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Cross-sectional association between severe periodontitis and diabetes mellitus: A nation-wide cohort study

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Abstract

Aim: To evaluate the cross-sectional association between severe periodontitis and diabetes mellitus (DM), in a representative sample of Spanish population.

Materials and Methods: The *di@bet.es* epidemiological study is a population-based cohort study aimed to determine the prevalence and incidence of DM in the adult population of Spain. The at-risk sample at the final examination (2016–2017) included 1751 subjects who completed an oral health questionnaire. This questionnaire, together with demographic and risk factors, had been previously validated to build an algorithm to predict severe periodontitis in the Spanish population. Logistic regression models were used to evaluate the association between severe periodontitis and DM with adjustment for confounding factors.

Results: In total, 144 subjects developed DM, which yielded 8.2% cumulative incidence. Severe periodontitis was detected in 59.0%, 54.7% or 68.8% of the subjects depending on three different selected criteria at the 2016–2017 exam. All criteria used to define severe periodontitis were associated with DM in unadjusted analysis, but the magnitude of the association decreased after adjusting for significant confounders. The criteria '≥50% of teeth with clinical attachment loss ≥5 mm' presented an odds ratio of 4.9 (95% confidence interval: 2.2–10.7; $p \leq .001$) for DM.

Conclusions: Severe periodontitis is associated with DM in the Spanish population.

KEYWORDS

diabetes mellitus, epidemiology, periodontitis, risk factor

Clinical Relevance

Scientific rationale for study: Most of the studies reporting a relationship between periodontitis and diabetes have been performed in Asian populations and/or have used indirect methods to diagnose diabetes. Therefore, there is a need to evaluate the association between severe periodontitis and diabetes mellitus in a representative sample of a European country (i.e., Spain).

Principal findings: Subjects with severe periodontitis (specifically those presenting ≥50% of sites with clinical attachment loss ≥5 mm) presented a ≈400% increased odds of presenting diabetes than subjects without severe periodontitis.

Practical implications: Our findings support prior research suggesting an association between periodontitis and diabetes. Future studies are necessary to determine whether periodontal treatment can prevent or delay diabetes development.

1 | INTRODUCTION

Diabetes mellitus (DM) is a global public health problem that creates challenges for the healthcare systems of many countries. According to the International Diabetes Federation (IDF), 537 million people worldwide suffer from diabetes, 6.7 million adults between the age of 20–79 were estimated to have died as a result of diabetes or its complications in 2021 and around 10% on the global heath expenditure in developed countries is spent on diabetes (International Diabetes Federation, 2021).

Periodontitis is a chronic infectious-inflammatory disease associated with dysbiotic dental plaque biofilms, characterized by the destruction of the tooth-supporting tissues (periodontal ligament and alveolar bone). Its global prevalence is also high, with around 796 million subjects with severe periodontitis (Bernabe et al., 2020).

Different reviews and consensus reports published in recent years have clearly pointed out the bidirectional relationship between DM and periodontitis. Numerous studies have shown that DM (both types 1 and 2) is a risk factor for periodontitis, increasing the risk approximately 3 times when compared to non-diabetic subjects, particularly if they have poor glycaemic control (Nelson et al., 1990; Seppala et al., 1993; Taylor et al., 1998). In addition, periodontitis negatively affects glycaemic control in people with DM and increases the risk of developing complications, with a relative risk of >3.0 for glycated haemoglobin (HbA1c) increases above 6.5% in a 5-year period among those periodontitis patients with probing depths ≥6 mm (Demmer et al., 2010; Morita et al., 2012; Shultis et al., 2007). This association is especially relevant in severe forms of periodontitis (stage III–IV periodontitis following the 2018 classification), because a stronger impact on systemic health and quality of life is expected in these cases (Genco & Sanz, 2020; Graziani & Tsakos, 2020).

Severe periodontitis has also been identified as a potential risk factor for DM in non-diabetic subjects. Periodontitis has been associated with an increase over time in HbA1c values (Demmer et al., 2010), an increase in the incidence of prediabetes (Saito et al., 2004) and an increase in the incidence of type 2 DM in initially non-diabetic subjects (Demmer et al., 2008). However, the impact of periodontitis on incident DM and glucose homeostasis in healthy individuals needs further evaluation in different populations (Genco et al., 2020). Since it seems that periodontitis contributes to poorer metabolic control in both persons with and without DM, early diagnosis is key to implementing interventions that can reduce the risk of developing diabetes and/or the onset of complications. In fact, providing non-surgical (steps 1 and 2) periodontal treatment to persons with type 2 DM and periodontitis is expected to significantly reduce not only tooth loss but also microvascular complications in a cost-effective manner (S. E. Choi et al., 2020).

Therefore, frequent oral and periodontal health assessment and, eventually, periodontal treatment seem important for metabolic control in people with DM and prediabetes. With this purpose, several self-reported questionnaires have been proposed, to estimate the prevalence of periodontitis in a time- and cost-effective manner

(Carra et al., 2018; Dietrich et al., 2009; Eke et al., 2013; Heaton et al., 2017; Verhulst et al., 2019). Specifically, the Centers for Disease Control and Prevention (CDC)/American Academy of Periodontology (AAP) questionnaire (Eke & Genco, 2007) has been previously validated in the Spanish population using a subsample of the *di@bet.es* study, whose objective was to determine the incidence of type 2 DM in Spain (Rojo-Martinez et al., 2020). In that validation study, it was demonstrated that a combination of self-reported questions, together with demographic data and certain risk factors for periodontitis (i.e., smoking habit, DM), is useful to estimate the prevalence of severe periodontitis in the Spanish population (Montero et al., 2020). Therefore, the objective of the present study was to evaluate the cross-sectional association between severe periodontitis using a validated, self-reported questionnaire and diabetes mellitus, in a representative sample of the Spanish population.

2 | MATERIALS AND METHODS

2.1 | Study design, setting and population

The *di@bet.es* epidemiological study is a population-based cohort study aimed to determine the prevalence and incidence of diabetes and impaired glucose regulation in adult Spanish population. The baseline examination was undertaken between 2008 and 2010 using a random cluster sampling of the Spanish population. The original *di@bet.es* study consisted of 5072 subjects randomly selected from the National Health System registries, distributed into 100 clusters (primary healthcare centres) (Soriguer et al., 2012). To determine the incidence of DM, the same population was re-evaluated in 2016–2017 (Rojo-Martinez et al., 2020). All subjects who completed the baseline study were invited by letter and by phone to attend the 2016–2017 clinical examination. The 725 subjects who had diabetes at baseline were excluded from all incidence calculations. As with the cross-sectional study, people with serious illness, pregnancy, recent delivery or lactation or surgery within the previous month were excluded.

The research was carried out in accordance with the Declaration of Helsinki. The study was approved by the Ethics and Clinical Research Committee of the Hospital Regional Universitario de Málaga (Málaga, Spain). All participants were informed about the nature of the study and provided written informed consent.

2.2 | Data collection

The participants were invited to attend a single examination visit at their health centre. Information was collected using an interviewer-administered, structured questionnaire, and an oral health questionnaire, followed by a physical examination, blood sampling and an oral glucose tolerance test (OGTT).

The structured questionnaire, with closed-ended questions, was used to collect the following information: sex, age, educational level (none, basic, high school or college/university), smoking (current, ex- or never smoker), personal history of diabetes (yes/no), high blood pressure (yes/no), dyslipidaemia (yes/no), family history of diabetes (at least one first-degree relative with DM), medications (specifically asking about diabetes, high blood pressure or dyslipidaemia medications), frequency of food consumption (questionnaire administered by a trained dietitian, including frequency of consumption of 50 food items grouped into 11 categories, allowing for the calculation of a 14-point Mediterranean diet score; Rojo-Martinez et al., 2014 and physical activity [International Physical Activity Questionnaire, IPAQ]; Craig et al., 2003). People who did not want to participate in the complete study were asked to take a short survey in order to collect information about the drugs they were taking (to determine the existence of clinical diabetes, hypertension or dyslipidaemia in treatment), or if they were on some type of diet, together with self-reported weight.

The physical examination included measurements of body weight, height as well as waist and hip circumferences, which were done using standardized methods. Besides, the body mass index (BMI = weight/height^2) was calculated. Central obesity was defined according to the World Health Organization (WHO) criteria (waist circumference ≥94 cm for men and ≥80 cm for women). Blood pressure was measured with the subject seated after 5 min of rest and again 2 min after the first measurement. A third measure was performed if there was a difference of >10% between the first two measurements.

Participants with baseline capillary blood glucose levels <7.8 mmol/L (measured by ONETOUCH system, LifeScan, Malvern, PA, USA), and not receiving treatment for diabetes, underwent a standard OGTT with 75 g of glucose dissolved in 200 mL of water. Fasting and 2-h venous samples were obtained (8–10 h fasting samples were obtained between 8:30 AM and 10:00 AM). After centrifugation, the serum was separated from the clot and frozen (in the 2008–2010 visit) or refrigerated (in the 2016–2017 visit). All samples were analysed in the same central laboratory in the 2008–2010 visit (Cerba International Laboratory, Barcelona, Spain) and in the 2016–2017 visit (General Laboratory of the Hospital Regional Universitario of Málaga, Málaga, Spain), as previously described (Rojo-Martinez et al., 2020). In both stages, glucose was determined by the hexokinase enzymatic method, total cholesterol by cholesterol oxidase enzymatic method, high-density lipoprotein (HDL) cholesterol by direct method and triglycerides by glycerol phosphate oxidase enzymatic method. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. Glycated haemoglobin (HbA1c) was determined only in the 2016–2017 visit by high-performance liquid chromatography (analyser ADAMS A1C HA-8180V, ARKRAY USA Clinical Diagnostics, Minneapolis, MN, USA).

2.3 | Diagnosis of diabetes and prediabetes

Diabetes was diagnosed if fasting plasma glucose (FPG) was ≥126 mg/dL (7 mmol/L), or 2 h post-load plasma glucose (PG) ≥200 mg/dL (11 mmol/L), or HbA1c ≥6.5%, or glucose-lowering medication was used. Prediabetes was diagnosed by FPG 100–125 mg/dL (5.6–6.9 mmol/L; impaired fasting glucose, IFG), 2 h post-

load PG in OGTT of 140–199 mg/dL (7.8–11.0 mmol/L; impaired glucose tolerance; IGT) or HbA1c 5.7%–6.4% (American Diabetes Association, 2019).

2.4 | Oral and periodontal health assessment

An oral health questionnaire, including eight questions, first validated by Eke and Dye (2009) and later by Montero and co-workers with subjects from the present study (Montero et al., 2020), was given to every participant at the follow-up examination (2016–2017). The questions are detailed in Appendix, both in English and Spanish, with only the latter being given to the participants. The accuracy of the self-reported questionnaire was validated in 18 of the 25 primary healthcare centres participating in the study located in the central area of Spain (231 patients), where a periodontist, blinded to the questionnaire responses, performed a complete periodontal examination with a UNC-15 probe, including measurements of probing pocket depth (PPD) and gingival margin recession (REC; allowing for clinical attachment loss [CAL] calculation) and bleeding on probing (BOP) at six sites/tooth in all teeth, with the exception of third molars (Montero et al., 2020). The results of the validation process showed that a predictive model, combining self-reporting on oral health status with demographic and well-established risk factors for periodontitis (e.g., age, gender, smoking status and educational level), allowed for a valid and reliable estimation of the prevalence of severe periodontitis (area under the curve [AUC] values ranging between 0.75 and 0.78, depending upon the criteria used to define severe periodontitis).

2.5 | Diagnosis of periodontitis

Severe periodontitis was determined based on previously validated combinations of self-reported information (derived from the questionnaire [questions 1–8] expressed as Q1, Q2, etc.) and demographic and risk factors, as published previously (Table S1) (Montero et al., 2020). Specifically, severe periodontitis was defined according to three criteria/outcomes:

i. the CDC/AAP case definition (Eke et al., 2012);
ii. the presence of ≥50% of teeth with CAL ≥5 mm;
iii. the presence of ≥25% of teeth with PPD ≥6 mm.

The corresponding models were (threshold scores were based on the probability levels to correctly classify the highest percentage of patients)

i. *CDC/AAP severe periodontitis* criteria = 1.322 × Q1 + 0.580 × sex + 0.049 × age − 0.510 × smoking − 2.585 (probability level = 0.48, correctly classifying 69.7% of the subjects);
ii. *presence of ≥50% of teeth with CAL ≥5 mm* criteria = 0.466 × Q2 − 0.487 × Q7 + 0.030 × age − 0.0621 × smoking − 1.376 × educational level − 1.020 (probability level = 0.395, correctly classifying 69.6% of the subjects);
iii. *presence of ≥25% of teeth with PPD ≥6 mm* criteria = 0.893 × Q1 + 0.322 × Q4 − 0.662 × Q5 − 0.804 × Q7 + 0.033 × age + 0.127 × smoking − 1.625 × educational level − 0.427 (probability level = 0.482, correctly classifying 70.4% of the subjects).

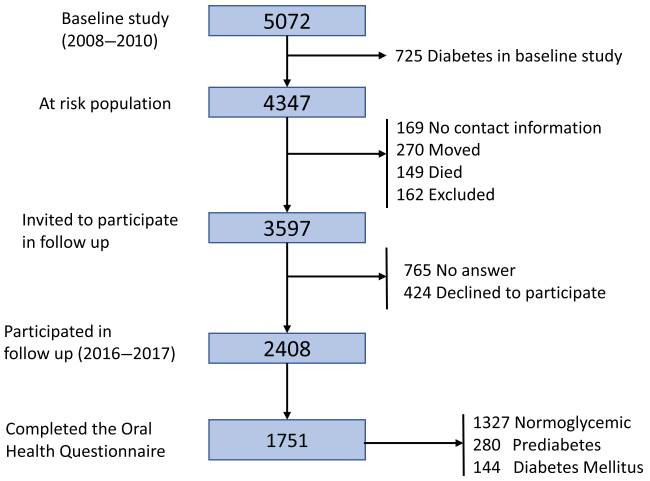

FIGURE 1 Flow-chart of the participants.

2.6 | Statistical analysis

Descriptive statistics were calculated for demographic and clinical characteristics, using chi-squared tests for categorical variables and *t*-tests and analysis of variance for continuous variables.

Different sets of ordinal logistic regression analyses (presented as odds ratios [ORs]) were carried out using the different definitions of self-reported severe periodontitis as independent variable, and glycaemic control category (normoglycaemia, prediabetes or DM) as dependent variable. For each set of logistic regression analyses, three different models were calculated:

- Model I: a crude model;
- Model II: an age- and sex-adjusted model;
- Model III: an adjusted model considering all putative confounders using the 'change-in-estimate' strategy (a change in the adjusted OR for a covariate of ≥10% compared to the crude OR). Potential confounding factors related to diabetes risk included age, sex, smoking status, BMI, central obesity, family history of diabetes mellitus, hypertension, dyslipidaemia, prevalence of prediabetes at baseline (2008–2010), IPAQ, a 14-point Mediterranean Diet Score (≤8 or >8) and educational level, all of them as recorded at the 2008–2010 examination.

All data analyses were performed with a software package (STATA v.13., StataCorp LLC, College Station, TX, USA).

TABLE 1 Characteristics of the population at the 2016–2017 examination, expressed either as mean (standard deviation [SD]) or *n* (%).

Variable	All samples ($n = 1751$)	Normoglycaemia ($n = 1327$)	Prediabetes ($n = 280$)	Diabetes mellitus ($n = 144$)	*p*- Value
Sex (% male)	701 (40.0%)	490 (36.9%)	138 (49.3%)	73 (50.7%)	.001
Age (years)	56.0 (14.3)	53.5 (13.8)	63.8 (13.3)	63.8 (12.0)	<.001
Body mass index (kg/m^2)	28.2 (5.2)	27.5 (4.6)	29.7 (4.9)	32.0 (8.3)	<.001
Obesity (%)	521 (30.4%)	327 (25.1%)	118 (43.4%)	76 (53.9.0%)	<.001
Waist circumference (cm)	93.4 (13.4)	90.9 (12.6)	99.9 (12.2)	103.8 (13.2)	.681
Central obesity (%)	1273 (72.9%)	893 (67.4%)	247 (89.2%)	133 (93.0%)	<.001
Smoking (%)					.175
Never smoker	862 (49.2%)	655 (49.4%)	141 (50.4%)	66 (45.8%)	
Former smoker	567 (32.4%)	415 (31.3%)	95 (33.9%)	57 (39.6%)	
Current smoker	322 (18.4%)	257 (19.4%)	44 (15.7%)	21 (14.6%)	
Educational level (%)					<.001
None	143 (8.2%)	85 (6.4%)	36 (12.9%)	22 (15.3%)	
Basic	550 (31.4%)	379 (28.6%)	111 (39.6%)	60 (41.7%)	
High school	721 (41.2%)	578 (43.6%)	93 (33.2%)	50 (34.7%)	
College	336 (19.2%)	284 (21.4%)	40 (14.3%)	12 (8.3%)	
Fasting plasma glucose (mg/dL)	94.6 (13.5)	91.3 (8.9)	104.9 (11.1)	122.4 (31.2)	<.001
Glycated haemoglobin (HbA1c, %)	5.4 (0.4)	5.4 (0.3)	5.6 (0.3)	6.1 (0.9)	<.001
Family history of diabetes (%)					.031
No	860 (49.1%)	670 (50.5%)	135 (48.2%)	55 (38.2%)	
Yes, one relative	476 (27.2%)	358 (27.0%)	77 (27.5%)	41 (28.5%)	
Yes, two or more relatives	415 (23.7%)	299 (22.5%)	68 (24.3%)	48 (33.3%)	
Systolic blood pressure (mmHg)	130.8 (19.1)	127.7 (18.0)	140.5 (19.9)	140.9 (18.4)	.087
Diastolic blood pressure (mmHg)	77.2 (10.3)	76.2 (10.1)	80.3 (10.3)	80.3 (10.2)	.877
High blood pressure (%)	827 (47.5%)	521 (39.4%)	197 (71.1%)	109 (76.8%)	<.001
Dyslipidaemia (%)	642 (36.7%)	407 (30.7%)	143 (51.1%)	92 (63.9%)	<.001
Coronary event (%)	60 (3.4%)	30 (2.3%)	20 (7.1%)	10 (7.0%)	<.001
Stroke (%)	27 (1.6%)	20 (1.5%)	3 (1.1%)	4 (2.8%)	.390
Peripheral vascular disease (%)	15 (0.9%)	11 (0.8%)	2 (0.7%)	2 (1.4%)	.760
IPAQ					.014
Low	750 (42.9%)	558 (42.1%)	130 (46.4%)	62 (43.4%)	
Moderate	706 (40.4%)	523 (39.4%)	117 (41.8%)	66 (46.2%)	
High	293 (16.8%)	245 (18.5%)	33 (11.8%)	15 (10.5%)	
14-Point MedDiet Score	8.7 (1.9)	8.7 (1.9)	8.8 (1.8)	8.5 (1.8)	.288
14-Point MedDiet score categorized					.709
Do not follow MedDiet (score ≤ 8)	774 (44.3%)	583 (44.0%)	123 (43.9%)	68 (47.6%)	
Follow MedDiet (score > 8)	975 (55.8%)	743 (56.0%)	157 (56.1%)	75 (52.5%)	

Abbreviations: IPAQ, International Physical Activity Questionnaire; MedDiet, Mediterranean Diet.

3 | RESULTS

Of the 5072 subjects included in the baseline examination (2008–2010), 2408 attended the 2016–2017 examination visit (Figure 1). Among the 1751 subjects who completed the oral health questionnaire, 220 (12.56%) presented prediabetes at baseline (72 [4.11%] impaired fasting glucose [IFG], 117 [6.68%] impaired glucose tolerance [IGT] and 31 [1.77%] both IFG and IGT). At the 2016–2017 re-examination visit, 144 subjects (8.22%) were new diabetes cases and 280 subjects (16.56%) presented IFG, IGT or both (Table S2).

The characteristics of the entire population are shown in Table 1. As expected, subjects with DM were significantly older, presented a higher BMI and more frequently central obesity, suffered more frequently from high blood pressure and dyslipidaemia and had a more sedentary lifestyle.

TABLE 2 Responses to the Oral Health Questionnaire, by glycemic control, at the 2016–2017 examination.

		All samples ($n = 1751$)		Normoglyacemia ($n = 1327$)		Prediabetes ($n = 280$)		Diabetes mellitus ($n = 144$)	
Question	**Response**	***N***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
'Gum Disease' (Q1)	Yes	292	16.7	218	16.4	48	17.1	26	18.1
	No[a]	1285	73.4	968	73.0	212	75.7	105	72.9
	Refused/Do not know	174	9.9	141	10.6	20	7.1	13	9.0
'Health of gums' (Q2)	Excellent/Very good/Good[a]	1097	65.2	853	67.1	170	62.3	74	53.6[b]
	Fair/Poor	585	34.8	418	32.9	103	37.7	64	46.4
	Refused/Do not know	0	0		0	0	0	0	0
'Scaling and root planning' (Q3)	Yes	896	51.2	680	51.2	144	51.4	72	50.0
	No[a]	738	42.2	561	42.3	118	42.1	59	41.0
	Refused/Do not know	117	6.7	86	6.5	18	6.4	13	9.0
'Loose teeth' (Q4)	Yes	381	21.8	259	19.5	79	28.2	43	29.9[b]
	No[a]	1261	72.0	985	74.2	185	66.1	91	63.2
	Refused/Do not know	109	6.2	83	6.3	16	5.7	10	6.9
'Bone loss' (Q5)	Yes	247	14.1	178	13.4	42	15.0	27	18.8
	No[a]	1357	77.5	1042	78.5	214	76.4	101	70.1
	Refused/Do not know	147	8.4	107	8.1	24	8.6	16	11.1
'Tooth appearance' (Q6)	Yes	340	19.4	243	18.3	65	23.2	32	22.2
	No[a]	1327	75.8	1020	76.9	202	72.1	105	72.9
	Refused/Do not know	84	4.8	64	4.8	13	4.6	7	4.9
'Dental floss' (Q7)	Never[a]	1063	64.4	767	61.1	191	73.5	105	76.6[b]
	1–7 times	589	35.7	488	38.9	69	26.5	32	23.4
	Refused/Do not know	0	0						
'Mouthwash' (Q8)	Never[a]	845	50.9	641	51.0	134	50.4	70	51.1
	1–7 times	814	49.1	615	49.0	132	49.6	67	48.9
	Refused/Do not know	0	0						

[a]Reference category.
[b]Statistically significant (χ^2-test; $p < .05$) differences in self-reported responses across categories by glycaemic control.

TABLE 3 Presence of self-reported severe periodontitis, using different criteria, among glycemic control groups at the final examination (2016–2017).

Variable	All sample ($n = 1751$)	Normoglycaemia ($n = 1327$)	Prediabetes ($n = 280$)	Diabetes mellitus ($n = 144$)	*p*-Value
Self-reported severe periodontitis					
CDC/AAP criteria	1033 (59.0%)	719 (54.2%)	202 (72.1%)	112 (77.8%)	<.001
≥50% of teeth with CAL ≥5 mm	957 (54.7%)	634 (47.8%)	201 (71.8%)	122 (84.7%)	<.001
≥25% of teeth with PPD ≥6 mm	1205 (68.8%)	845 (63.7%)	233 (83.2%)	127 (88.2%)	<.001

Abbreviations: AAP, American Academy of Periodontology; CAL, clinical attachment loss; CDC, Centers for Disease Control; PPD, probing pocket depth.

The responses to the eight questions of the oral health questionnaire are shown in Table 2. The percentage of 'Refused/Do not know' responses was low, with the highest one (9.9%) observed for 'Do you think you might have gum disease?' (Q1). The response rate to three questions, namely 'Health of gums' (Q2), 'Loose teeth' (Q4) and 'Dental Floss' (Q7), was significantly different between subjects with DM and normoglycaemic or prediabetes subjects. Subjects with diabetes answered less frequently 'Excellent/Very Good/Good' to Q2 about healthy gums, and reported a lower use of dental floss or other interdental devices (Q7). Conversely, 'loose teeth' (Q4) were more common in patients with DM.

Severe periodontitis was identified in 59.0%, 54.7% or 68.8% of the subjects, depending of the selected criteria, either CDC/AAP, '≥50% of teeth with CAL ≥5 mm' or '≥25% of teeth with PPD

TABLE 4 Characteristics of the population in the 2016–2017 examination, depending on the presence of self-reported severe periodontitis (Centers for Disease Control [CDC]/American Academy of Periodontology [AAP] criteria), expressed either as mean (standard deviation [SD]) or *n* (%).

Variable	Self-reported severe periodontitis (CDC/AAP criteria)		*p*-Value
	Yes (%)	No (%)	
Sex (% male)	505 (48.9%)	196 (27.3%)	<.001
Age (years)	62.0 (13.2)	47.4 (10.9)	<.001
Body mass index (kg/m^2)	28.7 (5.3)	27.6 (5.2)	<.001
Obesity (%)	337 (33.3%)	184 (26.2%)	.002
Waist circumference (cm)	96.3 (13.0)	89.4 (12.9)	<.001
Central obesity (%)	818 (79.4%)	455 (63.6%)	<.001
Smoking (%)			<.001
Never smoker	391 (37.9%)	471 (65.6%)	
Former smoker	402 (38.9%)	165 (23.0%)	
Current smoker	240 (23.2%)	82 (11.4%)	
Educational level (%)			<.001
None	122 (11.8%)	21 (2.9%)	
Basic	384 (37.2%)	166 (23.2%)	
High School	383 (37.1%)	338 (47.1%)	
College	144 (13.9%)	192 (26.8%)	
Family history of diabetes (%)			.035
No	534 (51.7%)	326 (45.4%)	
Yes, one relative	266 (25.8%)	210 (29.3%)	
Yes, two or more relatives	233 (22.6%)	182 (25.4%)	
Systolic blood pressure (mmHg)	135.2 (19.6)	124.5 (16.5)	<.001
Diastolic blood pressure (mmHg)	78.0 (10.3)	76.0 (10.2)	.001
High blood pressure (%)	605 (58.9%)	222 (31.1%)	<.001
Dyslipidaemia (%)	440 (42.6%)	202 (28.1%)	<.001
Coronary event (%)	55 (5.4%)	5 (0.7%)	<.001
Stroke (%)	24 (2.3%)	3 (0.4%)	<.001
Peripheral vascular disease (%)	13 (1.3%)	2 (0.3%)	.028
IPAQ			.002
Low	462 (44.8%)	288 (40.2%)	
Moderate	424 (41.1%)	282 (39.3%)	
High	146 (14.2%)	147 (20.5%)	
14-Point MedDiet score	8.8 (1.9)	8.6 (1.9)	.066
14-Point MedDiet score categorized			.124
Do not follow MedDiet (score ≤ 8)	441 (42.7%)	333 (46.4%)	
Follow MedDiet (score > 8)	591 (57.3%)	384 (53.6%)	
Presence of prediabetes at baseline (2008–2010)	170 (77.3%)	50 (22.7%)	<.001

Abbreviations: IPAQ, International Physical Activity Questionnaire; MedDiet, Mediterranean Diet.

≥6 mm', respectively (Table 3). Independently of the criteria used, subjects with prediabetes or diabetes presented more frequently severe periodontitis compared with normoglycaemic subjects ($p < .001$). Patients with severe periodontitis were significantly older (mean age 62.0 [standard deviation, SD = 13.2] vs. 47.4 [SD = 10.9]; $p < .001$), were more frequently obese (33.3% vs. 26.2%; $p = .002$) and had more central obesity (79.4% vs. 63.6%; $p < .001$), hypertension (58.9% vs. 31.1%; $p < .001$) and dyslipidaemia (42.6% vs. 28.1%; $p < .001$) than subjects without severe periodontitis. Subjects with severe periodontitis according to the CDC/AAP criteria performed less frequently physical exercise ($p = .002$). Moreover, they had a higher prevalence of coronary events (5.4% vs. 0.7%; $p < .001$), stroke (2.3% vs. 0.4%; $p < .001$) and peripheral vascular disease (1.3% vs. 0.3%; $p = .028$) (Table 4).

TABLE 5 Associations between self-reported severe periodontitis with glycaemic control at the 2016–2017 examination.

	Glycemic control					
	Model I		Model II		Model III	
Self-reported severe periodontitis	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
CDC/AAP criteria						
Normoglycaemia[a]	1		1		1	
Prediabetes	2.19 (1.65–2.91)	<.001	0.82 (0.58–1.16)	.268	0.72 (0.49–1.07)	.108
Diabetes mellitus	2.96 (1.97–4.45)	<.001	1.14 (0.71–1.80)	.589	0.88 (0.51–1.55)	.668
≥50% of teeth with CAL ≥5 mm						
Normoglycaemia[a]	1		1		1	
Prediabetes	2.78 (2.10–3.69)	<.001	1.27 (0.90–1.79)	.171	1.26 (0.79–2.00)	.339
Diabetes mellitus	6.06 (3.80–9.67)	<.001	3.31 (1.96–5.59)	<.001	4.90 (2.24–10.72)	<.001
≥25% of teeth with PPD ≥6 mm						
Normoglycaemia[a]	1		1		1	
Prediabetes	2.83 (2.03–3.94)	<.001	1.28 (0.87–1.89)	.202	1.07 (0.69–1.64)	.773
Diabetes mellitus	4.26 (2.54–7.16)	<.001	1.89 (1.07–3.33)	.027	1.20 (0.61–2.36)	.592

Note: Model I: crude ORs, no adjustment. Model II: adjusted for age and sex. Model III: adjusted for age, sex, smoking status, presence of prediabetes at baseline, body mass index, central obesity, family history of diabetes mellitus, hypertension, dyslipidaemia, International Physical Activity Questionnaire and educational level.

Abbreviations: AAP, American Academy of Periodontology; CAL, clinical attachment loss; CDC, Centers for Disease Control; CI, confidence interval; OR, odds ratio; PPD, probing pocket depth.

[a]Reference category.

In unadjusted logistic regression models, severe periodontitis, independently of the criteria considered, was significantly associated with either prediabetes or DM (Table 5, Model I). After adjustment for age and sex (Model II), the associations remained statistically significant for the '≥50% of teeth with CAL ≥5 mm' criteria and DM (OR = 3.31; 95% confidence interval, CI [1.96–5.59]; $p < .001$) and for the '≥25% of teeth with PPD ≥6 mm' criteria and DM (OR = 1.89; 95% CI [1.07–3.33]; $p = .027$). In fully adjusted models (Model III), the aforementioned associations remained statistically significant only for the '≥50% of teeth with CAL ≥5 mm' criteria (OR = 4.90; 95% CI [2.24–10.72]; $p < .001$).

4 | DISCUSSION

In this nation-wide cohort study, severe periodontitis was associated with diabetes in a representative sample of the Spanish population. Severe periodontitis was significantly associated with an increased risk of diabetes and prediabetes, independently of the criteria used to define the periodontal condition, in unadjusted models. After full adjustment for potential confounders, the association remained statistically significant when severe periodontitis was defined by the presence of ≥50% of teeth with CAL ≥5 mm.

Most studies assessing the association between periodontitis and diabetes have focused on the influence of type 2 DM in the development of periodontitis, whereas only a few studies have explored the impact of periodontitis on incident type 2 DM (Chiu et al., 2015; Demmer et al., 2008; Ide et al., 2011; Lin et al., 2014; Morita et al., 2012; Saito et al., 2004). The overall available evidence, summarized for the Workshop of the IDF and the European Federation of Periodontology (EFP), reported that individuals affected by periodontitis had a higher probability to develop type 2 DM when compared with non-periodontitis subjects, with a hazard ratio (HR) between 1.2 and 1.3 (Graziani et al., 2018). However, most of the identified studies were performed in Japan and Taiwan, which raises the question whether these results can be directly extrapolated to other populations. In the present study, which was performed in a nation-wide population-based cohort from Spain (*di@bet.es* study; Rojo-Martinez et al., 2020), a cross-sectional association between severe periodontitis and incident hyperglycaemia has been proved. Participants with severe periodontitis at 2016–2017 presented an unadjusted increased risk of developing diabetes between 2008–2010 and 2016–2017 in the range 3.0–6.1, while the range for prediabetes was 2.2–2.8. Even in fully adjusted models (adjusted for age, sex, smoking status, educational level, BMI, central obesity, family history of DM, hypertension, dyslipidaemia, presence of prediabetes at baseline and IPAQ), the cross-sectional association between severe periodontitis and DM persisted for those presenting extensive attachment loss (i.e., participants with ≥50% of teeth with CAL ≥5 mm had a OR = 4.9, 95% CI [2.2–10.7]; $p < .001$). The different estimates between this study and others (Chiu et al., 2015; Ide et al., 2011; Lin et al., 2014; Morita et al., 2012; Saito et al., 2004) may be due to the differences in the prevalence of diabetes in Japan and Taiwan (<8.0%) versus Spain (13.8%) (International Diabetes Federation, 2021).

As mentioned earlier, the association between diabetes and periodontitis may be confounded by multiple factors, including age, sex,

BMI, central obesity, family history of diabetes, hypertension or dyslipidaemia (Wilson et al., 2007). In fact, all these factors were associated with an increased risk of diabetes in the present study. The adjustment for all these potential confounders just attenuated the reported associations for some of the criteria used to define severe periodontitis. Moreover, as some of these factors (e.g., dyslipidaemia) may mediate in the association, it is possible that the results may be over-adjusted. Specifically, since there is evidence pointing out that periodontitis is associated with obesity and dyslipidaemia, this association may be explained by specific mechanistic pathways such as the elevated presence of pro-inflammatory adipokines (e.g., leptin and resistin) in serum levels of patients with periodontitis (Zhu et al., 2017) and with periodontal bacteria being able to induce lipid profile alterations (Y. H. Choi et al., 2018).

Some of the few studies reporting a relationship between periodontitis and incident DM have used indirect methods to diagnose diabetes. A prospective study in the United States identified subjects with incident DM on the basis of death certificates, self-reported pharmacological treatment or a discharge diagnosis of DM after admission to a health centre (Demmer et al., 2008), which cannot exclude the presence of undiagnosed DM at baseline. Similarly, a study from China determined the development of type 2 DM by electronic records reporting the use of anti-diabetes medications (Lin et al., 2014). In the present study, participants with confirmed DM at the baseline examination (2008–2010) were excluded, as well as those with undiagnosed DM based on FPG or OGTTs, to ensure that the study sample consisted of a non-diabetic cohort at baseline.

One of the limitations of the present study is the use of a combination of self-reported information and demographic and risk factors to define severe periodontitis, with only a group of patients being clinically assessed in order to develop and validate the algorithms (Montero et al., 2020). In any case, the algorithms have been validated for the CDC/AAP case definition for severe periodontitis and for two other extent and severity measures based on different thresholds at tooth level for CAL and PPD, as recommended by the European Union (EU)/U.S. Periodontal Epidemiology Working Group (Holtfreter et al., 2015). Even though a full-mouth periodontal examination is advised as the ideal tool, the referred algorithms have reported AUCs ≥0.75, making them useful not just for the surveillance of periodontitis in a given population but also for large-scale studies (in this study $n = 1751$) to evaluate the association between severe periodontitis and different systemic conditions on a cost-effective manner. Another limitation in the evaluation of the periodontal condition is that it was not evaluated at the baseline visit (2008–2010) but just at the follow-up re-evaluation (2016–2017). Thus, it cannot be excluded that periodontitis developed after diabetes started between 2008–2010 and 2016–2017. For this reason, considering that a cross-sectional subgroup of the original longitudinal cohort was analysed, the selected statistical analyses were designed for a cross-sectional study, despite the Di@bet.es being a cohort study (Rojo-Martinez et al., 2020). However, it is important to highlight that the results presented here are cross-sectional and describe the association between diabetes and periodontitis, and do not imply any cause–effect relationship.

In summary, this large-scale study, controlling for multiple potential confounders, has demonstrated that severe periodontitis is an independent indicator associated with an elevated risk to have type 2 diabetes mellitus in a nationally representative European population.

AUTHOR CONTRIBUTIONS

Eduardo Montero contributed to conception, design, data acquisition and interpretation, and drafted and critically revised the manuscript. Rocío Bujaldón, Mariano Sanz and Bettina Alonso contributed to data interpretation and critically revised the manuscript. Eduard Montanya, Alfonso L. Calle-Pascual, Gemma Rojo-Martínez, Luis Castaño, Josep Franch-Nadal, Elías Delgado and Felipe Chaves contributed to data acquisition and interpretation, and critically revised the manuscript. David Herrera contributed to conception, design and data interpretation, and critically revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

SELF-REPORT QUESTIONS RELATED TO PERIODONTAL HEALTH (ENGLISH VERSION AND TRANSLATION IN SPANISH)

Preamble: Gum disease is a common problem with the mouth. People with gum disease might have swollen gums, receding gums, sore or infected gums or loose teeth.

Preámbulo: Las enfermedades de las encías son un problema común en la boca. Las personas que sufren estas enfermedades pueden tener las encías inflamadas, retraídas, con dolor o molestias, infectadas y los dientes pueden desplazarse o moverse.

Q1. Do you think you might have gum disease? Yes/No

Q1. ¿Piensa usted que puede tener enfermedad en sus encías? Sí/No/No sabe/No contesta

Q2. Overall, how would you rate the health of your teeth and gums? Excellent/Very good/Good/Fair/Poor/Do not know/Refused

Q2. En general, ¿cómo considera que es el estado de salud de sus dientes y encías? Excelente/Muy bueno/Bueno/Regular/Malo/No sabe/No contesta

Q3. Have you ever had treatment for gum disease, such as scaling and root planing, sometimes called 'deep' cleaning? Yes/No/Do not know/Refused

Q3. ¿Alguna vez ha recibido tratamiento en las encías, tipo raspado y alisado radicular o 'curetaje' o 'limpiezas profundas'? Sí/No/No sabe/No contesta

Q4. Have you ever had any teeth become loose on their own, without an injuty? Yes/No/Do not know/Refused

Q4. ¿Alguna vez ha notado 'flojo' o que se le mueve algún diente, sin haber sufrido un traumatismo? Sí/No/No sabe/No contesta

Q5. Have you ever been told by a dental professional that you lost bone around your teeth? Yes/No/Do not know/Refused

Q5. ¿Alguna vez le ha dicho dentista que haya perdido hueso alrededor de los dientes, que tiene periodontitis o 'piorrea'? Sí/No/No sabe/No contesta

Q6. During the past 3 months have you noticed a tooth that does not look right? Yes/No/Do not know/Refused

Q6. ¿En los últimos tres meses, ha notado que alguno de sus dientes tenga algún problema? Sí/No/No sabe/No contesta

Q7. Aside from brushing your teeth with a toothbrush, in the last 7 days, how many times did you use dental floss or any other device to clean between your teeth?

_____ Number/Refused

Q7. ¿Aparte del cepillado de los dientes, cuántas veces ha usado la seda/hilo dental o algún otro medio o utensilio para limpiarse entre los dientes, en los últimos siete días?

_____ Número de veces/No contesta

Q8. Aside from brushing your teeth with a toothbrush, in the last 7 days, how many times did you use mouthwash or other dental rinse product that you use to treat dental disease or dental problems?

_____ Number/Refused

Q8. ¿Aparte del cepillado de los dientes, cuántas veces ha usado un enjuague o colutorio bucal, para el tratamiento de enfermedades o problemas bucodentales, en los últimos siete días?

_____ Número de veces/No contesta