T1DM patients. It should be kept in mind that 3% of the patients were completely edentulous and 40% showed stage III and IV periodontitis, thus supporting the hypothesis of a rapid progression of PD in T1DM patients.

The present results showed a significant association between mean CAL and the threshold value of HbA1c ≥ 7%. Interestingly, the increase in CAL for each mm showed an OR= 1.79 [1.03; 3.12] for HbA1c > 7%. Additionally, 93% of patients with mean CAL > 6 mm showed HbA1c ≥ 7%, thus corroborating the association between PD and poorly controlled diabetes. From this point of view, an association between PD and HbA1c levels has been clearly demonstrated in type 2 diabetes. The recent update of the EFP/AAP systematic review showed that type 2 diabetic patients with PD showed higher HbA1c levels and higher incidence of diabetic complications when compared with periodontally healthy type 2 diabetic controls [19]. Conversely, the level of existing evidence linking PD and type 1 diabetes is more controversial [21]. In the present sample of patients, a clear association between PD severity and HbA1c ≥ 7% was shown. The significance of the reported association seems to be very interesting since it was observed in a sample of well-controlled T1DM patients. None of the possible systemic markers investigated in the analysis showed association with HbA1c ≥ 7%, thus supporting the correct lifestyle and compliance of this sample of patients. Although further studies are necessary, this observational study seems to suggest that the "two-way" relationship [28] may also exist for T1DM

Table 3. Bivariate analyses for HbA1c > 7% as outcome variable. Statistically significant *p*-values are given in bold.

Factor	OR	*p*-value
Female	1.07	0.853
Mean age	1.02	0.253
Smoker	1.23	0.804
BMI	1.09	0.076
Systolic blood pressure	1.00	0.832
Diastolic blood pressure	1.02	0.268
Total cholesterol	1.01	0.122
HDL	1.01	0.538
Triglycerides	1.00	0.544
Diabetes duration	1.01	0.697
Patients with diabetic complications	1.42	0.435
Cardiovascular complications	1.35	1.0
Peripheral arteriopathy	1.35	1.0
Retinopathy	1.72	0.302
Neuropathy	1.13	1.0
Renal complications	3.29	0.434
Mean CAL (mm)	1.79	**0.040**
Mean PPD (mm)	1.78	0.115
FMPS (%)	1.01	0.119
FMBS (%)	1.01	0.238
Patients affected by periodontitis	1.26	0.562
Stage III/IV periodontitis	1.94	0.096
Number of TL	1.03	0.321
TL due to periodontitis	3.80	0.092
Electric toothbrush use	0.66	0.330
Toothbrushing times a day	1.24	0.416
Interproximal hygiene	0.70	0.437
Regular oral hygiene	0.71	0.443
Oral hygiene a day	1.03	0.844
Previous periodontitis diagnosis	1.48	0.432
Periodontal disease familiarity	0.84	0.694
Periodontal disease treatment	3.24	0.433

BMI body mass index, *HDL* high-density lipoprotein, *CAL* clinical attachment level, *PPD* periodontal probing depth, *FMPS* full-mouth plaque score, *FMBS* full-mouth bleeding score, *TL* tooth loss

and periodontitis. The possible link between PD and T1DM was also supported in the present study by the association between mean PPD and glucose CV, a novel parameter capturing daily fluctuations in blood glucose levels, thus predicting the risk of hypoglycemia. Interestingly, more severe PD stages were associated with higher values of glucose CV, suggesting that higher loss of bone and clinical attachment could probably stimulate more systemic inflammation also in T1DM patients. This finding seems to corroborate the possible systemic effect of periodontal infection, supporting the hypothesis that PD may generate a low-grade systemic inflammation via acute-phase and neutrophil oxidative stress response, impacting T1DM general conditions.

Table 4. Bivariate analyses for glucose CV as outcome variable. Statistically significant *p*-values are given in bold.

Factor	*p*-value
Female	0.628
Mean age	0.759
Smoker	0.616
BMI	0.257
Systolic blood pressure	0.220
Diastolic blood pressure	0.976
Total cholesterol	0.398
HDL	0.596
Triglycerides	0.710
Diabetes duration	0.068
Patients with diabetic complications	0.998
Peripheral arteriopathy	0.257
Retinopathy	0.800
Neuropathy	0.491
Renal complications	0.376
Mean CAL (mm)	**0.004**
Mean PPD (mm)	**0.005**
FMPS (%)	**0.030**
FMBS (%)	0.201
Patients affected by periodontitis	0.271
Stage III/IV periodontitis	**0.018**
Number of TL	0.165
TL due to periodontitis	0.085
Electric toothbrush use	0.413
Toothbrushing times a day	0.610
Interproximal hygiene	0.754
Regular oral hygiene	0.905
Oral hygiene a day	0.875
Previous periodontitis diagnosis	0.144
Periodontal disease familiarity	0.626
Periodontal disease treatment	0.512

BMI body mass index, *HDL* high-density lipoprotein, *CAL* clinical attachment level, *PPD* periodontal probing depth, *FMPS* full-mouth plaque score, *FMBS* full-mouth bleeding score, *TL* tooth loss

Table 5. Stepwise backward analysis for glucose CV. Statistically significant *p*-values are given in bold.

Variable	Estimate	Std error	95% CI	p-value
Intercept	31.04	2.76		
Mean PPD	2.87	0.99	0.90; 4.84	**0.005**

PPD periodontal probing depth

Out of the present sample of T1DM patients, 35% showed at least one systemic complication, and diabetic retinopathy (29%) and neuropathy (11%) were the most frequent. Considering the relatively low mean age of the present sample of patients (45.5 ± 14.6 years), this finding seems to strengthen

Table 6. Bivariate analysis to evaluate association between periodontal stage and glucose CV. Statistically significant *p*-values are given in bold.

PD stage	0	1	2	3	4	*p*-value
	N= 47	*N*=13	*N*=20	*N*=42	*N*=8	
CV	38.0 ± 7.3	35.9 ± 6.1	38.3 ± 6.2	39.9 ± 7.6	43.8 ± 5.5	**0.053**
PD stage ≥ 1	38.0 ± 7.3	39.4 ± 7.1				0.271
PD stage ≥ 3	37.7 ± 0.8			40.7 ± 7.3		**0.018**

PD periodontitis, *CV* glucose coefficient of variation

the importance of the HbA1c control optimization, in order to prevent and/or delay the related progression of diabetic complications. Interestingly, considering that classical factors failed to predict HbA1c in the current sample of patients and that only PD was associated with T1DM systemic glucose profile, the findings of the present study underline the importance of proper periodontal diagnosis and treatment also in order to prevent possible severe clinical sequelae of T1DM.

Limitations of the present study may be related to the sample of enrolled patients that could be considered not representative of the whole population, since it was recruited among patients in a university-based diabetes center. Furthermore, larger samples of patients are necessary for further observational studies. Finally, the cross-sectional study design precludes definitive, causal associations between the two investigated diseases.

Conclusions

The present study suggests that:

- Periodontitis is highly prevalent in a well-controlled T1DM population, selected in a university-based Diabetic Unit.
- Periodontal disease predicts HbA1c ≥ 7% levels and higher glucose CV, thus supporting the hypothesis of a systemic effect of PD also in T1DM patients.

Funding This study was self-funded.

Declarations

Ethical approval The study protocol was approved by the Ethical Board (PARODIA Project, approval number: CEAVC 30952/2019).

Conflict of interest Francesco Cairo has received consultancy fees and grants from Straumann and Geistlich Biomaterials. Ilaria Dicembrini has received speaking fees from Merck, Novartis, AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi, and Novartis. Edoardo Mannucci has received consultancy fees from Merck and Novartis; speaking fees from AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi; and Novartis, and research grants from Merck, Novartis, and Takeda. Other authors have nothing to disclose.

Informed consent Informed consent was obtained from all subjects included in the study.

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