Periodontitis predicts glycated hemoglobin levels and glucose variability in Type 1 Diabetes patients. The PARODIA Florence Project Cohort Study

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ABSTRACT

Background: The aim of the present study was aimed to assess the extent and severity of periodontal disease among type 1 diabetes patients (T1DM) and the possible association with diabetes systemic markers.
Material and Methods: Patients were consecutively selected in a Diabetic Unit. A full-mouth periodontal evaluation was performed. Data on systemic markers were collected from patient records. Descriptive statistics using mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables, were used. For inferential analysis, multilevel models were performed.

Results:
A total of 133 T1DM patients (mean age was 45,5 ± 14.6 years) were assessed; 65% patients showed periodontitis (mean CAL was 3.0□□□□□ mm). Stage III periodontitis was detected in 32% of patients while stage IV in 8%. At least one diabetic complication was reported in 35% of patients. The mean glycated hemoglobin levels HbA1c was 7.5% ± 1,4. Among all investigated factors, mean CAL (p=0.040) was associated with HbA1c ≥7% values; 93% of patients with mean CAL >6mm showed HbA1c ≥7%. Mean CAL (p=0.004), mean PPD (p=0.005), mean FMPS (p=0.030) and stage III/IV (p=0.018) predict Glucose Concentration Variability (CV).

Conclusions
Periodontitis is high prevalent in the present, well-controlled T1DM population and predicts HbA1c ≥7% probability and higher Glucose CV. Present findings suggest that periodontal infection may have systemic effect also in T1DM patients.

Introduction

Periodontal disease or periodontitis (PD) is a chronic inflammation caused by specific pathogens contained in dental plaque leading to host imbalance and destruction of connective tissue, bone resorption and tooth loss (Sanz & Quirinen 2005). PD shows a high prevalence (over than 40%) among individuals living in industrialized countries while severe forms affect more than 10% of population (Kassenbaum et al. 2010).

A significant body of evidence demonstrated that PD interact with several systemic diseases, including cardiovascular diseases and diabetes (Chapple & Genco 2013). Hypothetical mechanisms of interaction imply the possible induction of systemic inflammation from periodontal tissue thus increasing the level of circulating inflammatory markers leading to imbalance of chronic inflammatory process (Cairo et al. 2008; Cairo et al. 2009; D'Aiuto et al. 2018). Conversely, less agreement exits on the hypothesis of transient bacteremia of periodontal pathogens, reaching the blood stream and interacting with vascular surfaces (Cairo et al. 2004).

A bidirectional association between PD and type 2 diabetes mellitus (T2D) is supported by current evidence (Genco 2013). Poorly controlled T2DM is considered as risk factor for PD, leading to alteration of periodontal tissue via advanced glycation end products (AGEs) deposition and reduction of fibroblastic activity (Golub et al. 1978, Federoff et al. 1993), selecting periodontal pathogens (Zambon et al. 1988) and reducing the chemotaxis and diapedesis of polymorphonuclear leukocyte cells (PMN) (Salvi et al 1997). Conversely, severe PD leads to increase levels of glycated hemoglobin levels (HbA1C) in T2DM patients and it is associated with higher prevalence of diabetic complications (Sanz et al. 2018). A recent consensus concluded that periodontitis is significantly associated with poorer glycaemic control as measured by HbA1C in T2DM patients and the risk is more elevated in patients with poorer HbA1C at baseline (Sanz et al. 2018). Hypothetical mechanisms of interaction may be related to the elevation levels of pro-inflammatory mediators (Tumor Necrosis Factor-alfa; C-Reactive Protein CRP and mediators of oxidative stress) and associated dyslipidemia in case of PD that may complicate glycaemic control (Graziani et al. 2018). Initial evidence suggested that periodontal treatment may improve glyacemic control (Engebresson et al. 2013). More recently, a large, multicenter randomized trial demonstrated that periodontal treatment in T2DM patients improved HbA1C levels compared with controls, one year after treatment (D'Aiuto et al. 2018).

Association between PD and T1DM is more controversial. A consistent heterogeneity exits among studies in term of periodontal diagnosis/collected variables, population samplings and number of enrolled individuals (Dicembrini et al 2020). The overall assessment of studies suggested that there is a higher incidence of periodontal disease 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 (Dicembrini et al 2020). A recent consensus report concluded there is insufficient evidence of the possible association between periodontitis and poorer glycaemic control among people with T1DM (Sanz et al. 2018).

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

Material and Methods

Source of Data and Study Participants

The PARODIA 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 with systemic diabetes markers. 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.

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) diagnosis 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 three months.

Subjects with a history of other systemic disease such as cancer, HIV, bone metabolic disease, 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 were excluded.

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

Periodontal examination implies a full-mouth clinical examination performed 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 (PD),
- gingival recession (REC),
- furcation involvements
- tooth mobility.

The clinical attachment level (CAL) of each site was estimated as the sum PD + REC. Information regarding hygiene habits, frequency of dental appointments, smoking habits, and previous dental treatments were also collected. All periodontal variables were collected by a single experienced operator (LB).

Sample size and Statistical Analysis

The sample size was estimated using the sample size tables for logistic regression (Hsieh 1989), with α=0.05, a power of 80%, a percentage of patients with glycated hemoglobin ≥ 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 PD). 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 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 as exclusion criteria for the step- wise backward analysis.

Results

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

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 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□□□□□ 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 was performed (table 3). Among all investigated factors, Mean CAL (p=0.040) was associated with HbA1c ≥7% values. Interestingly, the increase in CAL for each mm showed a OR= 1.79 [1.03; 3.12] for HbA1c ≥7%: 93% of patients with mean CAL >6mm showed HbA1c ≥7%. The association between CAL and HbA1c ≥7 is reported in figure 1. 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 PD (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 was also performed, showing that mean PPD (2.87±0.99 [0.90-4.84]; p=0.005) predicts Glucose CV (table 5). Stage III and IV were significantly associated with Glucose CV (p=0.018) (table 6).

DISCUSSION

Over 30% of adults in United States and Northern Europe showed periodontal disease; in 13% of these individuals, the condition was severe (Hugoson et al. 1998; Kassenbaum et al. 2010). A meta- regression assessing the global burden of PD showed that prevalence of more severe forms was stable around 11% of population in the last two decades (Kassenbaum et al. 2010). Progression of untreated PD leads to tooth loss, impaired quality of life and significant systemic inflammation (Tonetti et al. 2017). In the last two decades, a significant body of evidence has shown that PD interplays with several important chronic diseases, including diabetes mellitus. Data on T2DM showed a significant, directional association between the two diseases, but present data on the systemic impact of PD in T2DM are currently inconclusive (Sanz et al. 2018). The present study was aimed to explore the possible association between PD and type 1 diabetes in a sample of Italian patients.

The present findings showed that 65% of current sample of patients showed sign of periodontitis with 32% showing stage III and 8% stage IV PD. Interestingly, the reported prevalence of PD in type 1 diabetic patients is significantly higher than that described in a recent SR (Dicembrini et al. 2020). 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 sample of patients, using the recent classification present World Workshop in Periodontology 2017(Tonetti et al. 2018). Our findings suggested a high prevalence of periodontal diseases among type 1 diabetic patients, thus supporting the role T1DM as a significant risk factor for PD. Classical studies showed type 2 diabetes mellitus is a significant risk factor for periodontitis (Preshaw et al. 2012) and this seem to be related to a number of factors including impairment of immune response, selection of periodontal pathogens and alteration of periodontal connective tissue due to AGEs deposition (Genco 2013). Data for T1DM on periodontitis are scanty and controversial, even if a large study on diabetic children showed greater incidence of periodontal destruction compared with no diabetic controls (Lalla et al. 2007). Findings from our study suggest the early periodontal diagnosis and treatment is critical in T1DM patients. It should be kept in mind in fact that 3% of present sample of young adults were completely edentulous and 40% showed stage III and IV periodontitis, thus supporting the hypothesis of rapid

progression of disease in T1DM patients.

The present outcomes showed a significant association between mean CAL and the threshold value of HbA1c ≥7%. Interestingly, the increase in CAL for each mm showed a OR= 1.79 [1.03; 3.12] for HbA1c >7%; 93% of patients with mean CAL >6mm showed HbA1c ≥7%, thus corroborating the association between periodontitis and worsening in type diabetic control. An association between PD and HbA1c level has been clearly demonstrated in type 2 diabetes. The recent update of EFP/AAP systematic review showed that patients with PD showed higher HbA1c levels and higher incidence of complications in type 2 diabetes when compared controls with no PD (Graziani et al. 2018). Conversely, the level of existing evidence linking PD and type 1 diabetes is more controversial (Dicembrini et al. 2020). In the present sample of patients, a clear association between disease severity and HbA1c≥7% was shown. The significance of presence association seems to be very meaningful since reported in a sample of young, well-controlled T1DM patients. None of possible systemic marker investigated in the analysis showed association with HbA1c ≥7%, thus supporting the correct life-style and compliance of this sample of patients. Although further studies are necessary, this observation seems to suggest that the "two-way" (Taylor et al. 2001) may exist also for T1DM and periodontitis. The possible link between PD and T1DM was also supported in the present study by the association between periodontal variables and Glucose CV, a novel parameter capturing daily fluctuations in blood glucose levels, thus predicting the risk of hypoglycemia. Interestingly, higher was PD severity and higher was Glucose CV. This observation seems to corroborate the possible systemic effect of periodontal infection, even if the present cross-sectional study design precludes causal associations.

Limitations of the present study may be related to the sample of patients, that may be considered not representative of the whole population since recruited among patients in a university-based diabetes center. Further, large sample of patients are also necessary for observation studies.

Conclusions

The present study suggests that:

- Periodontitis is high prevalent in a well-controlled T1DM population selected in a University-Based Diabetic Unit.
- Periodontal disease predicts HbA1c ≥7% probability and higher Glucose CV, thus supporting the hypothesis of systemic effect of PD also in T1DM patients.

Tables

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

Variable	
Female n°(%)	73 (55%)
mean Age (years)	45,5 ± 14.6 (19-81)
Smoker 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±9.3
HDL (mg/dl)	63.5±14.9
Triglyceride (mg/dl)	74.8±31.3
Diabetes duration (years)	19.3±13.4 [1-59]
Patients with diabetic complication n°(%)	46 (35%)
Cardiovascular	4 (3%)
Peripheral arteriopathy	4 (3%)
Retinopathy	39 (29%)
Neuropathy	14 (11%)
Renal complication	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

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	4 (3%)		
Patients with no periodontitis	47 (35%)		
Patients affected by periodontitis	83(62%)		
Stage I periodontitis	13 (10%)	Grade B 5	Localized 11
		Grade C 8	Generalized 2
Stage II periodontitis	20 (15%)	Grade A 2	Localized 17
		Grade B 5	Generalized 3
		Grade C 13	
Stage III periodontitis	42 (32%)	Grade A 1	Localized 25
		Grade B 14	Generalized 17
		Grade C 27	
Stage IV periodontitis	8 (6%)	Grade C 8	Generalized 8

Legend:

CAL: Clinical Attachment Level; PPD: Periodontal Probing Depth; FMPS: Full Mouth Plaque Score; FMBS: Full Mouth Bleeding Score;

Table 3. Bivariate analyses for, HbA1c >7% as outcome variable. Statistical significant p-value 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
Triglyceride	1.00	0.544
Diabetes duration	1.01	0.697
Patients with diabetic complication	1.42	0.435
Cardiovascular	1.35	1.0
Peripheral arteriopathy	1.35	1.0
Retinopathy	1.72	0.302
Neuropathy	1.13	1.0
Renal complication	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
Brush electric	0.66	0.330
Toothbrush 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

Legend:

CAL: Clinical Attachment Level; PPD: Periodontal Probing Depth; FMPS: Full Mouth Plaque Score; FMBS: Full Mouth Bleeding Score; BMI: Body Mass Index;

Table 4: Bivariate analyses for glucose CV as outcome variable. Statistical significant p-value 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
Triglyceride	0.710
Diabetes duration	0.068
Patients with diabetic complication	0.998
Peripheral arteriopathy	0.257
Retinopathy	0.800
Neuropathy	0.491
Renal complication	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
Brush electric	0.413
Toothbrush 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

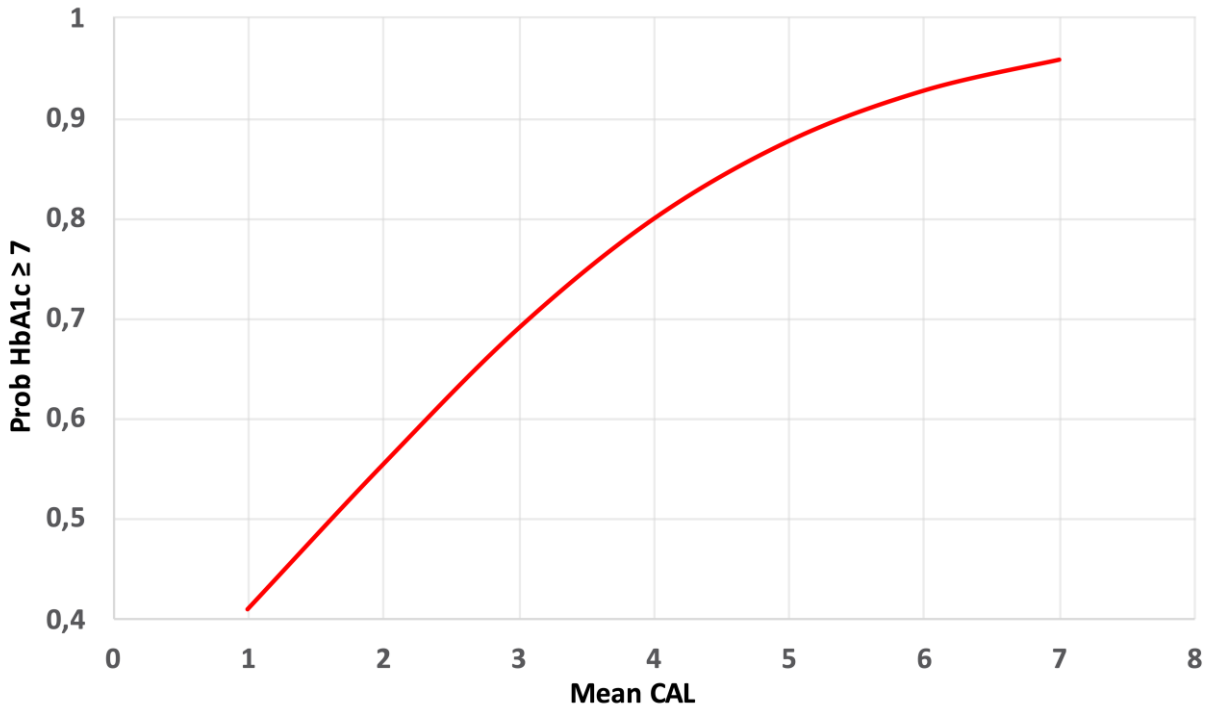
Table 5: Stepwise backward analysis for CV

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**

Table 6: Bivariate analysis to evaluate association between periodontal variables and Glucose CV.

PD stage	0 N= 47	1 N=13	2 N=20	3 N=42	4 N=8	p-value
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 stage 1/2 vs PD stage 3/4	-	37.3±6.2		40.7±7.3		**0.032**

Fig 1: Relationship between glycated hemoglobin levels≥ 7% (HbA1c ≥ 7%) and mean clinical attachment level (CAL).



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