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Periodontal disease, smoking, cardiovascular complications and mortality in type 1 diabetes

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ABSTRACT

Aim: To assess the role of periodontal disease (PD) as a predictor of coronary artery disease (CAD) and mortality in a prospective type 1 diabetes (T1D) cohort and to evaluate the role of smoking in this relationship.
Methods: Data were based on 320 participants of the Pittsburgh Epidemiology of Diabetes Complications study of T1D who, during 1992–94, received a partial mouth periodontal exam, and who were followed for up to 19 years to ascertain complication incidence. PD was defined as clinical attachment loss of ≥4 mm for at least 10% of the examined sites. Predictors of all-cause mortality; Hard CAD (CAD death, myocardial infarction or revascularization), and Total CAD (Hard CAD, angina, ischemic ECG) were assessed using Cox models.
Results: During 19 years of follow-up, 33.7% (97/288) developed CAD, 27.3% (83/304) developed Hard CAD, and 16.9% (54/320) died. Among current smokers, 46.4% (26/56) developed CAD, 42.7% (24/56) developed Hard CAD and 29.5% (18/61) died. PD was not associated with all-cause mortality, although it was a significant predictor of both CAD (HR = 1.12, CI = 1.01–1.23) and Hard CAD (HR = 1.30, CI = 1.11–1.51). As smoking modified the PD-CAD and PD-Hard CAD associations, analyses were stratified by smoking status. PD was associated with an increased risk of CAD (HR = 1.25, CI = 1.03–1.50) and Hard CAD (HR = 1.85, CI = 1.17–2.93) only among smokers.
Conclusion: PD was a significant predictor of CAD and Hard CAD among current smokers with T1D.

1. Introduction

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood. Recent data from the U.S. suggest that the incidence of T1D among youth has increased by 1.8% annually from 2001 to 2012.[1] T1D is associated with increased morbidity and mortality with an associated cost of $14.4 billion per year in direct medical expenses and indirect costs.[2] Periodontal disease (PD) is one of the main oral manifestations of T1D.[3]

PD is a chronic inflammatory disease of the surrounding tooth structure caused by pathogens, leading to tissue destruction and tooth loss. It is estimated that 47.2% of US adults have some form of PD, based on data from NHANES 2009–2012.[4] Smoking and hyperglycemia are two modifying risk factors for PD.[5] Smoking leads to a strong inflammatory reaction that has detrimental effects on the periodontium and can increase the risk of periodontitis 2–5 times.[5,6] Hyperglycemia in patients with diabetes leads to oxidative stress and the formation of advanced glycation end products (AGE) that activate various proinflammatory mediator cascades leading to periodontal tissue damage.[7,8]

PD has been linked to systemic diseases such as cardiovascular disease (CVD), diabetes and chronic kidney disease.[9–11] Although studies have found a strong association between PD and CVD, a large NHANES study suggested that smoking plays a significant role in the PD-CVD relationship as an effect modifier,[12] while others have found the relationship to be independent of smoking.[13] Both diabetes and PD have been individually identified as risk factors for CVD. The combined effect of PD and diabetes on the development of CVD has been studied widely in type 2 diabetes.[14] Thus, individuals with type 2 diabetes and PD were shown to have a higher incidence of coronary artery disease,[15] carotid atherosclerosis[16] and myocardial infarction.[17] Findings from the Study of Health in Pomerania further suggested that although measures of PD were independently associated with all cause and CVD mortality, there was no evidence of interaction between diabetes and periodontitis.[18] A single study in individuals with T1D suggested that PD was significantly associated with coronary artery calcium progression, a marker of subclinical atherosclerosis.[19] The aim of this study was therefore to assess the role of PD as a predictor of documented cardiovascular complications and mortality in a cohort of individuals with

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childhood-onset T1D and to evaluate the effect of smoking on this relationship.

2. Materials and methods

2.1. Study population

The Pittsburgh Epidemiology of Diabetes Complications (EDC) study is a prospective cohort study of childhood-onset (<17 years) T1D. All participants of the EDC study were diagnosed, or seen within 1 year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. The cohort has been described in detail elsewhere.[20,21] In brief, participants ($n = 658$) have been followed with biennial surveys since study initiation (1986–1988). Clinical examinations occurred biennially for the first 10 years and thereafter at 18- and 25-years post baseline. Between March 1992 and August 1994, of 412 participants scheduled for an EDC clinic visit, 406 enrolled in a dental study. Of these, 16 were missing all their teeth, two had scheduling conflicts that prevented complete oral health assessments, and 68 were excluded for possible risk of bacteremia, leaving 320 eligible to receive a comprehensive oral health assessment, including a periodontal examination. The methodology of the oral health assessment is described in detail elsewhere.[22] Briefly, a periodontal examination was conducted following the National Institute of Dental Research (NIDR) adult survey methodology.[23] Three facial sites (mesial, mid-cervical and distal) of the right maxillary/left mandibular or left maxillary/right mandibular quadrants were probed, excluding third molars. Clinical attachment loss and pocket depths were measured using a standard WHO Community Periodontal Index of Treatment Needs (CPITN) pressure-controlled probe by one of two calibrated dentist examiners. Bleeding on probing and visual assessment of supragingival calculus was assessed as present or absent on each tooth examined. In addition, all missing teeth excluding the third molar were recorded using modified criteria from the NIDR adult survey to determine the cause of extraction (disease or orthodontic treatment).

2.2. Assessment of PD

Participants who had clinical attachment loss of ≥4 mm in >10% of periodontal sites examined were defined as having PD. This definition reflects the Healthy People 2000 and 2010 definition of PD.[24,25] This parameter was selected to describe a clinically significant amount of disease, include an ample sample size for analysis and minimize misclassification of cases due to measurement error.[22]

2.3. Assessment of covariates

Covariates of interest were selected for analysis from the time of the oral health exam. The number of missing teeth was assessed clinically during the oral health exam. Demographic data, including age, sex, educational status (used as an indicator of socioeconomic status), and alcohol consumption were assessed via survey. Smoking status was assessed by self-report to the question "Have you smoked at least 100 cigarettes in your lifetime?" Participants who responded in the affirmative were asked if they currently smoke in a follow-up question. Those who responded positively were classified as current smokers, while all others, including former smokers, were considered non-smokers.

Fasting blood samples were taken to measure HbA1, lipids, lipoproteins, serum creatinine and serum albumin. HbA1 values were converted to DCCT (Diabetes Control and Complications Trial)-aligned values HbA1c using a regression equation derived from duplicate assays [DCCT HbA1c = 0.14 + 0.83 (EDC HbA1)].[26] Total cholesterol and triglycerides were determined enzymatically.[27,28] High density lipoprotein (HDL) cholesterol was determined using a modified precipitation technique.[29] Non-HDL cholesterol (non-HDLc) was calculated by subtracting HDL from total cholesterol. Blood pressure was measured according to the Hypertension Detection and Follow-Up protocol with a random-zero sphygmomanometer.[30] Hypertension was defined as blood pressure > 140/90 mm/Hg or use of blood pressure-lowering medications.

Serum and urinary albumin were measured by immunonephelometry[31,32] and creatinine was assayed by an Ectachem 400 Analyzer (Eastman Kodak Co., Rochester, NY). Albumin excretion rate (AER) was calculated for each of three timed urine samples (24-h, overnight and 4-h collections obtained over a 2-week period); the median of the three AERs was used in analyses and was natural logarithm transformed due to its skewed distribution. White blood cell (WBC) count and hemoglobin were measured using a Coulter Counter S-Plus IV. Height and weight were measured using standard methods to calculate body mass index (BMI).

2.4. Assessment of outcomes

Participants were followed until October 31, 2014 to ascertain complication status (median follow-up time, 19 years). Three main outcomes were assessed for this analysis. All-cause mortality; Hard Coronary Artery Disease (Hard CAD; CAD death, myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, or revascularization); and total Coronary Artery Disease (CAD; Hard CAD but also including angina, determined by the EDC study physician, and ischemic electrocardiogram changes (Minnesota codes 1.3, 4.1–4.3, 5.1–5.3, 7.1)). In the EDC study, mortality was ascertained using medical records, death certificates, autopsy reports, and/or interview with next of kin.

2.5. Statistical analysis

Differences in baseline characteristics were evaluated between PD cases and non-PD cases using the Student's *t*-test for normally distributed continuous variables, the Wilcoxon rank sum (Mann-Whitney U) test for non-normally distributed continuous variables and the chi-square or Fischer's exact test for categorical variables. The Cochran–Armitage test for trend was used for ordinal variables.

Kaplan Meier curves were used to assess survival probabilities between PD cases and non-PD cases for each of the outcomes. Predictors of CAD, Hard CAD and all-cause mortality were assessed using Cox models, excluding prevalent cases of CAD or Hard CAD, as appropriate, at the time of the oral health exam. Survival time was defined as the time in years from the oral health exam to the date of the first event for each outcome studied or censorship. The proportional hazards assumption was assessed visually and confirmed by testing time-dependent PD interaction variables. PD violated the proportional hazard assumption for both CAD and Hard CAD and was therefore added to models relating to these two outcomes as a time-varying covariate.

We assessed the role of current smoking as an effect modifier by including an interaction term between PD and current smoking in the models along with the lower order terms. Stratified analyses by current smoking status were conducted when effect modification was observed. Cox proportional hazards models stratifying by current smoking status were first constructed assessing the association between each potential risk factor and the outcome of interest, allowing only for diabetes duration. Variables that were significantly associated with the outcome were subsequently included in separate multivariable Cox models for current smokers and non-smokers. Backward elimination with a significance level of 0.05 was used to retain significant covariates in the models. All analyses were repeated replacing the dichotomous covariate for hypertension status with a continuous variable for systolic blood pressure. All statistical analyses were conducted using SAS® 9.4 software (SAS Institute Inc., Cary, NC, USA.)

Table 1
Baseline characteristics of EDC participants who received an oral health exam (1992–1994) by periodontal disease (PD).

	Non-PD cases ($n = 286$)	PD cases ($n = 34$)	*p*-Value
Age (years)	31.47 (7.67)	37.61 (6.06)	<0.0001
Age at onset (years)	8.09 (4.08)	10.71 (3.75)	0.0004
Duration of diabetes (years)	23.38 (7.34)	26.90 (7.47)	0.009
Female sex	130 (45.45)	12 (35.29)	0.26
More than high school education	208 (72.73)	18 (52.94)	0.02
≥7 oz alcohol/wk. ($n = 282,33$)	199 (70.57)	20 (60.61)	0.24
Current smoker	40 (13.99)	21 (61.76)	<0.0001
Number of missing teeth			
None	161 (56.29)	6 (17.65)	
1–4	97 (33.92)	10 (29.41)	<0.0001
≥5	28 (9.79)	18 (52.94)	
White blood cell count (x10^3/μL, $n = 283,34$)	7.11 (1.97)	8.80 (2.92)	<0.0001
BMI (kg/m^2 $n = 284,33$)	24.66 (3.35)	23.90 (3.26)	0.22
Hypertension	50 (17.48)	10 (29.41)	0.09
HDL cholesterol (mg/dL, $n = 285,34$)	52.07 (12.40)	53.01 (14.03)	0.68
Non-HDL cholesterol (mg/dL, n = 285,34)	134.2 (37.07)	145.3 (39.19)	0.10
Albumin excretion rate (μg/min)	14.74 (5.18–69.07)	23.82 (6.27–143.33)	0.44
HbA1c (%, n = 284,34)	9.25 (1.41)	9.40 (1.36)	0.53
CAD incidence ($n = 259,29$)	79 (30.50)	18 (62.07)	0.0006
Hard CAD incidence ($n = 273,31$)	68 (24.91)	15 (48.39)	0.005
All-cause mortality	43 (15.03)	11 (32.35)	0.01

Data are means (SD), medians (interquartile range) or n (%).

3. Results

Participants with prevalent CAD at the time of the oral health exam ($n = 32$) were excluded from analyses. The prevalence of PD in this cohort was 10.6%. Table 1 describes the baseline characteristics of the study population based on PD status. PD cases were significantly older, with a later age at the onset of T1D, more likely to have less than a high school education as well as more likely to have more missing teeth compared with non-PD cases. The prevalence of current smoking was significantly higher among PD cases compared with non-PD cases (current smoker 61.8% vs 14.0%). WBC count was also significantly higher among cases, although there were no differences in other biological markers by PD status. PD cases had a higher incidence of CAD, Hard CAD and all-cause mortality.

During 19 years of follow-up, 33.7% (97/288) developed CAD, 27.3% (83/304) developed Hard CAD, and 16.9% (54/320) died. Among current smokers, 46.4% (26/56) developed CAD, 42.7% (24/56) developed Hard CAD and 29.5% (18/61) died. Table 2 shows the characteristics of the study population at the time of the oral health exam by the follow-up status of each of the three outcomes of interest. Regardless of outcome studied, participants who experienced an event were older, with a longer duration of diabetes, more likely to be hypertensive, with higher levels of HbA1c, white blood cell count, non-HDL cholesterol and albumin excretion rate. Incident cases were also more likely to be missing a larger number of teeth and a greater proportion of incident cases had PD. Fig. 1 shows a clear separation of the Kaplan Meier survival curves according to PD status for all outcomes studied: CAD (Fig. 1a), hard CAD (Fig. 1b) and Mortality (Fig. 1c).

Table 2
Baseline characteristics for all EDC participants who received an oral health exam by incident outcome of interest.

Participant characteristics	CAD ($N = 288$)			Hard CAD ($N = 304$)			All-cause mortality ($N = 320$)		
	No ($n = 191$)	Yes ($n = 97$)	p-Value	No ($n = 221$)	Yes ($n = 83$)	p-Value	No ($n = 266$)	Yes ($n = 54$)	p-Value
Age (years)	29.73 (7.44)	35.33 (6.38)	<0.0001	30.38 (7.54)	35.78 (6.40)	<0.0001	31.19 (7.51)	36.67 (7.26)	<0.0001
Age at onset (years)	8.38 (4.18)	8.21 (4.01)	0.67	8.46 (4.05)	8.34 (4.31)	0.83	8.41 (4.09)	8.15 (4.29)	0.67
Duration of diabetes (years)	21.35 (6.65)	27.11 (7.20)	<0.0001	21.93 (6.86)	27.43 (7.03)	<0.0001	22.79 (6.98)	28.53 (7.74)	<0.0001
Female sex	87 (45.55)	44 (45.36)	0.23	99 (44.80)	38 (45.78)	0.88	122 (45.86)	20 (37.04)	0.23
More than high school education	139 (72.77)	65 (67.01)	0.78	157 (71.04)	57 (68.67)	0.69	187 (70.30)	39 (72.22)	0.78
Alcohol consumption	$N = 187$	$N = 96$		$N = 217$	$N = 82$		$N = 261$	N = 54	
≥7 oz/week	130 (69.52)	67 (69.79)	0.96	149 (68.66)	60 (73.17)	0.45	186 (71.26)	33 (61.11)	0.14
Current smoker	30 (15.71)	26 (26.80)	0.02	32 (14.48)	24 (28.92)	0.01	43 (16.17)	18 (33.33)	0.017
Periodontal disease	11 (5.76)	18 (18.56)	0.01	16 (7.24)	15 (18.07)	0.005	23 (8.64)	11 (20.37)	0.011
Number of missing teeth									
None	114 (59.69)	40 (41.24)	<0.0001	129 (58.37)	31	0.0004	154	13	<0.0001
1–4	55	40		68	(37.35)		(57.89)	(24.07)	
≥5	(28.80)	(41.24)		(30.77)	33		82	25	
	22	17		24	(39.76)		(30.83)	(46.30)	
	(11.52)	(17.53)		(10.86)	19		30	16	
					(22.89)		(11.28)	(29.63)	
HbA1c (%)	$N = 190$	N = 96		$N = 220$	N = 82		N = 266	$N = 52$	
	9.11	9.58	0.0065	9.12	9.63	0.0031	9.14	9.90	0.0003
	(1.42)	(1.27)		(1.35)	(1.35)		(1.33)	(1.60)	
White blood cell count (x10^3/μL)	N = 190	$N = 95$		N = 220	$N = 81$		$N = 264$	$N = 53$	
	7.021	7.78	<0.0001	6.98	7.74	0.004	7.06	8.42	<0.0001
	(1.98)	(2.39)		(1.98)	(2.10)		(2.03)	(2.40)	
BMI (kg/m^2)	$N = 189$	N = 96		$N = 219$	N = 82		$N = 263$	N = 54	
	24.14	25.20	0.94	24.42	24.96	0.21	24.58	24.61	0.94
	(3.02)	(3.70)		(3.19)	(3.69)		(3.35)	(3.30)	
Hypertension	18 (9.42)	27 (27.84)	<0.0001	25 (11.31)	27 (32.53)	<0.0001	35 (13.16)	25 (46.30)	<0.0001
HDL cholesterol (mg/dL)	$N = 196$	N = 96		N = 221	N = 82		N = 266	N = 53	
	52.49	52.05	0.79	52.31 (12.50)	52.36	0.98	52.26 (12.46)	51.74 (13.17)	
	(12.49)	(12.73)			(12.81)				0.79
Non-HDL cholesterol (mg/dL)	N = 191	N = 96		N = 221	N = 82		N = 266	N = 53	
	126.7 (34.02)	150.6 (38.56)	<0.0001	128.6 (33.74)	151.2 (41.13)	<0.0001	130.9 (33.50)	158.1 (46.91)	<0.0001
Albumin excretion rate (μg/min)	N = 190	N = 97		N = 220	N = 83		$N = 265$	N = 54	
	11.04	21.30	<0.0001	11.04	39.54	<0.0001	11.50	107.03	<0.0001
	(4.36–37.33)	(6.79–146.54)		(4.36–42.30)	(9.33–366.43)		(4.42–44.27)	(21.15–1209.51)	

Data are means (SD), medians (interquartile range) or n (%).

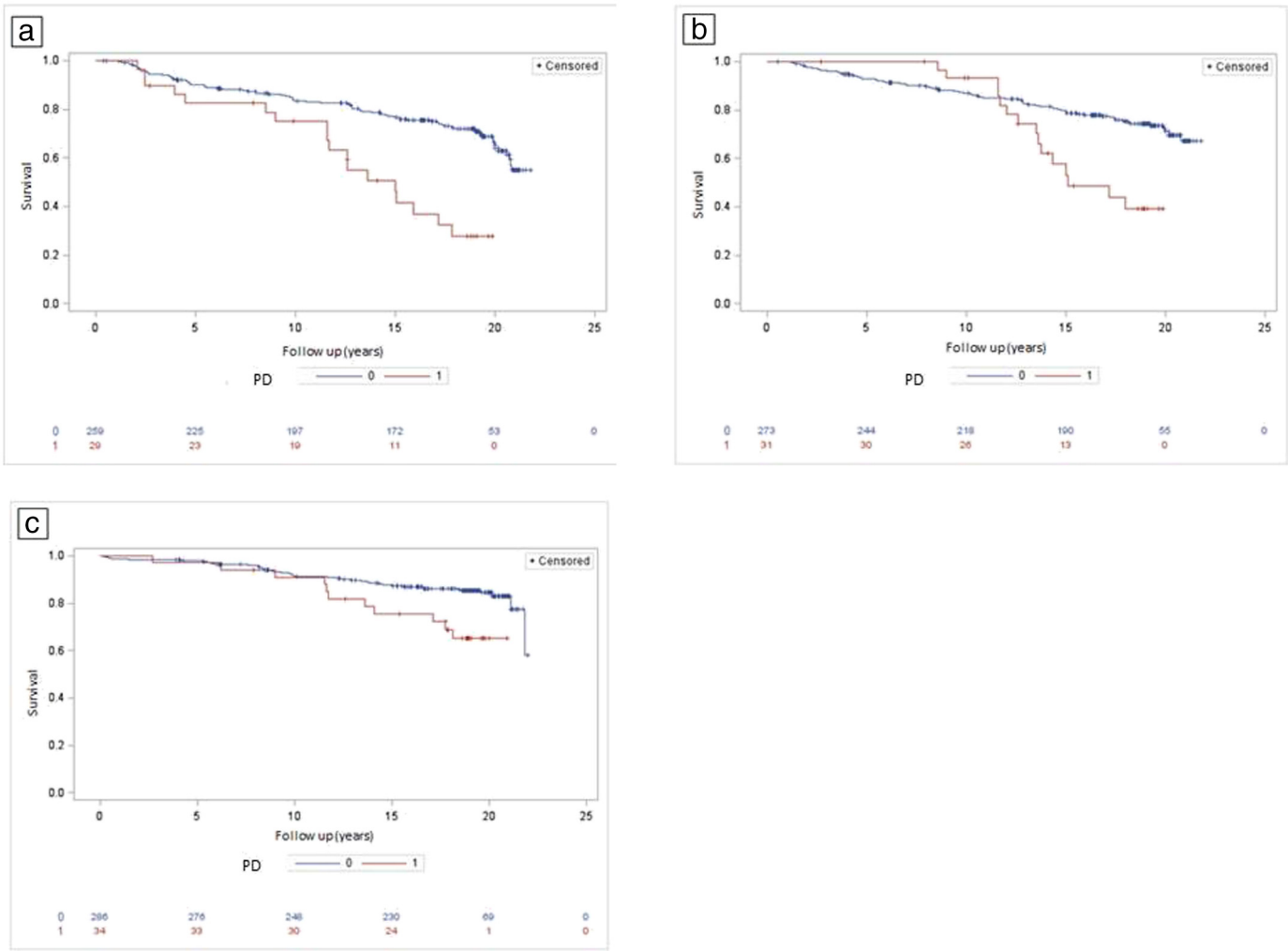

Fig. 1. Kaplan Meier survival curves stratified by periodontal disease (PD). a. CAD. b. Hard CAD. c. All-cause mortality (0 = non-PD cases, 1 = PD cases).

Results from Cox proportional hazard models for the risk of CAD and Hard CAD are displayed in Tables 3 and 4, respectively. In unadjusted Cox models, PD was significantly associated with a greater risk of CAD (HR = 1.11, CI = 1.01–1.23), Hard CAD (HR = 1.24, CI = 1.08–1.43) and all-cause mortality (HR = 2.41, CI = 1.24–4.7). However, after allowing for covariates, PD was no longer a significant predictor of all-cause mortality (HR = 0.87, CI = 0.41–1.83), although it remained significantly associated with both CAD (HR = 1.12, CI = 1.01–1.23) and Hard CAD (HR = 1.30, CI = 1.11–1.51) (not shown).

Significant effect modification of PD by current smoking status was observed for both CAD (p-interaction <0.01) and Hard CAD (p-interaction <0.001) but not for mortality (p-interaction = 0.65). Indeed, in unadjusted analyses stratifying by current smoking status, PD significantly predicted the development of CAD and Hard CAD among current smokers (HR_{CAD} = 1.29, CI = 1.07–1.56 and $HR_{Hard\ CAD}$ = 1.93, CI = 1.23–3.05) but not among those not currently smoking (HR_{CAD} = 1.10, CI = 0.85–1.42 and $HR_{Hard\ CAD}$ = 1.19, CI = 0.84–1.68). Adjusting for covariates did not alter these findings (Tables 3 and 4). When analyses were repeated replacing the categorical covariate for hypertension with a continuous variable for systolic blood pressure, similar results were obtained.

4. Discussion

In this prospective cohort study of individuals with childhood-onset T1D, we observed that PD significantly increased the risk of both CAD and Hard CAD among current smokers only. This is similar to the finding from the Coronary Artery Calcification in Type 1 Diabetes study, where self-reported PD was significantly associated with CAC progression at 6 years follow-up.[19] Our study presents stronger evidence of this association as we have verified measure of periodontal disease, a longer follow up time and verified clinical outcomes. A recent meta-analysis also showed that PD was associated with cardiovascular mortality and coronary heart disease among patients with type 2 diabetes, however there was not enough evidence for this association in T1D.[14] Studies in the general population found that PD was associated with all-cause mortality and was an independent risk factor for CVD, after adjusting for traditional risk factors including smoking and diabetes.[33,34] We observed a significant association between PD and all-cause mortality in the unadjusted models, although this association was no longer significant after adjusting for confounders. This different finding could be due to a smaller sample size and our study focusing on T1D patients only.

Because smoking is a major risk factor for PD and CVD[6] and based on findings from previous studies,[12] we tested for effect modification by current smoking status. We found current smoking to be an effect modifier as the PD – CAD/Hard CAD association was restricted to current smokers only. Both smoking and diabetes are known risk factors for periodontal disease.[35] Although it is known that compared to controls, T1D patients have elevated periodontal pro-inflammatory factors, different periodontal pathogen composition[36] and lower salivary flow rates,[37–39] further research is required to investigate how these factors, in addition to genetics, differ in T1D by smoking status. Among the type

Table 3
Cox proportional hazard models for the prediction of CAD.

	Crude model (n = 283, 95 events)	Model with interaction term for PD*smoking	Crude model for smokers (*n* = 55, 25 events)	Crude model for non-smokers (*n* = 228, 70 events)	Adjusted model for smokers (n = 55, 25 events)	Adjusted model for non-smokers (n = 228, 70 events)[a]
PD	1.25 (1.03–1.50)[b]	1.09 (0.84–1.40)	(time-dependent)	1.10 (1.002–1.21)[b]	1.15 (1.04–1.28)[c]	1.29 (1.07–1.56)[c]	1.10 (0.85–1.42)
PD*smoking		9.45 (1.80–49.74)[c]				
Diabetes duration					1.08 (1.01–1.54)[b]	1.09 (1.05–1.12)[d]
HbA1c					Not allowed	1.20 (1.01–1.42)[b]
Non-HDL cholesterol					Not allowed	1.02 (1.01–1.02)[d]
WBC					Not allowed	1.16 (1.01–1.33)[b]

Data are HR (95%CI).
Multivariable models allowed for univariate predictors of CAD.
[a] The model also allowed for log Albumin Excretion Rate and hypertension.
[b] p-Value <0.05.
[c] p-Value <0.01.
[d] p-Value <0.001.

2 diabetes population, a study found that two inhibitors of the osteoblastogenesis pathway, Sclerostin and Dickkopf, were upregulated in patients with chronic periodontitis and type 2 diabetes and/or smoking.[40] Joaquim et al[41], found no difference in key periodontal pathogens between smoking and non-smoking patients with type 2 diabetes compared to smoking and non-smoking non-diabetic patients who had generalized chronic periodontitis. In addition, there is no direct mechanism for how periodontitis affects diabetic complications; suggested pathways include oxidative stress, dyslipidemia, endothelial dysfunction and elevated CRP.[42] There is evidence that periodontal treatment improves short-term glycemic control and circulating levels of markers of inflammation in type 2 diabetes.[14] However, there is insufficient evidence on the effect of PD therapy on HBA1c levels in T1D.[14]

As the risk of CVD associated with PD among patients with diabetes is significant, screening for PD may provide a cost-effective modality for identifying patients at high CVD risk. A recent systematic review showed that most patients with diabetes were unaware of the PD-diabetes connection; they were not aware of their risk of PD and did not receive information about their oral health risk or advice about oral healthcare from their diabetes care provider.[43] This issue has been addressed in the recent guidelines developed by the International Diabetes Federation and the European Federation of Periodontology to integrate the health care, including oral health care, of patients with diabetes between physicians and dentists.[11] The guidelines state that children and adolescents with type 1 diabetes should be placed on annual oral screenings as soon as possible.[11] It is important to note that although smoking is a significant risk factor for periodontal disease, bleeding on probing, which is one of the classical signs of active periodontal disease, is usually masked in smokers due to the vasoconstrictive effect of nicotine on blood vessels.[44,45] Consequently, patients can be unaware of periodontal problems until the disease progresses to an advanced stage, which could increase their risk of CAD. Therefore, patients with T1D should be advised by their healthcare providers that PD, in addition to smoking, places them at increased risk of CVD complications beyond the traditional risk factors. These patients should be referred to a periodontist and placed on a periodontal treatment regimen.

4.1. Strengths and limitations

Our study has some limitations. The use of partial mouth measure with three facial sites only could have underestimated the prevalence of PD.[46] Partial mouth measures have been shown to bias epidemiological measures of association between PD and smoking, alcohol, obesity and diabetes.[47] However, when the EDC oral health exam took place in 1992–94, this partial mouth exam was commonly used as an acceptable measure of the prevalence of periodontal disease. In addition, we used a definition of periodontal disease (≥4 mm of attachment loss in ≥10% of examined sites). Research shows that the association of PD with systemic diseases differs according to the classification or definition of PD used.[48] Data for this cohort were collected to reflect the Healthy People 2000 and 2010 definition of PD[24,25] and do not allow the application of different definitions of PD. However, our main conclusion is that patients with T1D who have clinically verified PD and who currently smoke might be at increased risk of developing CVD

Table 4
Cox proportional hazard models for the prediction of Hard CAD.

	Crude model (*n* = 299, 81 events)	Model with interaction term for PD*smoking	Crude model for smokers (n = 55, 23 events)	Crude model for non-smokers (n = 244, 58 events)	Adjusted model for smokers (n = 55, 23 events)	Adjusted model for non-smokers (*n* = 244, 58 events)[a]
PD	1.85 (1.17–2.93)[c]	1.18 (0.83–1.70)	(time-dependent)	1.26 (1.09–1.46)[c]	1.35 (1.15–1.58)[d]	1.93 (1.23–3.05)[c]	1.19 (0.84–1.68)
PD*smoking		7.02 (1.31–37.59)[b]				
Diabetes duration					1.13 (1.05–1.21)[d]	1.09 (1.05–1.13)[d]
HbA1c					Not allowed	1.32 (1.10–1.60)[c]
Non-HDL cholesterol					Not allowed	1.01 (1.002–1.02)[c]
Log Albumin excretion rate					Not allowed	1.20 (1.05–1.38)[c]
WBC					Not allowed	1.17 (1.01–1.35)[b]

Data are HR (95%CI).
Multivariable models allowed for univariate predictors of CAD.
[a] The model also allowed for hypertension.
[b] p-Value <0.05.
[c] p-Value <0.01.
[d] p-Value <0.001.

complications. Moreover, oral health measures were assessed at one point and we cannot account for changes in PD over time. Smoking status was based on self-report and could be subject to reporting bias. Inflammation is suspected to play a role in the restriction of PD-CAD/HCAD association to smokers. However, we were unable to adjust for markers of inflammation beyond WBC count, as they were not collected for this sample. Adding markers of inflammation such as IL-8, TNF and CRP would help further understand the relationship between PD and smoking in the development of CVD complications of T1D. Despite these limitations, this study is unique in that it uses longitudinal data from a prospective study with 19 years of follow up with verified CVD events. This enables us to establish a strong association with the exposure (PD) proceeding the outcome (CVD complications) in T1D, a topic that is understudied.

4.2. Conclusion

PD could be used as an early clinical predictor of CAD complications in TID patients who smoke. In addition, T1D patients who smoke should receive coordinated care from both a periodontist and their usual healthcare provider to ensure optimal treatment of both their periodontal disease and CAD risk. Studies that investigate complications of diabetes should examine PD to further aid our understanding of the PD-diabetes complications association. Clinical trials to evaluate the effect of periodontal treatment on outcomes in patients with T1D are warranted.

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Declaration of Competing Interest

None.

References

1. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017;376:1419-29.
2. Tao B, Pietropaolo M, Atkinson M, Schatz D, Taylor D. Estimating the cost of type 1 diabetes in the U.S.: a propensity score matching method. PLoS One 2010;5, e11501.
3. Mauri-Obradors E, Estrugo-Devesa A, Jane-Salas E, Vinas M, Lopez-Lopez J. Oral manifestations of diabetes mellitus. A systematic review. Med Oral Patol Oral Cir Bucal 2017;22:e586-94.
4. Eke PI, Dye BA, Wei L, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol 2015;86:611-22.
5. Jepsen S, Caton JG, Albandar JM, et al. Periodontal manifestations of systemic diseases and developmental and acquired conditions: consensus report of workgroup 3 of the 2017 world workshop on the classification of periodontal and Peri-implant diseases and conditions. J Periodontol 2018;89:S237-48.
6. Johannsen A, Susin C, Gustafsson A. Smoking and inflammation: evidence for a synergistic role in chronic disease. Periodontology 2000. 2014;64(1):111–126.
7. Lappin DF, Robertson D, Hodge P, et al. The influence of glycated hemoglobin on the cross susceptibility between type 1 diabetes mellitus and periodontal disease. J Periodontol 2015;86:1249-59.
8. Chapple ILC, Mealey BL, Van Dyke TE, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: consensus report of workgroup 1 of the 2017 world workshop on the classification of periodontal and Peri-implant diseases and conditions. J Periodontol 2018;89:S74-84.
9. Ricardo AC, Athavale A, Chen J, et al. Periodontal disease, chronic kidney disease and mortality: results from the third National Health and nutrition examination survey. BMC Nephrol 2015;16:97.
10. Chang JF, Yeh JC, Chiu YL, Liou JC, Hsiung JR, Tung TH. Periodontal pocket depth, hyperglycemia, and progression of chronic kidney disease: a population-based longitudinal study. Am J Med 2017;130:61-9. [e61].
11. Sanz M, Ceriello A, Buysschaert M, et al. Scientific evidence on the links between periodontal diseases and diabetes: consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the international diabetes federation and the European Federation of Periodontology. J Clin Periodontol 2018;45:138-49.
12. Hyman JJ, Winn DM, Reid BC. The role of cigarette smoking in the association between periodontal disease and coronary heart disease. J Periodontol 2002;73:988-94.
13. Andriankaja OM, Genco RJ, Dorn J, et al. Periodontal disease and risk of myocardial infarction: the role of gender and smoking. Eur J Epidemiol 2007;22:699-705.
14. Graziani F, Gennai S, Solini A, Petrini M. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes an update of the EFP-AAP review. J Clin Periodontol 2018;45:167-87.
15. Southerland JH, Moss K, Taylor GW, et al. Periodontitis and diabetes associations with measures of atherosclerosis and CHD. Atherosclerosis 2012;222:196-201.
16. Zeng XT, Leng WD, Lam YY, et al. Periodontal disease and carotid atherosclerosis: a meta-analysis of 17,330 participants. Int J Cardiol 2016;203:1044-51.
17. Xu S, Song M, Xiong Y, Liu X, He Y, Qin Z. The association between periodontal disease and the risk of myocardial infarction: a pooled analysis of observational studies. BMC Cardiovasc Disord 2017;17:50.
18. Kebede TG, Holtfreter B, Kocher T, et al. Association of periodontal destruction and diabetes with mortality. J Dent Res 2017;96:56-63.
19. Groves DW, Krantz MJ, Hokanson JE, et al. Comparison of frequency and duration of periodontal disease with progression of coronary artery calcium in patients with and without type 1 diabetes mellitus. Am J Cardiol 2015;116:833-7.
20. Wagener DK, Sacks JM, LaPorte RE, MaCgregor JM. The Pittsburgh study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of IDDM. Diabetes 1982;31:136-44.
21. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh epidemiology of diabetes complications study experience. Diabetes 2006;55:1463-9.
22. Moore PA, Weyant RJ, Mongelluzzo MB, et al. Type 1 diabetes mellitus and oral health: assessment of periodontal disease. J Periodontol 1999;70:409-17.
23. Miller A, Brunelle J, Carlos J, Brown L, Löe H. The national survey of oral health in US employed adults and seniors: 1985–1986. Oral Health of United States Adults (NIH Publication No 87–2868). 1987.
24. Gift HC, Drury TF, Nowjack-Raymer RE, Selwitz RH. The state of the nation's oral health: mid-decade assessment of healthy people 2000. J Public Health Dent 1996;56:84-91.
25. US Department of Health and Human Services. Focus area 21 oral health. In: Healthy People 2010. 2000; 2nd https://www.healthypeople.gov/2010/Document/HTML/volume2/21Oral.htm.
26. Prince C, Becker D, Costacou T, Miller R, Orchard T. Changes in glycaemic control and risk of coronary artery disease in type 1 diabetes mellitus: findings from the Pittsburgh epidemiology of diabetes complications study (EDC). Diabetologia 2007;50:2280-8.
27. Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 1973;19:476-82.
28. Allain CC, Poon LS, Chan CS, Richmond W. Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470-5.
29. Warnick GR, Albers JJ. Heparin–Mn2+ quantitation of high-density-lipoprotein cholesterol: an ultrafiltration procedure for lipemic samples. Clin Chem 1978;24:900-4.
30. Hypertension detection and follow- up program. The hypertension detection and follow-up program cooperative group. Prev Med 1976;5:207-15.
31. Ellis D, Buffone G. New approach to evaluation of proteinuric states. Clin Chem 1977;23:666-70.
32. Ellis D, Coonrod BA, Dorman JS, et al. Choice of urine sample predictive of microalbuminuria in patients with insulin-dependent diabetes mellitus. Am J Kidney Dis 1989;13:321-8.
33. Hansen GM, Egeberg A, Holmstrup P, Hansen PR. Relation of periodontitis to risk of cardiovascular and all-cause mortality (from a Danish Nationwide cohort study). Am J Cardiol 2016;118:489-93.
34. Xu F, Lu B. Prospective association of periodontal disease with cardiovascular and all-cause mortality: NHANES III follow-up study. Atherosclerosis 2011;218:536-42.
35. Genco RJ. Current view of risk factors for periodontal diseases. J Periodontol 1996;67:1041-9.
36. Polak D, Shapira L. An update on the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Clin Periodontol 2018;45:150-66.
37. Coelho A, Paula A, Mota M, et al. Dental caries and bacterial load in saliva and dental biofilm of type 1 diabetics on continuous subcutaneous insulin infusion. J Appl Oral Sci 2018;26, e20170500.
38. Saes Busato IM, Antoni CC, Calcagnotto T, Ignacio SA, Azevedo-Alanis LR. Salivary flow rate, buffer capacity, and urea concentration in adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2016;29:1359-63.
39. Moore PA, Guggenheimer J, Etzel KR, Weyant RJ, Orchard T. Type 1 diabetes mellitus, xerostomia, and salivary flow rates. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:281-91.
40. Miranda TS, Napimoga MH, Feres M, et al. Antagonists of Wnt/beta-catenin signalling in the periodontitis associated with type 2 diabetes and smoking. J Clin Periodontol 2018;45:293-302.
41. Joaquim CR, Miranda TS, Marins LM, Silva HDP, Feres M, Figueiredo LC, Duarte PM. The combined and individual impact of diabetes and smoking on key subgingival periodontal pathogens in patients with chronic periodontitis. J Periodontal Res 2018;53(3):315-23, https://doi.org/10.1111/jre.12516.
42. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, Vegh D. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Diabetes Res Clin Pract 2018;137:231-41, https://doi.org/10.1016/j.diabres.2017.12.001.
43. Poudel P, Griffiths R, Wong VW, Arora A, Flack JR, Khoo CL, George A. Oral health knowledge, attitudes and care practices of people with diabetes: a systematic review. BMC Public Health 2018;18(1):577, https://doi.org/10.1186/s12889-018-5485-7.
44. Tarnowski M, Duda-Sobczak A, Lipski J, Zozulinska-Ziolkiewicz D, Wyganowska-Swiatkowska M. Tobacco smoking decreases clinical symptoms of gingivitis in patients with type 1 diabetes - a cross-sectional study. Oral Dis 2018.

45. Calsina G, Ramon JM, Echeverria JJ. Effects of smoking on periodontal tissues. J Clin Periodontol 2002;29:771-6.
46. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA. Accuracy of NHANES periodontal examination protocols. J Dent Res 2010;89:1208-13.
47. Akinkugbe AA, Saraiya VM, Preisser JS, Offenbacher S, Beck JD. Bias in estimating the cross-sectional smoking, alcohol, obesity and diabetes associations with moderate-severe periodontitis in the atherosclerosis risk in communities study: comparison of full versus partial-mouth estimates. J Clin Periodontol 2015;42:609-21.
48. Beck JD, Moss KL, Morelli T, Offenbacher S. Periodontal profile class is associated with prevalent diabetes, coronary heart disease, stroke, and systemic markers of C-reactive protein and interleukin-6. J Periodontol 2018;89:157-65.