Original Research

Hispanic adults with type 2 diabetes mellitus using lipid-lowering agents have better periodontal health than non-users

Oelisoa M. Andriankaja[ID], Kaumudi J. Joshipura, Michael A. Levine, Margarita Ramirez-Vick, Julio A. Rivas-Agosto, Jorge S. Duconge and Dana T. Graves

Abstract

Background: Recent studies suggest that lipid-lowering agents (LLA) may reduce chronic periodontitis, but it is unknown whether this benefit extends to people with type 2 diabetes (T2D).

Objective: We assessed the association between LLA use and periodontitis in Hispanic adults with T2D.

Design: This was a cross-sectional observational study.

Methods: We assessed the association of LLA use and periodontal parameters in 253 Puerto Ricans 40–65 years with T2D who participated in the Lipid-Lowering agents use in Periodontitis and Diabetes Study study. Participants were classified as (a) none- or <1 year, (b) 1–4 years, or (c) >4 years. The primary outcome consists of a tertile percent of sites with probing pocket depth (PPD) ≥ 4 mm and the secondary outcome includes tertiles of percent sites with clinical attachment loss (CAL) ≥ 4 mm. Multinomial logistic regression models adjusted for age, gender, smoking status, education, waist circumference, glycosylated hemoglobin A1C (HbA1c), bleeding on probing, examiner, and anti-inflammatory agents were used to estimate the association.

Results: LLA (92.5%, statins) was used by 52% of participants. LLA use 1–4 years was associated with lower odds of PPD ≥ 4 mm (OR: 0.22, p = 0.005; high *versus* low tertile) or lower odds of CAL ≥ 4 mm (OR: 0.33, p = 0.02, middle *versus* low tertile), compared to those with LLA minimal or no use. This association was lost for participants who used LLA for >4 years. LLA users for >4 years with periodontal disease had elevated HbA1c (OR: 1.36, p = 0.05).

Conclusion: The use of LLA for 1–4 years was associated with lower values of periodontal parameters *versus* minimal LLA use. This association was not present among people using LLA > 4 years users, but these participants had poorer glycemic control compared to other participants. In this cross-sectional study, the finding that LLA use 1- 4 years is associated with lower values of periodontal parameters of severity in T2D individuals may help clarify some of the controversies regarding the benefit of these medications in this population.

Correspondence to:
Oelisoa M. Andriankaja
Department of Oral Health Practice, College of Dentistry, University of Kentucky, 770 Rose Street, Dental Science Building, Office D-106B3, Lexington, KY 40536, USA
oelisoa.Andriankaja@uky.edu

Kaumudi J. Joshipura
Center for Clinical Research and Health Promotion, School of Dental Medicine, Medical Sciences Campus University of Puerto Rico, San Juan, Puerto Rico

Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

Michael A. Levine
Center for Bone Health, Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Margarita Ramirez-Vick
Endocrinology Section, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

Julio A. Rivas-Agosto
Center for Clinical Research and Health Promotion, School of Dental Medicine, Medical Sciences Campus University of Puerto Rico, San Juan, Puerto Rico

Jorge S. Duconge
School of Pharmacy, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

Dana T. Graves
Department of Periodontics, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA

Plain language summary

Lipid-lowering agents and lower values of periodontal parameters in individuals with type 2 diabetes

- Lipid-lowering agents (LLA), such as statins, are reported to reduce chronic periodontitis, making individuals with diabetes ideal candidates for this treatment due to their high prevalence of oral disease.

1

- The association between LLA use and periodontitis was assessed among Hispanic adults with type 2 diabetes (T2D).
- Short-term LLA use (but not long-term use) was associated with lower values of periodontal parameters in individuals with T2D.
- For long-term LLA use, high glycemic level was associated with high values of periodontitis.
- Thus, under the study design limitations, the finding may provide clinical implications and may help clarify some of the controversies regarding the benefits of LLA use in humans.
- Furthermore, the higher glycemic levels for periodontal patients with long-term LLA use points to the need to monitor these patients carefully.

Introduction

Periodontal disease (PD) is due to bacteria-induced inflammation that can lead to long-lasting gingival inflammation that affects the soft connective tissue and supporting bone. PD ranges from simple reversible gingivitis to a more serious chronic periodontitis formerly known as adult periodontitis. Although bacterial pathogens are the major cause of PD development, their presence alone is not sufficient for the disease to occur. The mechanism of action is dependent on a host-mediated tissue injury caused by the immune response that plays an important role in chronic periodontal tissue destruction.[1,2]

PD is a major cause of tooth loss, which can compromise mastication, esthetics, self-confidence, and quality of life.[3] The prevalence of PD is approximately 42% in dentate Americans aged 30–79 years[4] and is even greater among the Hispanic population. According to the available data, nearly 45% of older Puerto Ricans aged 70–97 years have moderate/severe PD, while the corresponding estimate for all Americans aged 75 years or older is 21%.[5] Yet, PD is preventable, especially at earlier age. Periodontal disease is associated with systemic conditions linked to increased chronic inflammation such as cardiovascular disease (CVD), diabetes, or rheumatoid arthritis.[6]

An association between diabetes mellitus and PD has been recognized for over 70 years.[7] Animal experiments and human studies have demonstrated that diabetes is a risk factor for PD.[8–11] Mechanistically, diabetes enhances periodontal inflammation, and animal studies have shown that it alters the oral microbiome to enhance its pathogenicity.[12,13] Recent studies suggest the association between these diseases is bi-directional as PD can worsen glycemic control.[10]

According to recent meta-analysis findings, individuals with type 2 diabetes (T2D) have a 34% increase in the risk of developing PD (incidence) compared to individuals without T2D.[10] In specific populations, such as the Pima Indians, who may be related to the Caribbean Taino Indians of Puerto Ricans[14], the evidence of the association is even stronger: The odds of having PD is three-to-four fold higher in individuals with T2D compared to normoglycemic individuals.[15] Early and prolonged progression of T2D increases the extent and severity of PD.[16] The impact of diabetes on PD severity and progression is inversely proportional to the degree of glycemic control.[7] The prevalence of T2D in 2019 was 16.7% in Puerto Rico as compared to 10.7% in the US mainland.[17] Given the increasing prevalence of T2D, it is likely that PD will also continue to

increase,[8,18] highlighting the critical need to develop strategies to treat or prevent PD in individuals with T2D to improve their oral health and quality of life.

Lipid-lowering agents (LLA) such as statins, fibrates, and omega-3 fatty acids have beneficial effects on chronic inflammatory diseases, including periodontitis.[19–22] Of these, statins are likely to have the greatest potential for treatment of PD as they have pleiotropic anti-inflammatory and immunomodulatory, antibacterial, as well as positive effects on bone metabolism, epithelization, and wound healing.[23–26] *In vitro* and some *in vivo* experimental or observational studies have reported beneficial effects of statins in the treatment of periodontitis or an association between statin use and improved periodontal outcomes.[24–27] Clinical trials involving statins and PD have largely focused on local delivery and the results have been controversial.[24] The potential association between LLA and periodontitis in individuals with T2D have been less explored, even though diabetic populations have a higher prevalence of PD and tooth loss and are more likely to be prescribed LLA. Therefore, our main objective was to assess whether LLA usage was associated with better periodontal status in individuals with T2D.

Materials and methods

Study population
The present study is a cross-sectional observational study. The study population consisted of 253 non-institutionalized, residents of Puerto Rico who were primarily of Hispanic origin and were recruited for the 'Lipid-lowering agents use in Periodontitis and Diabetes Study' (LLIPDS). Participants were drawn from the Puerto Rico Center for Diabetes (PRCD) (50%); from the general population (45%) among which, 7% of them came from the San Juan Overweight Adults Longitudinal study (SOALS); and from COSSMA (5%), a private decentralized healthcare organization located in Puerto Rico.

Eligibility criteria. To allow for outcome comparisons with our original study,[28] most of the following criteria derived from the previous SOALS'

study: inclusion criteria: (a) age 40–65 years, (b) at least four teeth for a valid periodontal measurement, and (c) T2D based on physician diagnosis, medication(s), or fasting blood glucose and glycosylated hemoglobin A1C (HbA1c) levels as described below; and exclusion criteria: (a) orthodontic appliances or gross oral pathology that might impair periodontal measurements; (b) regular use of steroids, anti-inflammatory drugs (except aspirin at doses of ≤150 mg/day), immunosuppressants, thiazolidinediones, or glitazones; (c) systemic complications, such as hemophilia or other bleeding disorders, chronic inflammatory diseases, or infectious disease within 6 months; (d) use of antibiotic therapy for any medical or dental condition prior to the clinical examination; or (e) use of any medication that affects periodontal status for 2 weeks or more within 1 month prior to the clinical examination; (f) diagnosis of congenital or chronic heart diseases, endocarditis, or rheumatic fever; (g) undergoing active dialysis treatment; (h) receiving anticoagulant therapy; (i) had undergone procedures related to CVD, including pacemaker or defibrillator implantation, or surgery on the heart or vessels involving the use of prosthetic material (e.g., stent); (j) had hip or other joint replacement surgery; or (k) were diagnosed with cancer with active radio/immunotherapy.

Ascertainment of diabetic status. Participants who met the main eligibility criteria that were assessed during the pre-clinical phone call screening and verbally consented to participate in the study were invited and scheduled for a clinical examination. Participants were asked to bring the written documentation from physicians, laboratory results, or use of diabetes medications labeled with their names at the clinical examination visit to confirm the presence of T2D. Participants from SOALS with likely T2D diagnosis had HbA1c ≥ 6.5% or fasting blood glucose ≥ 126 mg/dl.[29]

All eligible participants from the pre-clinical phone call screening were scheduled to attend the clinical examination. Prior to any study procedures, eligibility criteria were further confirmed, participants were explained again about purposes of the study, the study procedures, voluntarily participation in the study, participant's right to withdrawal at any time during the study
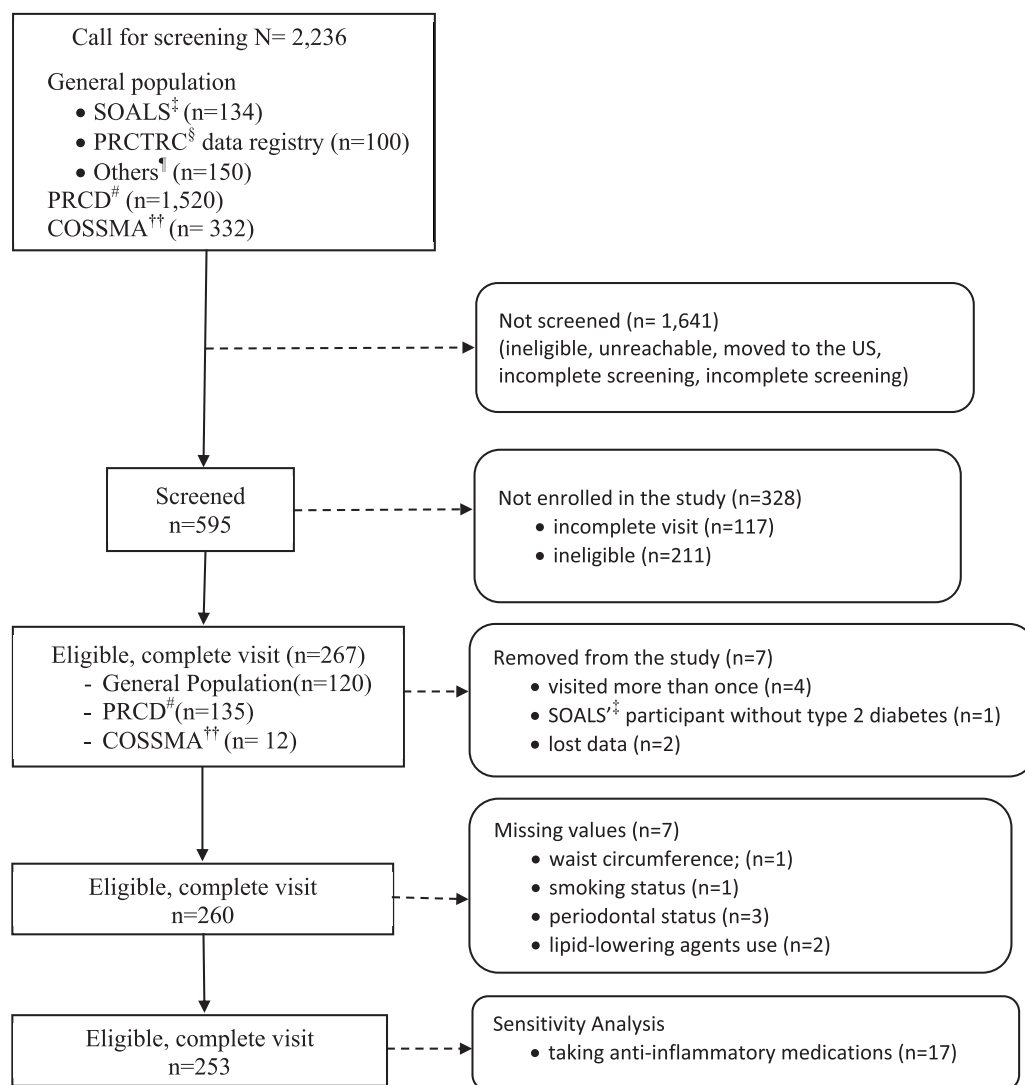
Call for screening N= 2,236

General population
- SOALS[‡] (n=134)
- PRCTRC[§] data registry (n=100)
- Others[¶] (n=150)

PRCD[#] (n=1,520)

COSSMA[††] (n= 332)

Not screened (n= 1,641)
(ineligible, unreachable, moved to the US, incomplete screening, incomplete screening)

Screened
n=595

Not enrolled in the study (n=328)
- incomplete visit (n=117)
- ineligible (n=211)

Eligible, complete visit (n=267)
- General Population(n=120)
- PRCD[#](n=135)
- COSSMA[††] (n= 12)

Removed from the study (n=7)
- visited more than once (n=4)
- SOALS'[‡] participant without type 2 diabetes (n=1)
- lost data (n=2)

Eligible, complete visit
n=260

Missing values (n=7)
- waist circumference; (n=1)
- smoking status (n=1)
- periodontal status (n=3)
- lipid-lowering agents use (n=2)

Eligible, complete visit
n=253

Sensitivity Analysis
- taking anti-inflammatory medications (n=17)

Figure 1. Selection of the 253 study participants, LLIPDS (26 April 26 2017 to 9 March 9 2020).
‡SOALS: San Juan Overweigh Adults Longitudinal Study.
§PRCTRC: Puerto Rico Clinical and Translational Research Consortium.
¶Others: e.g., participants' responses to the advertisements, words of mouths, etc. . .
#PRCD: Puerto Rico Center for Diabetes.
††COSSMA, Inc.: A non-profit organization based in Humacao, Puerto Rico with six primary healthcare clinics serving the population throughout Puerto Rico Island.
LLIPDS, Lipid-Lowering agents use In Periodontitis and Diabetes Study.

procedures, and participant's consent for the use of the data for research purposes. Written and signed informed consent was obtained from all participants prior to performance of the study procedures. The study was approved by the Institutional Review Board of the University of Puerto Rico (IRB # B0930116). The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Enrollment in the study. The LLIPDS study was conducted between April, 2017 and March, 2020. A total of 595 participants were screened and of these 267 were eligible and enrolled in the study (Figure 1). A total of 14 participants initially enrolled in the study were later excluded for protocol deviations leaving 253 participants for analyses. A sensitivity analysis determined that exclusion of 17 participants who had taken

anti-inflammatory drugs did not significantly impact the outcome measurements.

Periodontal status and tooth loss outcomes measurement

Periodontal status was assessed at six sites per tooth for all teeth except the third molars[30] using a periodontal probe with 2 mm markings (Hu Friedy PCP2). Probing pocket depth (PPD) was rounded down if the reading fell between two probe markings.[30] Examinations were performed by one of two dental examiners before participants' interview to avoid bias. Using the same periodontal probing protocol procedures, both dental examiners 1 and 2 were trained and calibrated for measurements of periodontal pocket depth by two different gold standards provided at two different consecutive time periods (BD, NHANES; HH, Forsyth Institute). They achieved a 96% and 97% agreement within 1 mm of PPD measurement, respectively. Prior to the switch in the tasks in the project, examiner 2 additionally received a training and calibration with examiner 1 to achieve at least 96% within 1 mm of PPD measurement on inter-examiner agreement to ensure the data quality. The PPD measure performed by the dental examiner 1 was compared with the PPD performed by the dental examiner 2. There was no statistical difference in the percentage of sites with PPD $\geqslant$ 4 mm between the two dental examiners ($p = 0.342$). The primary outcome was percent of sites with PPD $\geqslant$ 4 mm,[31] which was categorized in low (reference), medium, or high tertiles based on its distribution. Likewise, the secondary outcome included tertile of percent of sites with clinical attachment loss (CAL) $\geqslant$ 4 mm categorized in low (reference), medium, and high tertiles. Alternative periodontal outcomes included tertiles of number of teeth lost or having at least one site (or tooth) with PPD $\geqslant$ 5 mm, with the latter indicating the severity of disease. Silness and Loe Plaque Index,[32] bleeding on probing (BOP) on any two (one from buccal and one from lingual surfaces) of the six sites examined per tooth was recorded.[33]

LLA and other data collection

Participants were asked to bring their current medications and/or a list of all their current medications at the visit and completed a thorough interview-based questionnaire that collected information on LLA and other medications, dosage, and duration of use. In addition, to prove medication compliance, up to three pharmacy addresses where participants usually bought their medications were recorded, and the study personnel verified the pharmacy information within 2–3 weeks after the visit from approximately the first 30 eligible participants at the beginning of the study. Types of LLA included statins, fibrates, niacin, bile acid binding resins, cholesterol absorption inhibitor, omega-3 fatty acids, combinations, and injectable medications. The intake of food items, such as milk enriched with omega-3 milk fatty acids can provide benefits similar to LLA to lower cholesterol, but this information was not available. Data were directly recorded in RedCap.[34] Participants were classified as LLA users if they were currently taking LLA and LLA non-users if they reported no current or previous use of LLA. Duration of LLA use was categorized as follows: (a) none or minimal <1 year, (b) 1–4 years, and (c) >4 years based on previous reports.[35,36] Statin-potency was categorized as low, moderate, or high based on its dosage and low-density lipoprotein-cholesterol reduction goals.[37] The questionnaire also gathered demographic data, and diabetes duration (years). Lifestyle health habits included smoking status defined as never smoked (i.e. report to never smoked or has smoked <100 cigarettes in lifetime), former smoker (had smoked at least 100 cigarettes but had stopped smoking prior to the study visit), and current smoker (smoked at least 100 cigarettes and continue smoking).[38] Alcohol consumption was defined as 'current drinker' (had at least 12 drinks of any type of alcoholic beverage in lifetime and had at least one drink in past 12 months) or 'non-current drinker' (i.e. lifetime abstainer: had fewer than 12 drinks in lifetime; former drinker: had at least 12 drinks in lifetime but no drinks in the past 12 months).[39] The questionnaire also collected exercise information (yes/no, 'Have you exercised in the past 12 hrs.?'). The diabetes duration of the SOALS participants was based on the date they were provisionally diagnosed with diabetes up to the date when their glucose levels were remeasured in the current study. Waist circumference and height were measured two to three times to the nearest 0.1 cm, and averaged. Weight was measured two to three times to the nearest 0.5 kg using a standard calibrated stadiometer TANITA, Made in

Japan, Tanita Corporation of America Inc. (Analyzer-TBF-310A), and averaged as well. Body mass index (BMI) was computed from the weight and the height measures (kg/m^2). Blood pressure was taken three times after 1–2 min intervals,[40] and the average was computed. Participants were classified as hypertensive if they reported a physician-diagnosed hypertension, currently took antihypertensive medications, or had an average SBP ≥ 130 mm Hg or average DBP ≥ 80 mm Hg at the clinical examination.[41] HbA1c was measured using a Siemens Kit, Made in UK, Siemens Healthcare Diagnostics Inc. for DCA 2000 and DCA Vantage Analyzer. Other biochemical measures, such as fasting serum glucose, insulin, and a lipid panel, were performed at Clendo Reference Laboratories in Puerto Rico.[42] Homeostatic model assessment (HOMA) of insulin resistance (IR) was computed as [fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5].[43]

Statistical analyses

A brief summary of the general characteristics of the study population was provided. Characteristics of the study population by periodontal status were described using mean (± standard deviation), median (25th, 75th percentiles) or frequency (percent) as appropriate. LLA and other variables were assessed by tertile of percent of sites with PPD ≥ 4 mm. We assessed potential correlations between the covariates and avoided including two highly correlated covariates in the same model. Multinomial or binary logistic regression models were used to assess the associations between LLA duration of use and periodontal or tooth loss parameters. We controlled for major risk factors for periodontitis including age, gender, years of education, BMI or waist circumference, smoking status, alcohol consumption, and exercise. We also adjusted for plaque index or BOP. Other potential confounders, including levels of lipid panels, fasting glucose or HbA1c, duration of diabetes, self-reported use of anti-inflammatory agents, or dental examiners were considered for inclusion in the model using change in estimate procedures.

Results

The general characteristics, oral health status, and the distribution of periodontal outcomes and alternative periodontal parameters of the study population are described in Table 1. The average age of the study population was approximately 55 (±5.93) years. A total of 44% of the participants were male gender, 36% former or current smokers, and 43% classified to have current alcohol intake. The duration of their diabetic status ranged from 1 to 37 years with the mean duration of 10 years. Most of the participants were obese (mean BMI 34.92 ± 10.67), and nearly 66% of them were hypertensive.

All the LLA used were oral medications. Approximately 52% of the participants were current LLA users. Among LLA users, the median duration of use was 4.21 (1.17, 6.5) years. Statins were the most used LLA (92.5%), followed by fibrates (5.3%), and the remaining 2.2% (others) were omega-3, cholestyramine, or ezetimibe (data not shown). Among statin users, approximately 28% (33/118) took high-potency statins (7 participants in LLA use <1 year; 9 in LLA use 1–4 years; and 17 in LLA > 4 years).

The highest tertile of percent of sites with PPD ≥ 4 mm ranged from nearly 4% to 86.5% and for percent of sites with CAL ≥ 4 mm from 7.6 to 88%; 52.6% of the participants had tooth loss ranging from 2 to 14 (medium/high tertiles), and 29.6% of the participants had at least one tooth with PPD ≥ 5 mm. Based on the Centers for Disease Control and Prevention (CDC)/ American Academy of Periodontology (AAP) periodontitis case definition,[44] approximately 62% of the participants had moderate or severe forms of this disease.

The general and oral health characteristics of the study population by tertiles of percent of sites with PPD ≥ 4 mm are shown in Table 2. T2D participants with the highest tertile percent of sites with PPD ≥ 4 mm were more likely to be males ($p < 0.01$), former or current smokers (overall, $p = 0.06$), and were less likely to be educated ($p < 0.001$) than their counterparts with low or medium tertile of percent of sites with PPD ≥ 4 mm. T2D participants had higher levels of HbA1c ($p = 0.03$), higher LDL-cholesterol ($p = 0.01$), higher fasting glucose ($p = 0.03$), insulin ($p = 0.01$), or HOMA-IR ($p < 0.001$) across the tertiles of percent of sites with PPD ≥ 4 mm. There was no statistically significant difference in HDL-cholesterol across the tertile of percent of sites with PPD ≥ 4 mm. The LLA other than

Table 1. Distribution of the general and oral health characteristics and alternative periodontal parameters of the study population (*N* = 253 participants, *N* = 34,274 sites).

Characteristics	Distribution			
	N or *N* (%)	Mean ± SD	Median	Range: Min–Max
(a) General characteristics				
Age	253	54.52 ± 5.93	55	41–65
Male gender	112 (44.27)			
Educational level (≤12 yrs)	88 (34.78)			
Smoking status				
Never	162 (64.03)			
Former	63 (24.90)			
Current	28 (11.07)			
Current alcohol consumption	108 (42.69)			
Exercise (yes)	77 (30.68)			
BMI (kg/m^2)	253	34.92 ± 10.67	32.67	19.80–103.21
Waist circumference (cm)	253	105.34 ± 16.94	104.67	39–147
Hypertension (yes)	167 (66.01)			
Diabetes duration	243	10.79 ± 7.77	10	1–37
Metformin medication (yes)	126 (49.80)			
Anti-inflammatory agents (yes)	17 (6.72)			
HbA1c (%)	253	8.04 ± 1.95	7.6	5.2–14
Fasting glucose (mg/dL)	253	162.23 ± 68.97	141	84–651
Fasting insulin (mIU/L)	253	17.69 ± 17.05	12.90	0.2–143.20
HOMA-IR	253	7.37 ± 8.36	4.77	0.06–77.08
HDL-C (mg/dL)	253	47.22 ± 13.43	45.0	24–109
LDL-C (mg/dL)	253	95.0 ± 37.15	91.0	46–269
Total cholesterol (mg/dL)	253	175.66 ± 43.99	170	46–361
Triglycerides (mg/dL)	253	166.92 ± 89.30	151	39–712
LLA current users (yes)	132 (52.17)			
LLA duration of use (yr)	253	5.87 ± 6.14	4.21	0.02–31.29
Statin-potency (*N* = 238)				
None or LLA < 1 yr	120 (50.42)			

(Continued)

Table 1. (Continued)

Characteristics	Distribution			
	N or *N* (%)	Mean $\pm$ SD	Median	Range: Min–Max
Low/medium	85 (35.71)			
High	33 (13.87)			
(b) Oral health parameters				
Plaque Index	246	1.02 ± 0.53	0.96	0.05–3
Sites with BOP	253	22.36 ± 12.06	21	0–54
Missing teeth	253	2.37 ± 2.88	2	0–14
(c) Periodontal parameters				
Percent of sites with PPD ≥ 4 mm	253	6.24 ± 11.61	1.25	0–86.54
First tertile	94 (37.15)	0	0	0
Second tertile	75 (29.64)	1.80 ± 0.88	1.41	0.89–3.80
Third tertile	84 (33.20)	17.18 ± 15.01	11.29	3.85–86.54
Percent of sites with CAL ≥ 4 mm	253	10.01 ± 15.87	3.23	0–88
First tertile	84 (33.20)	0.21 ± 0.41	0	0–1.11
Second tertile	85 (33.60)	3.66 ± 1.75	3.23	1.16–7.45
Third tertile	84 (33.20)	26.23 ± 18.87	20.42	7.61–88
Number of missing teeth	253	2.38 ± 2.88	2	0–14
First tertile	120 (47.43)	0.4 ± 0.49	0	0–1
Second tertile	58 (22.92)	2 ± 0	2	2–2
Third tertile	75 (29.64)	5.83 ± 3.07	5	3–14
≥ 1 tooth with PPD ≥ 5 mm (yes)	75 (29.64)			
Periodontitis-CDC/AAP definition				
No/mild	96 (37.94)			
Moderate	119 (47.04)			
Severe	38 (15.02)			
Teeth with PPD ≥ 4 mm & BOP at the same tooth	253	2.93 ± 4.58	1	0–23
Teeth with CAL ≥ 3 mm & PPD ≥ 4 mm at the same site	253	7.81 ± 6.02	7	0–24

BMI, body mass index; BOP, bleeding on probing; CAL, clinical attachment loss; CDC/AAP, Centers for Disease Control and Prevention/American Academy of Periodontology; HbA1c, glycosylated hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; LLA, lipid-lowering agents; PPD, probing pocket depth; yr, year; yrs, years.

Table 2. General and oral health characteristics by tertiles of percent of sites with PPD ⩾ 4 mm (N = 253 participants, N = 34,274 sites).

Characteristics	First tertile (low) (n = 12,725 sites)	Second tertile (medium) (n = 10,815 sites)	Third tertile (high) (n = 10,734 sites)	p Value*
(a) General characteristics	Mean ± SD, Median (Q1, Q3), or N (%)			
Age (yr)	54.80 ± 5.65	54.57 ± 5.59	54.17 ± 6.55	0.78
Male gender	30 (31.91)	34 (45.33)	48 (57.14)	<**0.01**
Educational level (⩽12 yrs)	23 (24.47)	18 (24)	47 (55.95)	<**0.001**
Smoking status				0.06
Never	67 (71.28)	51 (68)	44 (52.38)	
Former	17 (18.09)	19 (25.33)	27 (32.14)	
Current	10 (10.64)	5 (6.67)	13 (15.48)	
Current alcohol consumption	37 (39.36)	35 (46.67)	36 (42.86)	0.63
Exercise (yes)	29 (31.18)	24 (32.43)	24 (28.57)	0.86
Hypertension (yes)	65 (69.15)	49 (65.33)	53 (63.10)	0.69
Metformin medication (yes)	39 (41.49)	41 (54.67)	46 (54.76)	0.13
Anti-inflammatory agents (yes)	9 (9.57)	4 (5.33)	4 (4.76)	0.37
BMI (kg/m^2)	35.19 ± 12.05	35.56 ± 11.40	34.05 ± 8.13	0.78
Waist circumference (cm)	103.06 ± 18.21	106.73 ± 14.80	106.64 ± 17.16	0.26
HbA1c (%)	7.61 ± 1.70	8.29 ± 2.04	8.30 ± 2.07	**0.03**
Fasting glucose (mg/dL)	129 (114.8, 163.8)	136 (117, 209)	154(125, 201.3)	**0.03**
Fasting insulin (mIU/L)	11 (6.9, 17.1)	13.7 (9.4, 21.8)	14.5 (8.3, 24.5)	**0.01**
HOMA-IR	65.2 (45.1, 112.2)	96.1 (57.7, 166.0)	107.3(41.3, 200.0)	<**0.001**
HDL-C (mg/dL)	49.36 ± 13.57	45.99 ± 12.48	45.93 ± 13.92	0.15
LDL-C (mg/dL)	92.32 ± 30.43	95.6 ± 39.50	97.46 ± 41.79	**0.01**
Total cholesterol (mg/dL)	173.74 ± 38.40	175.39 ± 46.23	178.06 ± 48.03	0.09
Triglycerides (mg/dL)	159.72 ± 80.51	169.03 ± 85.11	173.10 ± 101.93	0.07
Diabetes duration	9.59 ± 6.49	12.25 ± 8.64	10.86 ± 8.16	0.21
LLA current users (yes)	52 (55.32)	40 (53.33)	40 (47.62)	0.57
LLA duration of use (yr)	3 (1.17, 6.5)	4 (1.74, 8.04)	5.09 (1.0, 9.05)	0.57
Statin-potency (N = 238)				0.23
None or LLA < 1 yr	46 (51.69)	30 (41.67)	44 (57.14)	

(Continued)

Table 2. (Continued)

Characteristics	First tertile (low) ($n = 12,725$ sites)	Second tertile (medium) ($n = 10,815$ sites)	Third tertile (high) ($n = 10,734$ sites)	p Value*
Low/medium	29 (32.58)	29 (40.38)	27 (35.06)	
High	14 (15.73)	13(18.06)	6 (7.79)	
(b) Oral health parameters		Mean ± SD		p Value*
Plaque index	0.90 ± 0.47	0.97 ± 0.44	1.21 ± 0.61	**<0.01**
Sites with BOP	18.39 ± 10.14	21.99 ± 12.11	27.12 ± 12.441	**<0.001**
Missing teeth	2.73 ± 3.54	1.6 ± 1.79	2.67 ± 2.76	**0.03**
Periodontitis-CDC/AAP definition				**<0.001**
No/mild	64 (68.09)	28(37.33)	4 (4.76)	
Moderate	30 (31.91)	45(60.00)	44 (52.38)	
Severe	0	2 (2.67)	36 (42.86)	
Teeth with PPD ≥ 4 mm and BOP at the same tooth	0	1 (1, 2)	5.5 (3, 11.5)	**<0.001**
Teeth with CAL ≥ 3 mm & PPD ≥ 4 mm at the same site	3 (1, 6)	7 (3, 9)	13 (8, 17.5)	**<0.001**

BMI, body mass index; BOP, bleeding on probing; CAL, clinical attachment loss; CDC/AAP, Centers for Disease Control and Prevention/American Academy of Periodontology; HbA1c, glycosylated hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LLA, lipid-lowering agents; PPD, probing pocket depth; yr, year; yrs, years.
*Using analysis of variance (ANOVA), Chi-square, Kruskal–Wallis H, or K-sample equality-of-median test. *P*-value in bold indicates the level of significance of $p < 0.05$.

statins taken ≥ 1 year were removed from the data yielding a total of $N = 238$ (i.e. instead of 253), and the reference group was the same as the initial group of 'None or LLA < 1 year.' There was no statistical difference in the distribution of the statin potency across the three tertile groups either. Overall, there was a difference in the plaque index ($p < 0.01$), number of sites with BOP ($p < 0.001$) and number of missing teeth ($p = 0.03$) across the three tertile groups (Table 2). Likewise, there was an overall difference in periodontitis CDC/AAP case definition ($p < 0.001$), number of teeth with PPD ≥ 4 mm and BOP ($p < 0.001$), or number of teeth with CAL ≥ 3 mm & PPD ≥ 4 mm at the same site ($p < 0.001$), across the three tertiles of percent of sites with PPD ≥ 4 mm.

The crude and adjusted odds ratios (adjusted for age, gender, education, smoking status, alcohol consumption, waist circumference, HbA1c, BOP, examiner, and anti-inflammatory agents) of the associations between the LLA users and medium or high tertile percent of sites with PPD ≥ 4 mm showed no significant reduction compared to the first tertile (Table 3). Participants taking LLA between 1 and 4 years had 78% lower odds of having high tertile percent of sites with PPD ≥ 4 mm than those with none or minimal LLA use (adj. OR: 0.22, 95% CI: 0.08–0.64). There was no association between LLA use between 1 and 4 years and lower or medium tertile percent sites with PPD ≥ 4 mm as compared to those with minimal LLA use. Moreover, there was no association between LLA use >4 years and tertiles of percent of PPD ≥ 4 mm (Table 3). The sensitivity analysis excluding enrolled participants reporting use of anti-inflammatory agents ($N = 17$) showed similar results (i.e. reference: LLA non-users or users <1 year: LLA

Table 3. Association between LLA use and tertiles of percent of sites with PPD ⩾ 4 mm (N = 253 participants, N = 34,274 sites).

LLA use	Second tertile (medium) (n = 10,815 sites)		Third tertile (high) (n = 10,734 sites)	
	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
LLA users (ref.: No)	0.92 (0.50–1.70) p = 0.80	0.79 (0.41–1.53) p = 0.49	0.73 (0.41–1.33) p = 0.31	0.58 (0.28–1.17) p = 0.13
LLA duration of use (ref. < 1 yr)				
1–4 yrs	0.76 (0.35–1.65) p = 0.49	0.68 (0.30–1.56) p = 0.36	**0.33 (0.13–0.80) p = 0.02***	**0.22 (0.08–0.64) p = 0.005***
>4 yrs	0.97 (0.46–2.02) p = 0.93	0.84 (0.38–1.84) p = 0.66	1.02 (0.51–2.04) p = 0.95	0.91 (0.40–2.08) p = 0.83
	Sensitivity analysis (N = 236)[b] (N = 31,872 sites)			
LLA duration of use (ref. < 1 yr)	Second tertile (medium) (n = 10,248 sites)		Third tertile (high) (n = 10,218 sites)	
1–4 yrs	0.96 (0.43–2.13) p = 0.91	0.87 (0.37–2.05) p = 0.75	**0.34 (0.13–0.88) p = 0.03***	**0.23 (0.08–0.70) p = 0.01***
>4 yrs	1.09 (0.51–2.35) p = 0.83	1.0 (0.44–2.27) p = 0.99	1.06 (0.51–2.18) p = 0.88	0.98 (0.41–2.33) p = 0.97

[a]Adjusted for age, gender, education (⩽12 yrs, 12 yrs), smoking status (never or smoker, current), alcohol consumption (non-current, current), waist circumference, HbA1c, BOP, examiner, and anti-inflammatory agents.
[b]Anti-inflammatory agents (n = 17) excluded from the data.
BOP, bleeding on probing; CAL, clinical attachment loss; 95% CI, 95% confidence interval; HbA1c, glycosylated hemoglobin A1C; LLA, lipid-lowering agents; OR, odds ratio; yr, year; yrs, years.
*P-value in bold indicates the level of significance of p < 0.05.

1–4 years and high tertile of PPD ⩾ 4 mm: adj. OR: 0.23, 95% CI: 0.08–0.70; no association between LLA use 1–4 years and medium percent of sites with PPD ⩾ 4 mm; and no association between LLA use >4 years and the percent of sites with PPD ⩾ 4 mm). Likewise, additional adjustment for covariates with missing values, such as 'diabetes duration' (10 missing) or 'exercise' (2 missing) provided similar patterns (Supplemental Table S1) and replacing the covariate 'BOP' in the models with that of 'plaque index', which had seven missing values provided similar estimates (Supplemental Table S2). Due to the low number of high-potency statin use in each LLA duration of use category and several switches in dosage primarily due to drug intolerance, we could not compare the statin-potency between the LLA categories.

Participants taking LLA for 1–4 years had an adjusted OR = 0.33 (95% CI: 0.13, 0.86) for medium (not the highest) percent of sites with CAL ⩾ 4 mm compared to participants with minimal LLA usage (Table 4). Similarly, there was no association between LLA use >4 years and the tertiles percent of sites with CAL ⩾ 4 mm. The sensitivity analysis by excluding from the data participants reporting taking anti-inflammatory agents (N = 17) after being enrolled showed consistent similar results. Tertiles of number of teeth lost (Supplemental Table S3) did not show any association with LLA use. The association between LLA >4 years and high tertile of teeth lost was borderline (adj. OR: 11.90, 95% CI: 0.91–3.97). The outcome of at least one tooth with PPD ⩾ 5 mm for a disease severity (Table 5) showed similar patterns as the primary or secondary outcomes (LLA use for 1–4 years: adj OR: 30, 95% CI: 0.11–0.78); no association with LLA use >4 years).

To further validate the results a number of alternative periodontal parameters were measured. They included periodontitis CDC/AAP case definition, a continuous form of the primary outcome percent of sites with PPD ⩾ 4 mm (log-transformed),

Table 4. Association between LLA use and tertiles of percent of sites with CAL ≥ 4 mm (N = 253 participants, N = 34,274 sites).

LLA use	Second tertile (medium) (n = 10,815 sites)		Third tertile (high) (n = 10,734 sites)	
	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
LLA users (ref.: No)	0.77 (0.42–1.41) p = 0.40	0.70 (0.36–1.38) p = 0.30	0.95 (0.52–1.75) p = 0.88	0.85 (0.42–1.72) p = 0.66
LLA duration of use (ref. < 1 yr)				
1–4 yrs	**0.40 (0.17–0.94) p = 0.04***	**0.33 (0.13–0.86) p = 0.02***	0.67 (0.31–1.46) p = 0.31	0.55 (0.22–1.36) p = 0.20
>4 yrs	1.01 (0.49–2.08) p = 0.98	0.81 (0.36–1.82) p = 0.61	1.08 (0.52–2.22) p = 0.85	0.81 (0.35–1.89) p = 0.63
	Sensitivity analysis (N = 236)[b] (N = 31,872 sites)			
LLA duration of use (ref. < 1 yr)	Second tertile (medium) (n = 10,248 sites)		Third tertile (high) (n = 10,218 sites)	
1–4 yrs	**0.38 (0.15–0.96) p = 0.04***	**0.34 (0.12–0.92) p = 0.04***	0.76 (0.34–1.70) p = 0.50	0.63 (0.25–1.59) p = 0.33
>4 yrs	0.94 (0.45–1.99) p = 0.88	0.80 (0.34–1.85) p = 0.60	1.01 (0.48–2.13) p = 0.99	0.71 (0.30–1.71) p = 0.45

[a]Adjusted for age, gender, education (≤12 yrs, 12 yrs), smoking status (never or smoker, current), alcohol consumption (non-current, current), waist circumference, HbA1c, BOP, examiner, and anti-inflammatory agents.
[b]Anti-inflammatory agents (n = 17) excluded from the data.
BOP, bleeding on probing; CAL, clinical attachment loss; 95% CI, 95% confidence interval; HbA1c, glycosylated hemoglobin A1C; LLA, lipid-lowering agents; OR, odds ratio; yr, year; yrs, years.
*P-value in bold indicates the level of significance of p < 0.05.

Table 5. Association between LLA use and having at least one tooth with PPD ≥ 5 mm (N = 253 participants, N = 6483 teeth).

LLA use	Had at least one tooth with PPD ≥ 5 mm	
	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
LLA duration of use (ref. < 1 yr)		
1–4 yrs	**0.34 (0.14–0.83) p = 0.02***	**0.30 (0.11–0.78) p = 0.01***
>4 yrs	0.82 (0.43–1.53) p = 0.53	0.82 (0.40–1.68) p = 0.58

[a]Adjusted for age, gender, education (≤12 yrs, 12 yrs.), smoking status (never or smoker, current), alcohol consumption (non-current, current), waist circumference, HbA1c, BOP, examiner, and anti-inflammatory agents.
BOP, bleeding on probing; 95% CI: 95% confidence interval; HbA1c, glycosylated hemoglobin A1C, LLA, lipid-lowering agents; OR, odds ratio; PPD, probing pocket depth; yr, year; yrs, years.
*P-value in bold indicates the level of significance of p < 0.05.

number of teeth with PPD ≥ 4 mm and BOP on the same tooth (log-transformed), or number of teeth with CAL ≥ 3 mm and PPD ≥ 4 mm at the same site (log-transformed), were done (Table 6). The trends remained consistent even though the statistical significance in some of the subgroups of

Table 6. Association between LLA use and periodontitis CDC/AAP definition or other periodontal parameters ($N = 253$ participants, $N = 34{,}274$ sites, $N = 6483$ teeth).

Periodontitis-CDC/AAP definition	Moderate PD ($n = 3013$ teeth)		Severe PD ($n = 949$ teeth)	
LLA use	**Crude OR (95% CI)**	**Adjusted[a] OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted[a] OR (95% CI)**
1–4 yrs	0.72 (0.36–1.48) $p = 0.38$	0.60 (0.27–1.34) $p = 0.21$	0.55 (0.18–1.65) $p = 0.29$	0.45 (0.13–1.58) $p = 0.21$
4 yrs	1.01 (0.53–1.93) $p = 0.96$	0.73 (0.35–1.52) $p = 0.40$	1.06 (0.44–2.54) $p = 0.89$	0.89 (0.33–2.46) $p = 0.83$
Percent of sites with PPD $\geqslant 4$ mm	**Increase in the percent of sites with PPD $\geqslant 4$ mm**			
LLA use	**Crude β (SE)**	**Adjusted[a] β (SE)**		
1–4 yrs	**−0.34 (0.15)** **$p = 0.02$***	**−0.37 (0.18)** **$p = 0.04$***		
>4 yrs	0.10 (0.14) $p = 0.49$	0.03 (0.15) $p = 0.83$		
Teeth with PPD $\geqslant 4$ mm and BOP at the same tooth[b]	**Increase in number of teeth with PPD $\geqslant 4$ mm and BOP at the same tooth**			
LLA use	**Crude β (SE)**	**Adjusted[a] β (SE)**		
1–4 yrs	**−0.34 (0.15)** **$p = 0.02$***	**−0.31 (0.15)** **$p = 0.03$***		
>4 yrs.	0.10 (0.14) $p = 0.49$	0.15 (0.13) $p = 0.24$		
Teeth with CAL $\geqslant 3$ mm & PPD $\geqslant 4$ mm at the same site	**Increase in number of teeth with CAL $\geqslant 3$ mm & PPD $\geqslant 4$ mm at the same site**			
	Crude β (SE)	**Adjusted[a] β (SE)**		
1–4 yrs	−0.25 (0.15) $p = 0.10$	−0.23 (0.14) $p = 0.10$		
>4 yrs	−0.03 (0.13) $p = 0.81$	−0.08 (0.11) $p = 0.49$		

[a]Adjusted for age, gender, education ($\leqslant 12$ yrs, 12 yrs), smoking status (never or smoker, current), alcohol consumption (non-current, current), waist circumference, HbA1c, BOP (or plaque index for teeth with PPD $\geqslant 4$ mm and BOP), examiner, and anti-inflammatory agents.
[b]Log-transformed of the periodontal variables and use of multiple linear regression models with robust standard errors.
β, beta coefficient; BOP, bleeding on probing; CAL, clinical attachment loss; CDC/AAP, Centers for Disease Control and Prevention/American Academy of Periodontology; 95% CI, 95% confidence interval; HbA1c, glycosylated hemoglobin A1C; LLA, lipid-lowering agents; OR, odds ratio; PD, periodontal disease; PPD: probing pocket depth; SE: standard error; yrs, years.
*P-value in bold indicates the level of significance of $p < 0.05$.

Table 7. Association between glycemic or insulin measures and medium/high tertiles of percent of PPD ≥ 4 mm (reference: lowest tertile) by duration of LLA use (N = 253 participants, N = 34,274 sites).

Glycemic measures		LLA < 1 year (n = 140) (n = 18,951 sites)	LLA 1–4 years (n = 46) (n = 6549 sites)	LLA > 4 years (n = 67) (n = 8774 sites)	p Value (LLA > 4 years)
HbA1c (%)	Mean ± SD	7.88 ± 1.86	7.83 ± 1.86	8.51 ± 2.14	
	OR (95% CI)[a]	1.23 (0.96, 1.59)	1.09 (0.73, 1.63)	**1.36 (1.00, 1.85)**	**0.05***
Fasting glucose (mg/dL)	Median (Q1, Q3)	140.5 (116, 188.5)	135 (119, 156.5)	153 (117, 193)	
	OR (95% CI)	1.00 (0.98, 1.01)	1.00 (0.99, 1.01)	**1.01 (1.00, 1.02)**	**0.05***
Fasting insulin (mIU/L)	Median (Q1, Q3)	12.4 (8.1, 18.4)	11.4 (7.3, 17.4)	16.5 (8.9, 27.2)	
	OR (95% CI)	1.00 (0.98, 1.03)	1.00 (0.96, 1.04)	1.01 (0.97, 1.05)	0.58
HOMA-IR	Median (Q1, Q3)	78.3 (45.4, 140.9)	72.4 (41.5, 128.6)	155.6 (56.1, 204.2)	
	OR (95% CI)	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)	1.00 (1.00, 1.01)	0.22

Each glycemic measure evaluated in a separate model.
[a]Adjusted for age, gender, education (≤12 years, 12 years), smoking status (never or smoker, current), alcohol consumption (non-current, current), waist circumference, BOP, and anti-inflammatory agents.
BOP, bleeding on probing; 95% CI, 95% confidence interval; HbA1c, glycosylated hemoglobin A1C; HOMA-IR, homeostatic model assessment of insulin resistance; LLA, lipid-lowering agents; OR, odds ratio; PPD, probing pocket depth.
*P-value in bold indicates the level of significance of p < 0.05. The value number was rounded-up to 0.05.

the periodontal parameters was lost due probably to the lower proportions of the participants within them.

It is striking that among LLA users >4 years, the mean HbA1c was significantly greater than for participants who used LLA for less than 4 years (Table 7). Participants with an increase in HbA1c level had 36% higher odds of having medium/high percent of sites with PPD ≥ 4 mm (adj. OR: 1.36, 95% CI: 1.00–1.85) than with a lower mean of HbA1c level.

Discussion
We found that administration of LLA such as statins for 1–4 years is associated with lower values of periodontal measures in individuals with T2D, but the benefit is lost for LLA use beyond 4 years. Moreover, the loss of long-term benefits from statins may be influenced by poorer glycemic control that enhances risk factors for periodontitis among T2D-participants. The results of this study may have important clinical ramifications for individuals with T2D and PD who are treated with LLA.

HMG-CoA reductase inhibitors, referred to as statins, are the most prescribed lipid-lowering drugs used to prevent/treat CVD.[45,46] Previous studies suggest that statins might improve periodontal parameters based on their anti-inflammatory and antibacterial properties.[24,25] Few clinical studies have reported the impact of orally administered statins on PD or tooth loss.[24,26,36,47–50] Our study showed that individuals with T2D who reported taking LLA between 1 and 4 years have lower values of periodontal parameters compared to T2D participants with minimal LLA use. However, this benefit was lost for participants taking LLA for more than 4 years.

Similar studies in individuals with no T2D have been conflicting. Some studies reported associations between statin use and lesser periodontitis severity[26,27,48,50]; two studies showed little relationship between statin use and tooth loss.[49,51] A retrospective study by Cunha-Cruz et al. from 1021 individuals reported that any statin use during the first 3 years after the initial periodontal exam was associated with a 48% reduction in tooth loss in subsequent years. Meisel et al[47] showed statin use over 5 years was associated with nearly 28% reduction in the risk of tooth loss in a population-based longitudinal study in Pomerania but did not show a reduction in PD progression probably due to the limited periodontal analysis. A

recent prospective study based of a large population-based electronic database from the Korean National Health Insurance Service-Health Screening (KNHIS-HS) cohort reported an increase in the risk of developing chronic periodontitis with long-term use of statins (>1 year) compared to short-term users (≤1 year).[52] However, the interpretation of the results is tempered by determination of periodontitis using an insurance code rather than clinical measurements.

Our previous findings from the baseline data of the SOALS, which included overweight or obese individuals showed LLA to be associated with both lower systemic and gingival/periodontal inflammation.[53] In the present study, among individuals with T2D in whom systemic inflammation is common, oral intake of LLA appeared to be associated with a clinically healthier periodontium, but only for 1–4 years duration. The reasons for the limited benefits may be due to the small sample size power of the analysis or the impact of statins on T2D onset or severity or an unanticipated consequence of LLA treatment. We found that LLA > 4 years was linked to higher HbA1c levels in participants with periodontitis. This is consistent with reports that statins are associated with an increased risk of new-onset of T2D[54] and/or worsened glucose control.[55]

In the present study, LLA use of 1–4 years was associated with lower odds of having high tertile percent of sites with PPD ≥ 4 mm, and lower odds of having medium percent of sites with CAL ≥ 4 mm as compared to low tertile of respective outcomes. Oral clinical parameters, PI and BOP were not treated as outcomes, and were used to adjust the statistical models to assess the magnitude of the estimates of the association between LLA use and PDs or tooth loss. We defined BOP based on the presence of bleeding at the buccal and lingual surface of each tooth when any site on those surfaces was bleeding after probing.[56] Ideally, we could have used any of the six tooth sites with BOP (interproximal distal at buccal side, mid-buccal, and interproximal mesial at buccal side, interproximal mesial at lingual side, mid-lingual, and interproximal distal at lingual side). However, when there was high level of bleeding while probing, the flow of the blood from one site contaminated the other sites in the pocket, and the exact source of the blood flow was difficult to determine. Thus, we only recorded bleeding from any random two of the six sites at

the lingual and buccal surfaces of each tooth to increase measurement accuracy.

We understand that controlling for too many covariates in addition to data stratification by outcome levels may cause overfit of the multivariable model when the study aims to assess the association between an exposure and clinical outcome.[57,58] However, the crude estimates of the associations by the outcome category were similar to the adjusted estimates. Moreover, the estimates obtained from reduced models by dropping other covariates, such as 'examiner ID, and anti-inflammatory agents' were similar to full models carried out in this work. It should be noted that some investigators prefer maximizing the covariate analysis,[59] especially in retrospective studies, to make the independent association more reliable.

The present study used periodontal parameters derived from the original proposal, which was submitted and accepted back in 2016, and the data were collected based on the original protocol. Thus, the latest classification of periodontitis from 2018 was not used.[60] Note that each periodontal parameter or case definition of PD has its own advantages or drawbacks, and so far, no perfect and/or satisfying PD case definition has been established. Recent findings, such as those from the study by Nascimento *et al.* reported the new classification system not to adequately capture the periodontal response to therapy in their study population.[61] Nonetheless, we have attempted to use the periodontitis CDC/AAP definition, which is based on both PPD and CAL parameters collected at the four interproximal sites of each tooth, which is used for population surveillance or prevalence studies.[44] We measured PPD and CAL at six sites per tooth. Although CAL on the direct buccal and lingual may be due to gingival recession, we included these measurements in the data analysis since periodontal inflammation, a focus of our study, is one of the primary factors contributing to gingival recession.[62–66] Moreover, two other approaches were utilized,[67–70] which included the increase in number of teeth with PPD ≥ 4 mm and BOP on the same tooth,[67] or increase in number of teeth with CAL ≥ 3 mm and PPD ≥ 4 mm at the same site[68] to assess the associations. The periodontal parameter of 'having a site with CAL ≥ 3 mm and PPD ≥ 4 mm at the same site' would help to reduce, at least partially, the potential confounding of gingival

recession at the buccal and lingual sites, although that would create a new bias with missing of sites with CAL but no pocket depth at the interproximal areas. Likewise, the parameter 'having a tooth or site with PPD ≥ 4 mm and BOP' has quite the same drawbacks as the primary outcome 'site with PPD ≥ 4 mm', which reflects the presence of periodontal inflammatory status without considering the CAL.

We used PPD as the primary outcome. Since PPD measures may include pseudo-pockets, we also examined CAL and tooth loss. These alternative outcome measurements also have disadvantages as sites with CAL may reflect gingival recession without formation of periodontal pockets and there are multiple reasons for tooth loss.[71]

Due to the very small number of participants taking fibrates (5%) or other medications, such as omega-3, cholestyramine, or ezetimibe (2%), we could not present the results by these types of LLA use. However, these medications have the same indication of use as the statins to treat dyslipidemia even though the mechanisms of actions and the properties may differ,[72] and we combine them with the statins to be under the group of LLA as defined in the original proposal of the present study. We ensured valid and reliable data with rigorous LLA assessment and periodontal measures conducted using the NHANES protocol.[30,73] We assessed and adjusted for important potential confounders, including sociodemographic data, lifestyle habits, oral hygiene measures (BOP or plaque index), and diabetes medications (metformin or insulin) and/or duration. Further adjustment of the models for factors related to other medications, such as blood pressure or neurological medications; serum lipid (i.e. HDL-C, LDL-C, total cholesterol, and triglycerides), glucose, or insulin levels; brushing or flossing teeth; dental exams or treatment, such as participants' reports on the reason(s) to visit dental office within the last 12 months, which included routine dental examination (96/253), dental cleaning (165/253), diagnosis of PD (6/253); or history of previous periodontal treatment did not significantly change the estimates of the associations. The extensive exclusion criteria were challenging for recruitment, but necessary to ensure the homogeneity of the sample population, reduce confounding factors, assure ethical principles, and improve the study validity.

Certain limitations need to be considered. Since this is a convenience sample, it is possible that the findings will not be generalizable. However, there is little reason to expect that the relationship between LLA and periodontitis/tooth loss would be different for a random population. Recall bias is inherent to a cross-sectional design. However, meticulous questions, including past and present detailed history of medication use (e.g., switch to other medications, the reason(s) to stop taking the medications, etc.), were administered in each subsequent year, which might have helped to boost participants' memory. Healthy user bias might have occurred as well rendering to the beneficial effect of LLA use, that is, those who reported taking LLA might have likely been more aware of their health and engaged in a healthier lifestyle. However, further adjustment for lifestyle factors (e.g., smoking or alcohol drinking status, oral hygiene or doing exercise, etc.) did not alter the estimates of the associations. Another limitation included the definition of 'former smoker', which was defined as having smoked at least 100 cigarettes, but had stopped smoking prior to the study visit regardless of the duration of non-smoking given the impact of smoking cessation on periodontitis.[74] However, due to the low quality and complexity of the information on participant's report on several times of attempts to stop smoking, we regrouped and used the smoking status in category of 'current' *versus* non-current smoking throughout the data analysis. Finally, the cross-sectional nature of the study of the association does not enable a causal interpretation. Both LLA and periodontal status were measured at one time point, and we cannot disentangle the temporal sequence. The study of the independent association between LLA use and the values of periodontal parameters in individuals with T2D is challenging due to the interaction and/or correlation between the various conditions, such as obesity, lipid measures, glycemic control, and periodontitis. Moreover, obesity, T2D, and PD may share underlying common biological mechanisms, as these chronic health conditions often occur in the same individuals revealing a comorbid condition,[75,76] making it difficult to disentangle the independent effect of one on others.

Conclusion

This cross-sectional study suggests LLA use for 1–4 years to be associated with lower values of periodontal parameter outcomes in patients with

T2D. Large, prospective clinical studies or trials are needed to explore this further. Interestingly, our study also supports a relationship between poorer glycemic control and PD as HbA1c levels were significantly higher in individuals with PPD ⩾ 4 mm among LLA users >4 years. Under the study design limitations, the finding that short-term LLA use is associated with lower values of periodontal parameters in a diabetic population, but not long-term use has clinical ramifications and may help clarify some of the controversies regarding the benefit in humans. Furthermore, the poorer glycemic control for periodontal patients with long-term LLA use points to the need to monitor these patients carefully.

Declarations

Ethics approval and consent to participate
All eligible participants from the phone calls were scheduled to attend the clinical examination. Prior to any study procedures, eligibility criteria were further confirmed, participants were explained again about purposes of the study, the study procedures, the voluntarily condition of participation in the study, participant's right to withdrawal at any time during the study procedures, and participant's permission for the publication of the study's findings. Written and signed informed consent was obtained from all participants prior to performance of the study procedures. The study was approved by the Institutional Board Review of the University of Puerto Rico (IRB # B0930116) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication
A written and signed informed consent for publication of the findings from participants' data was obtained from each participant. Following the study sponsor's rules and policies (National Institute of Dental and Craniofacial Research, NIDCR), the signed informed consent forms are retained in a secured and locked cabinet (to protect the participants' confidentiality) at the University of Puerto Rico *for* at least 3 years following the close of the study.

Author contributions
Oelisoa M. Andriankaja: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

ORCID iD
Oelisoa M. Andriankaja https://orcid.org/0000-0002-0917-7633

Supplemental material
Supplemental material for this article is available online.

References

1. Zhou M and Graves DT. Impact of the host response and osteoblast lineage cells on periodontal disease. *Front Immunol* 2022; 13: 998244.

2. Van Dyke TE and Serhan CN. Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. *J Dent Res* 2003; 82: 82–90.

3. Kononen E, Gursoy M and Gursoy UK. Periodontitis: a multifaceted disease of tooth-supporting tissues. *J Clin Med* 2019; 8: 1135.

4. Eke PI, Borgnakke WS and Genco RJ. Recent epidemiologic trends in periodontitis in the USA. *Periodontol 2000* 2020; 82: 257–267.

5. Montero-Aguilar M, Munoz-Torres F, Elias-Boneta AR, *et al.* High levels of periodontal disease among the older adult population in San Juan, Puerto Rico. *Community Dent Health* 2012; 29: 224–228.

6. Persson GR. What has ageing to do with periodontal health and disease? *Int Dent J* 2006; 56: 240–249.

7. Kocher T, Konig J, Borgnakke WS, *et al.* Periodontal complications of hyperglycemia/diabetes mellitus: epidemiologic complexity and clinical challenge. *Periodontol 2000* 2018; 78: 59–97.

8. Graves DT, Ding Z and Yang Y. The impact of diabetes on periodontal diseases. *Periodontol 2000* 2020; 82: 214–224.

9. Hajishengallis G, Lamont RJ and Graves DT. The enduring importance of animal models in understanding periodontal disease. *Virulence* 2015; 6: 229–235.

10. Wu CZ, Yuan YH, Liu HH, *et al.* Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. *BMC Oral Health* 2020; 20: 204.

11. Albert DA, Ward A, Allweiss P, *et al.* Diabetes and oral disease: implications for health professionals. *Ann N Y Acad Sci* 2012; 1255: 1–15.

12. Overmyer KA, Rhoads TW, Merrill AE, *et al.* Proteomics, lipidomics, metabolomics and 16S DNA sequencing of dental plaque from patients with diabetes and periodontal disease. *Mol Cell Proteomics* 2021; 20: 100126.

13. Andriankaja OM, Galicia J, Dong G, *et al.* Gene expression dynamics during diabetic periodontitis. *J Dent Res* 2012; 91: 1160–1165.

14. Schroeder H, Sikora M, Gopalakrishnan S, *et al.* Origins and genetic legacies of the Caribbean Taino. *Proc Natl Acad Sci U S A* 2018; 115: 2341–2346.

15. Emrich LJ, Shlossman M and Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. *J Periodontol* 1991; 62: 123–131.

16. Papapanou PN. Epidemiology of periodontal diseases: an update. *J Int Acad Periodontol* 1999; 1: 110–116.

17. CDC. *Centers for disease control and prevention.* Atlanta, GA: BRFSS Prevalence & Trends Data, 2021.

18. Pego-Fernandes PM, Bibas BJ and Deboni M. Obesity: the greatest epidemic of the 21st century? *Sao Paulo Med J* 2011; 129: 283–284.

19. Feingold KR and Grunfeld C. The effect of inflammation and infection on lipids and lipoproteins. In: Feingold KR, Anawalt B, Boyce A, *et al.* (eds) *Endotext.* South Dartmouth, MA: MDText.com, Inc., 2000.

20. Elkhouli AM. The efficacy of host response modulation therapy (omega-3 plus low-dose aspirin) as an adjunctive treatment of chronic periodontitis (clinical and biochemical study). *J Periodontal Res* 2011; 46: 261–268.

21. El-Sharkawy H, Aboelsaad N, Eliwa M, *et al.* Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 Fatty acids and low-dose aspirin. *J Periodontol* 2010; 81: 1635–1643.

22. Sculley DV. Periodontal disease: modulation of the inflammatory cascade by dietary n-3 polyunsaturated fatty acids. *J Periodontal Res* 2014; 49: 277–281.

23. Margaritis M, Sanna F and Antoniades C. Statins and oxidative stress in the cardiovascular system. *Curr Pharm Des*. Epub ahead of print September 2017. DOI: 10.2174/1381612823666170926130338

24. Petit C, Batool F, Bugueno IM, *et al.* Contribution of statins towards periodontal treatment: a review. *Mediators Inflamm* 2019; 2019: 6367402.

25. Tahamtan S, Shirban F, Bagheriya M, *et al.* The effects of statins on dental and oral health: a review of preclinical and clinical studies. *J Transl Med* 2020; 18: 155.

26. Poston CJ, Pierce TC, Li Y, *et al.* Statin intake is associated with MMP-1 level in gingival crevicular fluid of patients with periodontitis. *Oral Dis* 2016; 22: 438–444.

27. Magan-Fernandez A, Papay-Ramirez L, Tomas J, *et al.* Association of simvastatin and hyperlipidemia with periodontal status and bone metabolism markers. *J Periodontol* 2014; 85: 1408–1415.

28. Joshipura KJ, Munoz-Torres FJ, Dye BA, *et al.* Longitudinal association between periodontitis and development of diabetes. *Diabetes Res Clin Pract* 2018; 141: 284–293.

29. Petersmann A, Muller-Wieland D, Muller UA, *et al.* Definition, classification and diagnosis of diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2019; 127: S1–S7.

30. Dye BA, Li X, Lewis BG, *et al.* Overview and quality assurance for the oral health component of the National Health and Nutrition Examination Survey (NHANES), 2009–2010. *J Public Health Dent* 2014; 74: 248–256.

31. Hirotomi T, Yoshihara A, Ogawa H, *et al.* A preliminary study on the relationship between stimulated saliva and periodontal conditions in community-dwelling elderly people. *J Dent* 2006; 34: 692–698.

32. Silness J and Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condtion. *Acta Odontol Scand* 1964; 22: 121–135.

33. Andriankaja OM, Munoz-Torres FJ, Vivaldi-Oliver J, *et al.* Insulin resistance predicts the risk of gingival/periodontal inflammation. *J Periodontol* 2018; 89: 549–557.

34. Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.

35. Jagtap D, Rosenberg CA, Martin LW, *et al.* Prospective analysis of association between use of statins and melanoma risk in the Women's Health Initiative. *Cancer* 2012; 118: 5124–5131.

36. Cunha-Cruz J, Saver B, Maupome G, *et al.* Statin use and tooth loss in chronic periodontitis patients. *J Periodontol* 2006; 77: 1061–1066.

37. Chou R, Dana T, Blazina I, *et al.* Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US preventive services task force. *JAMA* 2016; 316: 2008–2024.

38. Centers for Disease C and Prevention. Cigarette smoking among adults–United States, 2000. *MMWR Morb Mortal Wkly Rep* 2002; 51: 642–645.

39. (CDC) CFDCaP. National Center for Health Statistics. National Heatlh Interview Survey. *Glossary-Alcohol* 2022.

40. Pickering TG, Hall JE, Appel LJ, *et al.* Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation* 2005; 111: 697–716.

41. Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71: e13–e115.

42. Joshipura KJ, Andriankaja MO, Hu FB, *et al.* Relative utility of 1-h oral glucose tolerance test as a measure of abnormal glucose homeostasis. *Diabetes Res Clin Pract* 2011; 93: 268–275.

43. Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.

44. Eke PI, Page RC, Wei L, *et al.* Update of the case definitions for population-based surveillance of periodontitis. *J Periodontol* 2012; 83: 1449–1454.

45. Taylor F, Huffman MD, Macedo AF, *et al*. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013; 2013: CD004816.

46. Tramacere I, Boncoraglio GB, Banzi R, *et al*. Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. *BMC Med* 2019; 17: 67.

47. Meisel P, Kroemer HK, Nauck M, *et al*. Tooth loss, periodontitis, and statins in a population-based follow-up study. *J Periodontol* 2014; 85: e160–e168.

48. Sangwan A, Tewari S, Singh H, *et al*. Effect of hyperlipidemia on response to nonsurgical periodontal therapy: statin users versus nonusers. *Eur J Dent* 2016; 10: 69–76.

49. Pajak-Lysek E, Polak M, Kopec G, *et al*. Associations between pharmacotherapy for cardiovascular diseases and periodontitis. *Int J Environ Res Public Health* 2021; 18: 770.

50. Zhang H, Zhang Y, Chen X, *et al*. Effects of statins on cytokines levels in gingival crevicular fluid and saliva and on clinical periodontal parameters of middle-aged and elderly patients with type 2 diabetes mellitus. *PLoS One* 2021; 16: e0244806.

51. Saxlin T, Suominen-Taipale L, Knuuttila M, *et al*. Dual effect of statin medication on the periodontium. *J Clin Periodontol* 2009; 36: 997–1003.

52. Kwon MJ, Byun SH, Kim JH, *et al*. Longitudinal follow-up study of the association between statin use and chronic periodontitis using national health screening cohort of Korean population. *Sci Rep* 2022; 12: 5504.

53. Andriankaja OM, Jimenez JJ, Munoz-Torres FJ, *et al*. Lipid-lowering agents use and systemic and oral inflammation in overweight or obese adult Puerto Ricans: the San Juan overweight adults longitudinal study (SOALS). *J Clin Periodontol* 2015; 42: 1090–1096.

54. Na E, Cho S, Kim DJ, *et al*. Time-varying and dose-dependent effect of long-term statin use on risk of type 2 diabetes: a retrospective cohort study. *Cardiovasc Diabetol* 2020; 19: 67.

55. Sunjaya AP, Sunjaya AF, Halim S, *et al*. Risk and benefits of statins in glucose control management of type II diabetes. *Int J Angiol* 2018; 27: 121–131.

56. Chaves ES, Wood RC, Jones AA, *et al*. Relationship of "bleeding on probing" and "gingival index bleeding" as clinical parameters of gingival inflammation. *J Clin Periodontol* 1993; 20: 139–143.

57. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004; 66: 411–421.

58. Hawkins DM. The problem of overfitting. *J Chem Inf Comput Sci* 2004; 44: 1–12.

59. Zhang Z. Too much covariates in a multivariable model may cause the problem of overfitting. *J Thorac Dis* 2014; 6: E196–E197.

60. Caton JG, Armitage G, Berglundh T, *et al*. A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification. *J Clin Periodontol* 2018; 45(Suppl. 20): S1–S8.

61. Nascimento GG, Dahlen G, Lopez R, *et al*. Periodontitis phenotypes and clinical response patterns to non-surgical periodontal therapy: reflections on the new periodontitis classification. *Eur J Oral Sci* 2020; 128: 55–65.

62. Kassab MM and Cohen RE. The etiology and prevalence of gingival recession. *J Am Dent Assoc* 2003; 134: 220–225.

63. Dominiak M and Gedrange T. New perspectives in the diagnostic of gingival recession. *Adv Clin Exp Med* 2014; 23: 857–863.

64. Fragkioudakis I, Tassou D, Sideri M, *et al*. Prevalance and clinical characteristics of gingival recession in Greek young adults: a cross-sectional study. *Clin Exp Dent Res* 2021; 7: 672–678.

65. Baker DL and Seymour GJ. The possible pathogenesis of gingival recession. A histological study of induced recession in the rat. *J Clin Periodontol* 1976; 3: 208–219.

66. Wennstrom JL. Lack of association between width of attached gingiva and development of soft tissue recession. A 5-year longitudinal study. *J Clin Periodontol* 1987; 14: 181–184.

67. 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(Suppl. 1): S74–S84.

68. Lopez NJ, Smith PC and Gutierrez J. Higher risk of preterm birth and low birth weight in women with periodontal disease. *J Dent Res* 2002; 81: 58–63.

69. Lopez NJ, Smith PC and Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. *J Periodontol* 2002; 73: 911–924.

70. Sutthiboonyapan P, Wang HL and Charatkulangkun O. Flowcharts for easy periodontal diagnosis based on the 2018 new periodontal classification. *Clin Adv Periodontics* 2020; 10: 155–160.

71. Beck JD and Koch GG. Characteristics of older adults experiencing periodontal attachment loss as gingival recession or probing depth. *J Periodontal Res* 1994; 29: 290–298.

72. Pahan K. Lipid-lowering drugs. *Cell Mol Life Sci* 2006; 63: 1165–1178.

73. CDC. Centers for Disease Control and Prevention. National Center for Health Statistics (NCHS). *National Health and Nutrition Examination Survey Oral Health Examiners Manual, 2009–2010*. Hyattsville, MD: US Department of Health and Human Services, 2011.

74. Leite FRM, Nascimento GG, Baake S, *et al*. Impact of smoking cessation on periodontitis: a systematic review and meta-analysis of prospective longitudinal observational and interventional studies. *Nicotine Tob Res* 2019; 21: 1600–1608.

75. Hajishengallis G. Interconnection of periodontal disease and comorbidities: evidence, mechanisms, and implications. *Periodontol 2000* 2022; 89: 9–18.

76. Luong A, Tawfik AN, Islamoglu H, *et al*. Periodontitis and diabetes mellitus co-morbidity: a molecular dialogue. *J Oral Biosci* 2021; 63: 360–369.

Visit Sage journals online
journals.sagepub.com/home/taj

S Sage journals