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Type 1 Diabetes and Oral Health: Findings from the Epidemiology of Diabetes Interventions and Complications (EDIC) Study

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Abstract

Objective: To describe long-term oral health outcomes and examine associations between sociodemographic factors, clinical characteristics, and markers of diabetes control on tooth loss in participants with type 1 diabetes enrolled in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Research Design and Methods: Oral health outcomes related to tooth loss were reported at annual visits during EDIC years 22–26 (2015–2019). Generalized estimating equation models were used to assess the association of individual risk factors and tooth loss, over repeated time points.

Results: A total of 165 (17%) participants with type 1 diabetes reported 221 oral health outcomes related to tooth loss over a five-year period. After controlling for age and current tobacco use, the presence of diabetic peripheral neuropathy was significantly associated with an increased odds of tooth loss (OR=1.88, 95% CI 1.24, 2.87) while higher mean HDL/LDL cholesterol ratio was significantly associated with a decreased odds of tooth loss (OR=0.87, 95% CI=0.79, 0.97).

Conclusions: These findings suggest that diabetes-related complications, either resulting from or independent of poor glycemia, may be directly associated with oral health conditions, and support the need for individuals with type 1 diabetes and providers to implement lifestyle and medical interventions to reduce periodontal risks.

Keywords

type 1 diabetes; oral health outcomes; periodontitis; tooth loss; disease progression

INTRODUCTION

Tooth loss is a prevalent health outcome in adults and is associated with detrimental impacts on quality of life.[1] The prevalence of tooth loss increases with age and is a significant problem for people 60 years and older.[2] It has been reported that just over a quarter (26%) of adults aged 65 or older have 8 or fewer teeth with 17% of adults aged 65 or older reporting total loss of teeth.[3] Periodontitis, a chronic inflammatory disease of the gingivae and supporting structures of the teeth, and dental caries, a bacterial disease of calcified tissues of the teeth, are the primary drivers of tooth loss in adults. [4, 5]

Diabetes mellitus has long been recognized as a risk factor for periodontitis, with consistent reports of a higher prevalence, incidence, severity and progression of periodontitis in people with diabetes.[6] Furthermore, the level of glycemic control has been shown to influence risks of severe periodontal disease.[7] While the literature on diabetes and dental caries is more limited and inconsistent, there have been several reports of high caries frequency in patients with diabetes.[8,9] Finally, several population-based studies have demonstrated that adults with diabetes are at higher risk of experiencing tooth loss than adults without diabetes.[8,10] The bulk of the research on diabetes, periodontal disease, dental caries, and

tooth loss has focused primarily on adults with type 2 diabetes with few studies having comprehensively characterized tooth loss in adults with type 1 diabetes.[8] The objective of this study was to examine tooth loss and identify sociodemographic factors, clinical characteristics, and diabetes-related risk factors among adult participants with long-standing type 1 diabetes enrolled in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

MATERIALS AND METHODS

Population and Study Setting

The DCCT was a multicenter, randomized controlled clinical trial designed to compare the effects of intensive insulin therapy and conventional therapy on the development and progression of microvascular complications of type 1 diabetes. From 1983–1989, 1441 participants aged 13–39 years from 27 clinical centers (25 in the US and 2 in Canada) were randomized to one of the two treatment regimens and enrolled into a primary prevention or secondary intervention cohort based on diabetes duration and presence of complications.[11] The intensive treatment regimen was designed to achieve glycemic control as close to the non-diabetic range as safely as possible with 3 or more daily insulin injections or use of an insulin pump, with dose selection guided by frequent self-monitoring of blood glucose. Conventional therapy consisted of 1–2 daily insulin injections without pre-specified target glucose levels and absence of symptomatic hyperglycemia and frequent or severe hypoglycemia. At the end of the DCCT in 1993, after a mean follow-up of 6.5 years, intensive therapy was observed to significantly reduce the onset and progression of several diabetes complications compared with conventional treatment. Intensive therapy was recommended, and all participants were instructed in intensive therapy methods and returned to their own health care providers for ongoing diabetes care. At the completion of the DCCT, all participants were eligible to participate in the EDIC observational follow-up study (1994-present) and 1375 (96% of the surviving cohort) agreed to participate. A detailed description of EDIC study procedures and baseline characteristics has been published.[12]

Oral Health Evaluations, Risk Factors, and Coexisting Complications

Beginning in EDIC follow-up year 22 (2015), annual EDIC examinations included the following oral health questions: *'Since the last evaluation, has the participant been diagnosed with any of the following conditions? Dental abscess, dental extractions, unexplained loss of teeth, or periodontal disease/gingivitis.'* The response for each of these four items was 'yes' or 'no'. For the purposes of this analysis, a more specific tooth loss outcome was defined as a "yes" response to either or both of the dental extractions and unexpected loss of teeth items during EDIC Years 22–26 (2015–2019). Dental extractions were included in the definition of this tooth loss outcome because routine dental extractions (such as wisdom teeth) would be uncommon based on the age of this cohort.

Quarterly DCCT[11] and annual EDIC[12] assessments included a detailed medical history of demographic and behavioral risk factors including alcohol use, tobacco use, education, body mass index (BMI), and blood pressure. Fasting lipids (triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol)

were measured annually during DCCT and alternate years during EDIC. C-reactive protein (mg/dL) was measured once at DCCT closeout. HbA1c was measured by high-performance liquid chromatography quarterly during DCCT and annually during EDIC. Proliferative diabetic retinopathy (PDR) was defined as neovascularization observed on fundus photograph grading and/or by confirmed scatter photocoagulation at any time during the DCCT/EDIC study.[13] Kidney disease was defined as sustained eGFR <60 mL/min/1.73 m^2 on ≥2 consecutive visits or sustained moderate albuminuria (albumin excretion rate (AER) ≥30 mg/24 hours) on ≥2 consecutive visits, or as severe albuminuria (AER ≥300 mg/24 hours) at any time during the DCCT/EDIC study.[14, 15] Comprehensive diabetic peripheral neuropathy (DPN) measures were obtained twice during the DCCT (baseline, year 5) and once during EDIC years 13–14 (2006–2007). DPN was defined as the presence of confirmed clinical neuropathy which required at least two abnormal findings among symptoms, sensory signs, or reflex changes consistent with DPN as assessed by a qualified neurologist, plus abnormal nerve conduction studies in at least two anatomically distinct nerves at any time during the DCCT/EDIC study.[16] In addition, DPN was assessed annually during EDIC with the Michigan Neuropathy Screening Instrument (MNSI), comprised of a symptom questionnaire and a clinical examination that included structured foot inspection, presence of ulcerations and assessment of ankle reflexes and vibration perception using a tuning fork, as previously described.[17, 18] DPN was defined as ≥7 positive responses on the MNSI questionnaire or a clinical examination score ≥2.5. Cardiovascular autonomic neuropathy (CAN) was assessed up to five times during DCCT (baseline, years 2, 4, 6, and 8) and twice during EDIC (years 13/14 and 16/17) with standardized cardiovascular reflex tests and defined as either a R-R variation <15, or R-R variation between 15 and 19.9 plus either a Valsalva ratio ≤1.5, or a supine-to-stand drop of ≥10 mmHg in diastolic blood pressure as previously reported.[18, 19] All cardiovascular disease (CVD) events were adjudicated and classified by a committee masked to DCCT treatment group assignment and HbA1c levels.[20]

Statistical Considerations

The incidence of each oral health outcome was assessed annually during EDIC years 22–26 both as the frequency of participants reporting outcomes as well as the frequency of events. Descriptive analyses examined the distribution of sociodemographic and clinical characteristics and measures of glycemic control, prior DCCT treatment, and microvascular and neuropathic complications by the presence or absence of the composite tooth loss outcome during EDIC years 22–26. The Wilcoxon rank sum test and the chi-squared test were used to assess differences in quantitative and categorical variables between participants who did and did not report the presence of the composite tooth loss outcome during the 5-year follow-up period, respectively. Separate generalized estimating equations (GEE) were used to evaluate the associations between individual time-dependent risk factors and presence of the composite tooth loss outcome over repeated time points, unadjusted and minimally adjusted for age. Quantitative covariates were characterized by the time-weighted mean of all follow-up values since DCCT baseline up to each EDIC visit, weighting each value by the time interval between the measurements. Microvascular and neuropathic complications were defined as the presence of any complication between DCCT baseline and each annual EDIC visit. A multivariable logistic regression model was then evaluated

for the composite tooth loss outcome. Variables were entered into the logistic regression model applying a backward elimination modeling technique, where associations significant at $p<0.20$ were retained at each step. A final combined multivariable logistic regression model was evaluated using all of the variables selected by the modeling technique, and variables significant at $p<0.05$ were kept in the final multivariable model, adjusting for age. Current smoking status and cardiovascular disease were also retained in the final model for interpretation. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R statistical software (The R Project for Statistical Computing).

RESULTS

The incidence of the individual oral outcomes assessed over the five-year period are presented in Table 1. At EDIC year 22, 90 (9%) of participants reported the occurrence of any oral health outcome in the past year, including 28 (3%) who reported dental abscesses, 57 (6%) dental extraction, 7 (1%) unexpected loss of teeth, and 21 (2%) periodontal disease/gingivitis. A total of 63 (7%) of participants reported the composite tooth loss outcome (i.e., dental extraction and/or unexpected tooth loss) at EDIC year 22 and the incidence of the composite tooth loss outcome remained low (5% based on events, 3.5% based on participants) in EDIC years 23–26. A total of 165 participants (17%) reported 221 dental extraction and/or unexpected tooth loss events over the five-year study period.

Table 2 summarizes the sociodemographic, clinical, and metabolic characteristics of study participants at EDIC year 22 by the presence or absence of the composite tooth loss outcome over the five-year period. Participants who reported the composite tooth loss outcome during the follow-up period were significantly more likely to use tobacco products, less likely to consume alcohol, had higher mean LDL cholesterol and triglyceride levels, and lower mean HDL cholesterol levels compared to those not reporting the composite tooth loss outcome. Additionally, those who reported the composite tooth loss outcome had a higher prevalence of macroalbuminuria, DPN based on MNSI questionnaire score, and history of cardiovascular disease.

The unadjusted and minimally adjusted (for age only) odds of reporting the composite tooth loss outcome, per unit change in the covariate, are shown in Table 3. Several significant associations observed in bivariate analyses persisted after adjustment for age. When controlling for the effects of age, a 10 mg/dl increase in mean LDL cholesterol or mean triglyceride levels was significantly associated with a 10% ($p=0.04$) and 8% ($p=0.03$) increased odds of reporting the composite tooth loss outcome, respectively. The following risk factors were also significantly associated with higher odds of the composite tooth loss outcome when minimally adjusted for age: current tobacco use, lower mean HDL cholesterol, higher C-reactive protein levels, history of any macroalbuminuria, DPN defined as a score of ≥7 on the MNSI questionnaire, and history of cardiovascular disease. When controlling for the effects of age, a 1-percentage point increase in current HbA1c levels was associated with a 19% increased odds of reporting the composite tooth loss outcome, albeit these results did not meet statistical significance ($p=0.08$). The final multivariable GEE model for the composite tooth loss outcome is presented in Table 4. A 0.1-unit increase in HDL/LDL cholesterol ratio was significantly associated with a reduction in odds of

the composite tooth loss outcome (OR=0.87, 95%CI=0.79, 0.97) after adjustment for all other factors in the table. The presence of DPN, defined as a score of ≥7 on the MNSI questionnaire, was most significantly associated (z-test value 2.97) with an increased odds of the composite tooth loss outcome (OR=1.88, 95%CI=1.24, 2.87). Tobacco use and a history of cardiovascular disease were also associated with tooth loss albeit the findings did not reach statistical significance (p=0.06) when adjusted for all other factors in the table.

DISCUSSION

These analyses describe the burden of oral health outcomes and the associations between diabetes-related risk factors and tooth loss outcomes among adult men and women with long-standing type 1 diabetes participating in the DCCT/EDIC study. We found that the HDL/LDL cholesterol ratio had a statistically significant negative association with the risk of the composite tooth loss outcome after adjusting for age. Further, while a history of cardiovascular disease and current tobacco use were also found to be associated with the composite tooth loss outcome, DPN was the predominant risk factor for tooth loss, independent of both age, cardiovascular disease, current tobacco use, and cholesterol levels.

The annual incidence of the composite tooth loss outcome overall was approximately 5% based on events and 3.5% based on participants in the DCCT/EDIC cohort. Previous studies have primarily reported prevalence estimates in individuals with type 1 diabetes.[8] An NHANES study involving 2,508 subjects 50 years and older reported a prevalence of tooth loss of 15% in participants reporting diabetes.[10] Additionally, an epidemiological study evaluating data from Behavioral Risk Factor Surveillance System reporting on tooth removal due to caries or periodontal disease, reported a prevalence of 38% in diabetic patients.[21] Neither study, however, differentiated between type 1 and type 2 diabetes. The lower report of tooth loss in our cohort is most likely related to reliance on self-report of periodontal disease and assessment of incident rather than prevalent events. Additionally, the DCCT/EDIC cohort, with a mean HbA1c of approximately 8% and long-term participation in a longitudinal clinical study, may not reflect the level of diabetes control and extent of tooth loss of the general adult type 1 diabetes population.

When considering the potential association between diabetes-related risk factors and tooth loss, the primary contributory factors to dental extractions and/or tooth loss including periodontal disease and dental caries must be considered. Glycemic control is known to play a significant role in the development of periodontal complications.[7] (ref Demmer) Despite a lower rate of periodontal related disease in the DCCT/EDIC cohort compared to previously published reports[23], we did observe that individuals in the DCCT/EDIC cohort experienced an increase in the risk of tooth loss with increasing current and time weighted mean HbA1c, albeit these results did not reach statistical significance. Hypothesized mechanisms by which hyperglycemia could affect periodontal disease include hyperinflammatory response to infection, uncoupling of bone destruction and repair due to more rapid collagen turnover, and the effects of advanced glycation end products.[24] In studies where greater caries frequency in people with diabetes were observed, investigators hypothesized that poor glycemic control and resulting hyperglycemia can result in increased concentration of glucose in saliva and/or gingival crevicular fluid. Diabetes-related decreased salivary flow

could also contribute to increased risk of caries by increasing the substrate available for cariogenic bacteria to metabolize and produce enamel- and dentin-demineralizing acids.[8]

Other known complications of diabetes may also increase the risk or severity of periodontal disease, both independent of the effects of hyperglycemia or as a result thereof. In the DCCT/EDIC cohort, we found that DPN was associated with a higher risk of the composite tooth loss outcome. Mechanisms of development of microvascular complications of diabetes include generation of AGEs, oxidative stress, tissue specific metabolic flux dysregulations, mitochondrial dysfunction and chronic inflammation.[25] While these various pathways have been studied in the retina, kidney and nervous system, similar mechanisms are thought to affect the periodontium. The association between neuropathy and risk of periodontal disease and tooth loss has been described in populations both with and without diabetes.[24, 26] Although hyperglycemia and glucotoxicity traditionally have been considered the primary risk factors for nerve fiber damage, more recent evidence from experimental and human studies demonstrate that subclinical chronic inflammation coupled with activation of the IKKβ/NF-κB axis and downstream cytokine and chemokine release play critical roles in the development of both peripheral and autonomic neuropathy and are also linked with periodontal disease.[26, 27] Further, microvascular damage may be related to diffuse microangiopathy of endoneurial capillaries with resultant ischemia and alteration of the blood nerve barrier.[28] Similar vessel changes are observed in the periodontium leading to an increase in surrogate periodontal factors like bleeding tendencies.[29]

There is a strong dose-dependent association between cigarette smoking and tooth loss.[30] Further, smoking is a well-established risk factor for periodontal disease[31] as it impairs the functional systemic and local components of the immune system involved in maintenance of periodontal health.[32] Our results are consistent with previous reports and suggest increased risk of tooth loss with report of current smoking. Additionally, we found several cardiovascular disease risk indicators to be significantly associated with report of periodontal outcomes, including lower HDL and higher LDL and triglycerides. A history of cardiovascular disease was significantly associated with tooth loss in the age-adjusted model but lost significance in the final multivariable model. Previous studies have observed elevated LDL and triglyceride values in subjects with chronic periodontal disease.[33] Similar to our findings, pooled analysis from 18 studies involving 1,651 participants without diabetes showed significantly lower HDL levels in patients with chronic periodontitis than in healthy subjects.[34] It is hypothesized that elevated lipid levels alter immune cell function and increase production of pro-inflammatory cytokines compromising tissue response and affecting wound healing, thereby increasing the susceptibility to periodontitis.[35]

The current study is the largest to examine oral health outcomes among adults with type 1 diabetes. Its strengths include the minimal loss to follow-up and frequent validated measurement of key covariates. The longitudinal follow-up allows for the exploration of the long-term impact of diabetes on oral health outcomes. It is also important to recognize that this study has several limitations. The first and most significant is the reliance on a binary single item definition of self-reported oral health outcomes. The items potentially lack specificity and could lead to under-reporting, but its availability annually over the five-year study provides a unique opportunity to evaluate annualized patterns of oral health

outcomes. Further studies with more standardized assessments of periodontal disease and dental caries, including oral exams, are warranted. Finally, DCCT/EDIC participants are predominantly Caucasian and may have better than average health monitoring and control of their diabetes. A study of a more diverse multiethnic population of adult men and women with type 1 diabetes outside a research setting may demonstrate a wider range of glycemic control and higher rates of oral health outcomes.

CONCLUSIONS

In this study of adults with long-standing type 1 diabetes, we found that the presence of DPN and poor cholesterol control were associated with increased risk of tooth loss. These findings suggest that diabetes-related complications, either resulting from or independent of poor glycemia, may be directly associated with oral health conditions in the DCCT/EDIC cohort. These results can inform individuals with type 1 diabetes and their providers of the importance of detecting and managing oral health risk by lifestyle and medical intervention.

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Guarantor Statement:

BB is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Sharing:

Data collected for the DCCT/EDIC study through June 30th 2017 are available to the public through the NIDDK Central Repository (https://repository.niddk.nih.gov/studies/edic/). Data collected in the current cycle (July 2017-June 2022) will be available within two years after the end of the funding cycle.

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Table 1.

Frequency of Oral Health Outcomes Reported by EDIC Year

	EDIC Year 22	EDIC Year 23	EDIC Year 24	EDIC Year 25	EDIC Year 26	N Events	N Participants
Number of Participants	950	883	881	862	871		
Dental Abscess	28 (3)	17 (2)	14 (2)	15 (2)	18 (2)	92	76
Dental Extraction	57 (6)	29 (3)	31 (4)	50 (6)	41 (5)	208	157
Unexpected Loss of Teeth	7 (1)	3 (<1)	2 (<1)	3 (<1)	4 (<1)	19	16
Periodontal Disease/ Gingivitis	21 (2)	16 (2)	19 (2)	15 (2)	16 (2)	87	63
Any Oral Health Outcome	90 (9)	52 (6)	54 (6)	68 (8)	62 (7)	326	229
Composite Tooth Loss Outcome*	63 (7)	32 (4)	33 (4)	51 (6)	42 (5)	221	165
Number of Events	113	65	66	83	79		
0	860 (91)	831 (94)	827 (94)	794 (92)	809 (93)		
1	68 (7)	41 (5)	42 (5)	54 (6)	49 (6)		
2	21 (2)	9 (1)	12 (1)	13 (2)	10 (1)		
3	1 (<1)	2 (<1)	0	1 (<1)	2 (<1)		
4	0	0	0	0	1 (<1)		

Data are N(%) based on self-report: "Since the last evaluation, has the participant been diagnosed with any of the following conditions?" using response at EDIC year 22 as baseline. This question was administered between EDIC years 22 and 26 and refers to oral health outcomes that occurred in the past year, since the last visit.

*Defined as dental extraction and/or unexpected tooth loss.

Table 2.

EDIC Year 22 Characteristics of Participants According to the Presence or Absence of the Composite Tooth Loss Outcome During EDIC Years 22–26

	All	Composite Tooth Loss Outcome Absent	Composite Tooth Loss Outcome Present	p-value
	n=950	n=785	n=165	
Sociodemographic & Clinical Factors				
Age (years)	56 (46.8)	56.3±6.9	56.8±6.5	0.384
Sex (female)	481 (50.6)	400 (51.0)	81 (49.1)	0.726
Current Tobacco User	115 (12.1)	87 (11.1)	28 (17.0)	**0.048**
Any Tobacco Use	465 (48.9)	384 (48.9)	81 (49.1)	0.999
Current Drinker	449 (47.3)	387 (49.3)	62 (37.6)	**0.008**
College Graduate	598 (62.9)	500 (63.7)	98 (59.4)	0.342
Current BMI (kg/m^2)	28±95.6	28.8±5.6	29.0±5.7	0.892
Diastolic BP (mm Hg) *	73 ±45.0	73.4±4.9	73.7±5.3	0.249
Systolic BP (mm Hg) *	119.0±8.2	118.9±8.1	119.8±8.5	0.290
Total Cholesterol (mg/dl) *	180.4±23.6	180.0±23.3	182.3±25.0	0.214
HDL Cholesterol (mg/dl) *	56.6±13.4	57.2±13.5	54.0±12.8	**0.009**
LDL Cholesterol (mg/dl) *	107.2±20.0	106.6±19.8	109.9±21.0	**0.025**
Triglycerides (mg/dl) *	82.8±39.5	80.9±37.1	91.9±48.5	**0.008**
Diabetes-related Characteristics				
DCCT Intensive Treatment Group	484 (50.9)	395 (50.3)	89 (53.9)	0.447
DCCT Primary Prevention Cohort	479 (50.4)	393 (50.1)	86 (52.1)	0.693
Diabetes Duration (years)	34.6±4.9	34.6±4.8	34.5±4.9	0.665
Current HbA1c (%)	7.9±1.2	7.9±1.2	8.0±1.3	0.546
HbA1c (%) *	8.0±0.9	7.9±0.9	8.1±1.0	0.103
Insulin Dose (units/kg/day) *	0.65±0.16	0.64±0.16	0.66±0.16	0.105
C-Reactive Protein (mg/dl) †	0.55±0.97	0.51±0.88	0.74±1.32	0.069
Proliferative Diabetic Retinopathy ‡	256 (26.9)	204 (26.0)	52 (31.5)	0.174
Sustained eGFR <60 mL/min/1.73 m^2 ‡	75 (8.0)	56 (7.3)	19 (11.7)	0.081
Sustained AER ≥30 mg/24 hours ‡	296 (31.1)	244 (48.2)	52 (48.6)	0.999
AER ≥300 mg/24 hours ‡	104 (10.9)	77 (18.6)	27 (28.7)	**0.039**
Confirmed Clinical Neuropathy ‡	303 (31.9)	241 (30.7)	62 (37.6)	0.103
MNSI: Questionnaire Score ≥7	80 (8.5)	57 (7.3)	23 (14.4)	**0.006**
MNSI: Exam Score ≥2.5	394 (42.1)	323 (41.6)	71 (44.4)	0.580
Cardiovascular Autonomic Neuropathy ‡	441 (46.4)	355 (45.2)	86 (52.1)	0.126
Cardiovascular Disease ‡§	104 (10.9)	77 (9.8)	27 (16.4)	**0.021**

Means (±standard deviation) or N(%) are presented. HDL=high-density lipoprotein, LDL=low-density lipoprotein AER=albumin excretion rate, eGFR=estimated glomerular filtration rate, MNSI=Michigan Neuropathy Screening Instrument.

[*] Risk factors were characterized by the time-weighted mean of all follow-up values since DCCT baseline up to EDIC year 22, weighting each value by the time interval since the last measurement.

[†] Measured once at DCCT closeout.

[‡] Any report between DCCT baseline and EDIC year 22.

[§] Ascertainment as of 12/31/2013, corresponding to EDIC year 20/21.

Table 3.

Odds Ratios for the Composite Tooth Loss Outcome Per Unit Change in Each Covariate, Unadjusted and Minimally Adjusted for Age

	Unadjusted		Age-Adjusted	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Sociodemographic & Clinical Characteristics				
Age (per 1 year)	1.02 (1.00, 1.04)	0.1030	--	--
Sex (female vs. male)	1.01 (0.73, 1.39)	0.9672	1.03 (0.74, 1.42)	0.8662
Current Tobacco User (yes vs. no)	**1.67 (1.12, 2.48)**	**0.0111**	**1.70 (1.15, 2.53)**	**0.0083**
Any Tobacco User (yes vs. no)	1.10 (0.79, 1.51)	0.5801	1.07 (0.77, 1.49)	0.6709
Current Drinker (yes vs. no)	0.77 (0.57, 1.04)	0.0852	0.76 (0.56, 1.03)	0.0797
College Graduate (yes vs. no)	0.95 (0.69, 1.32)	0.7772	0.98 (0.71, 1.35)	0.9171
BMI (per 1 kg/m^2)	1.01 (0.98, 1.03)	0.7099	1.01 (0.98, 1.03)	0.6607
Diastolic BP (per 5 mm Hg) *	1.05 (0.89, 1.23)	0.5841	1.05 (0.89, 1.24)	0.5462
Systolic BP (per 5 mm Hg) *	1.07 (0.96, 1.19)	0.2098	1.05 (0.94, 1.17)	0.4143
Total Cholesterol (per 10 mg/dl) *	1.04 (0.97, 1.12)	0.2704	1.04 (0.96, 1.12)	0.3156
HDL Cholesterol (per 10 mg/dl) *	**0.84 (0.74, 0.96)**	**0.0114**	**0.84 (0.73, 0.96)**	**0.0082**
LDL Cholesterol (per 10 mg/dl) *	**1.10 (1.00, 1.20)**	**0.0399**	**1.10 (1.00, 1.20)**	**0.0439**
Triglycerides (per 20% increase) *	**1.09 (1.01, 1.17)**	**0.0243**	**1.08 (1.01, 1.17)**	**0.0256**
Diabetes-related Characteristics				
DCCT Intensive Treatment Group (conv. vs. int.)	0.85 (0.62, 1.18)	0.3353	0.87 (0.63, 1.20)	0.3996
DCCT Primary Cohort (secondary vs. primary)	0.90 (0.65, 1.24)	0.5195	0.93 (0.67, 1.29)	0.6654
Diabetes Duration (per 1 year)	1.00 (0.97, 1.04)	0.8762	1.00 (0.97, 1.03)	0.9792
Current HbA1c (per 1%)	1.11 (0.97, 1.27)	0.1453	1.11 (0.97, 1.27)	0.1268
HbA1c (per 1%) *	1.17 (0.97, 1.42)	0.1002	1.19 (0.98, 1.44)	0.0787
Insulin Dosage (per 0.1 unit/kg/day) *	1.04 (0.95, 1.14)	0.3731	1.06 (0.96, 1.16)	0.2403
C-Reactive Protein (per 1 mg/dl) †	1.14 (0.99, 1.31)	0.0601	**1.15 (1.01, 1.31)**	**0.0355**
Proliferative Diabetic Retinopathy (yes vs. no)‡	1.13 (0.80, 1.60)	0.4869	1.13 (0.80, 1.60)	0.4725
Sustained eGFR <60 mL/min/1.73 m^2 (yes vs. no)‡	1.43 (0.96, 2.14)	0.0783	1.35 (0.91, 2.02)	0.1378
Sustained AER ≥30 mg/24 hours (yes vs. no)‡	1.17 (0.80, 1.70)	0.4206	1.17 (0.81, 1.71)	0.4064
AER ≥300 mg/24 hours (yes vs. no)‡	**1.93 (1.23, 3.01)**	**0.0040**	**1.96 (1.25, 3.07)**	**0.0033**
Confirmed Clinical Neuropathy (yes vs. no)‡	**1.40 (1.00, 1.95)**	**0.0481**	1.34 (0.96, 1.87)	0.0881
MNSI Questionnaire Score ≥7 (yes vs. no)	**2.00 (1.31, 3.04)**	**0.0013**	**1.95 (1.28, 2.97)**	**0.0018**
MNSI Exam Score ≥2.5 (yes vs. no)	1.02 (0.77, 1.35)	0.8866	0.99 (0.74, 1.31)	0.9317
Cardiovascular Autonomic Neuropathy (yes vs. no)‡	1.35 (0.98, 1.86)	0.0697	1.29 (0.92, 1.80)	0.1432
Cardiovascular Disease (yes vs. no)§‡	**1.69 (1.09, 2.61)**	**0.0179**	**1.60 (1.03, 2.50)**	**0.0366**

Odds ratios and p-values from separate generalized estimating equation (GEE) models. HDL=high-density lipoprotein, LDL=low-density lipoprotein AER=albumin excretion rate, eGFR= estimated glomerular filtration rate, MNSI: Michigan Neuropathy Screening Instrument. Composite tooth loss outcome defined as dental extraction and/or unexpected tooth loss.

*Risk factors were characterized by the time-weighted mean of all follow-up values since DCCT baseline up to EDIC Year 22, weighting each value by the time interval since the last measurement. Triglyceride values were log transformed, and the odds ratios are presented per 20% increase in the covariate (1.2^{β}).

†Measured once at DCCT closeout.

‡Any report between DCCT baseline and EDIC year 22.

§Ascertainment as of 12/31/2013, corresponding to EDIC year 20/21.

Table 4.

Final Multivariable GEE Model for the Composite Tooth Loss Outcome

	Odds Ratio (95% CI)	z-test value	p-value
MNSI Questionnaire Score ≥7 (yes vs. no)	**1.88 (1.24, 2.87)**	**2.97**	**0.0030**
HDL/LDL Cholesterol Ratio (per 0.1) *	**0.87 (0.79, 0.97)**	**2.63**	**0.0084**
Cardiovascular disease (yes vs. no) †‡	1.55 (0.98, 2.45)	1.88	0.0606
Current Tobacco User (yes vs. no)	1.50 (0.98, 2.29)	1.88	0.0600
Age (per 1 year)	1.02 (0.99, 1.04)	1.45	0.1468

Odds ratios and p-values from multivariable generalized estimating equation (GEE) model. HDL=high-density lipoprotein, LDL=low-density lipoprotein, MNSI=Michigan Neuropathy Screening Instrument. Covariates are listed in order of significance as indicated by the absolute value of the z-test value. Composite tooth loss outcome defined as dental extraction and/or unexpected tooth loss.

*Risk factors were characterized by the time-weighted mean of all follow-up values since DCCT baseline up to EDIC year 22, weighting each value by the time interval since the last measurement.

†Any report between DCCT baseline and EDIC year 22.

‡Ascertainment as of 12/31/2013, corresponding to EDIC year 20/21.