Clinical Oral Investigations
https://doi.org/10.1007/s00784-019-02875-3

ORIGINAL ARTICLE

Prediabetes and diabetes prevalence in the Workers' Oral Health Study

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Received: 30 October 2018 / Accepted: 21 February 2019

Abstract

Objective To examine the association between periodontitis, diabetes, and prediabetes, assessed by fasting plasma glucose (FPG).

Materials and methods Workers' Oral Health Study is a cross-sectional survey conducted on a representative sample of the Spanish employed population including 5154 participants (59.5% men, aged 16–65). Examination of periodontal status assessed Community Periodontal Index (CPI) and clinical attachment levels (CAL). Biochemical determinations included fasting plasma glucose (FPG), triglycerides, and total cholesterol. Logistic regression analysis with adjustment for potential confounders was used to evaluate the association between periodontitis and abnormal glucose regulation.

Results Ninety-five participants (2.2%) of the study population had diabetes, while 373 (8.8%) presented prediabetes. Prediabetes was not associated with CPI or CAL in fully adjusted multivariate logistic regressions models. Diabetes was significantly associated with subjects having a CPI 4 after adjustment for potential confounders (odds ratio OR = 1.9, 95% confidence interval (CI) 1.1–3.1). This association was stronger in subjects < 45 years (OR = 4.0, 95% CI 1.2–12.7).

Conclusion Periodontitis was associated with diabetes mellitus, but not with prediabetes, in a representative sample of the Spanish employed population. The association was stronger for younger subjects, which emphasizes the need for early detection of diabetes in younger patients affected by periodontitis, particularly because periodontal therapy may help to improve glycemic control.

Clinical relevance Periodontitis is associated with diabetes mellitus, having at the same time a negative effect on glycemic control. It is important to develop proper early diagnosis strategies for both conditions, particularly in young male adults.

Keywords Periodontal diseases · Periodontitis · Prediabetes · Diabetes · Dental health surveys

Introduction

Prediabetes (either impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or A1c levels of 5.7–6.4%) is a condition currently relevant since there is evidence that it is a strong predictor for future development of diabetes [1, 2]. Data on fasting glucose levels from epidemiologic studies and surveys in 370 countries with approximately 2.7 million participants have reported a clear global trend towards increased glycemic levels since 1980 [3]. The International Diabetes Federation (IDF) in its 2017 Diabetes Atlas has projected that in 2045 the number of people with IGT, between 20 and 79 years, will increase to 587 million, or 8.3% of the adult population [4]. In Spain, according to the Di@bet.es study, almost 30% of the adult population has some carbohydrate disturbance, with an overall prevalence of diabetes mellitus of 13.8%, and with prevalence rates for IFG and IGT of 3.4% and 9.2% respectively [5]. The health implications of this increase are important since prediabetes itself is not only associated with diabetes development, but it has also been associated with higher frequency of cardiovascular, renal, or neurologic complications [2, 6, 7].

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Published online: 01 March 2019

Concomitantly, National Health and Nutrition Examination Survey (NHANES) 2009–2012 in the USA have reported an estimated 46% prevalence of periodontitis in adults 30 years or older, which represents 64.7 million subjects affected of this disease in the USA, with 8.9% being severe periodontitis [8]. Similarly, in Europe, it is estimated that around 50% of the adult population suffers from some form of periodontitis, with more than 10% affected by severe forms of the disease [9–11]. This high prevalence of the severe forms of the disease has been regarded as an important public health problem, not only for its oral implications (tooth loss and decreased masticatory function) but also for its effects on the social and quality of life of those affected [12, 13]. Moreover, severe periodontitis has been associated with different chronic systemic inflammatory diseases, such as diabetes. In fact, there is clear epidemiological evidence on the association between periodontitis and diabetes [14, 15] and on the negative effects of periodontitis on glycemic control [16]. Furthermore, some of the biological mechanisms by which periodontitis is a risk factor for the onset of diabetes, its metabolic control, and the advent of complications have been recently elucidated [17].

In spite of the clear association between severe periodontitis as a significant risk factor for the development of diabetes in previously non-diabetic subjects [18], the possible association between periodontitis and prediabetes or prediabetes states has not yet been elucidated. Although several cross-sectional studies have reported a significant association between periodontitis and prediabetes [19–22], others did not demonstrate this significance [23–26]. In the Study of Health in Pomerania (SHIP) [25], a significant association between periodontitis and edentulousness and poorly controlled type 2 diabetes mellitus was reported, but not with prediabetes or well-controlled diabetes.

The aim of this epidemiological investigation was to study the association between periodontitis and prediabetes in a representative sample of the Spanish employed population. This study was part of a wider survey, WORALTH (**W**orkers' Oral Health), studying the oral health status and oral health care needs of the Spanish adult employed population [11].

Material and methods

Study design

WORALTH Study is an oral epidemiological survey using the WHO criteria for oral health surveys [27] that was conducted on a representative sample of the Spanish employed population, from April 2008 to June 2011. The specific epidemiological methodology of this survey was detailed in the previous publication reporting the periodontal data [11]. In brief, workers were examined during their regulated annual health evaluation within the context of a broader epidemiological study of cardiovascular risk assessment comprising a structured interview, physical examination, and laboratory determinations (ICARIA, Ibermutuamur CArdiovascular RIsk Assessment) [28–31].

After applying a proportionate stratified random sampling method according to the geographical area, age, and gender of workers, 5130 subjects were included in the oral health examination, after excluding 47 subjects who refused to attend the oral examinations and 24 fully edentulous subjects (Fig. 1). The sample size of each stratum had been previously defined in relation with the Spanish Labour Force Survey, 2nd quarter [32], and the protocol had been reviewed and approved by Ibermutuamur Ethics Committee.

Socio-demographic and behavioral variables

These variables were obtained from the medical examination (age, gender, smoking status) and the questionnaire of oral health (country of origin, education and income levels, dental visits). Subjects were stratified in different categories according to the different variables:

- Age: under 25 years old, 25–34 years, 35–44 years, 45–54 years, and 55 years or older.
- Smoking habits: never, former (who quit at least 12 months ago), and current smokers.
- Country of origin: from Spain and "other countries".
- Occupation: white-collar (non-manual occupations) and blue-collar (manual occupations)
- Education level: low (primary school), medium (secondary school), or high (university).
- Income level (based on the net income of the family unit): ≤ 1200 euro/month, 1200–3600 euro/month, and > 3600 euro/month.
- Visits to the dentist: regular visits (at least once during the previous year) and irregular

General health conditions

Data from physical examinations included weight, height, waist circumference, and two measures of blood pressure. Body mass index (BMI) was calculated and stratified in three groups: obese (≥ 30 kg/m^2), overweight (25–29 kg/m^2), and normal (< 25 kg/m^2). Waist circumference (WC) was measured while the subject was standing, using the midpoint between the lowest rib and the iliac crest as a reference, and subjects were stratified in Normal (< 94 cm in males and < 80 cm in females), High (≥ 94 cm in males and ≥ 80 cm in females), and Very High (≥ 102 cm in males and ≥ 88 cm in females) [33].

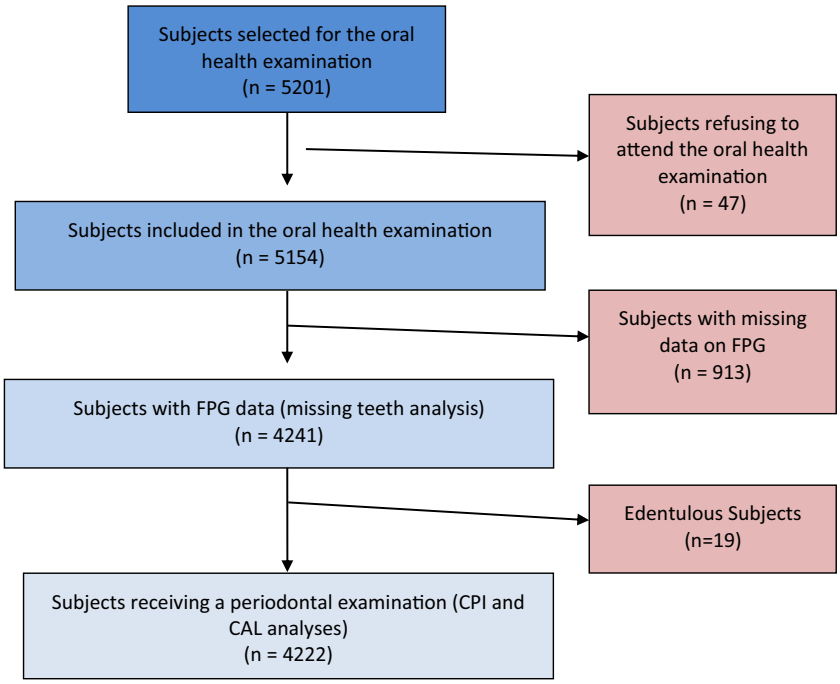

Fig. 1 Flow-chart of the subjects included/excluded in the WORALTH study and in the glycemic control analysis. FPG fasting plasma glucose, CPI Community Periodontal Index, CAL clinical attachment loss

Biochemical analysis

Analyses were carried out in reference laboratories using standard protocols and following Spanish Society of Clinical Biochemistry and Molecular Pathology's (SEQC) quality control recommendations. The variation coefficient for the main serum analyses was within the range accepted by the SEQC [34].

Subjects were advised to fast 12 h prior to the blood analysis. The biochemical determinations included fasting plasma glucose (FPG), triglycerides, total cholesterol, and high-density lipoprotein (HDL)-cholesterol. Low-density lipoprotein (LDL)-cholesterol was also calculated using Friedewald's equation [35].

According to the FPG, subjects were categorized into three groups [36]:

- Normal glucose level: FPG < 100 mg/dL (5.6 mmol/L)
- Prediabetes: FPG ≥ 100 but < 126 mg/dL (7.0 mmol/L)
- Diabetes: (i) FPG ≥ 126 mg/dL, (ii) were taking medication for diabetes, or (iii) they had a prior diagnosis of diabetes

Oral and periodontal examination

Following the WHO criteria [27], periodontal conditions were assessed by the Community Periodontal Index (CPI) and clinical attachment levels (CAL). The ten index teeth were assessed at three buccal sites (mesiobuccal, midbuccal, distobuccal) and three lingual sites (mesiolingual, midlingual, distolingual), and the highest value was recorded at each sextant. Training and calibration sessions were conducted by an experienced WHO epidemiologist, and crossed-examinations with gold standard were carried out to determine the degree of inter-examiner agreement. Calibration data was provided in the previous publication [11].

Data analysis

Participants were excluded from analyses in case of missing data on fasting plasma glucose ($n = 913$). The final analyses included 4241 participants, of which 4222 received a periodontal examination.

Descriptive statistics were calculated by categories of FPG (normal glucose level, prediabetes, and diabetes). Three sets of binomial logistic regression analyses were carried out with the following dependent variables: (i) subjects who had as highest code CPI 4, (ii) subjects with CAL ≥ 6 mm, and (iii) subjects with ≤ 15 missing teeth versus subjects with ≥ 16 missing teeth. The independent variable was glucose regulation (diabetes mellitus, prediabetes, and normal glucose regulation as the reference category). For each of the three sets of logistic regression analyses, three different models are presented as follows: (i) an unadjusted model; (ii) a model adjusted for age and sex; and (iii) a model adjusted for age, sex, occupation, education, smoking, BMI, waist circumference, triglycerides, total cholesterol, systolic/diastolic blood pressure, and frequency of dental attendance.

The analyses were carried out using STATA version 13.1 with SVY package (StataCorp, College Station, TX, USA).

Results

The sample consisted of 60.58% males with a mean age of 38.69 years (standard deviation (SD) 10.89). In Table 1, the characteristics of the participants were described according to the pre-established fasting glucose level categories. Ninety-five participants had diabetes (2.24%) and 373 IFG (8.80%). Unadjusted comparisons showed that age, gender (male), educational level, occupation (white collar/blue collar), smoking habit, BMI, waist circumference, triglycerides, total cholesterol, and systolic/diastolic blood pressure were associated with poorer glucose regulation.

Table 1 Characteristics of participants by categories of glucose regulation ($N = 4241$)

	n	Normal glucose level	Prediabetes	Diabetes	*p* value
n (%)	4241	3773 (89.0%)	373 (8.8%)	95 (2.2%)	
Gender					< 0.001
Male	2569	2200 (85.6%)	281 (10.9%)	88 (3.4%)	
Female	1672	1573 (94.1%)	92 (5.5%)	7 (0.4%)	
Age (years)					< 0.001
< 25	377	359 (95.2%)	18 (4.8%)	0 (0%)	
25–34	1339	1272 (95.0%)	62 (4.6%)	5 (0.4%)	
35–44	1239	1137 (91.8%)	89 (7.2%)	13 (1.1%)	
45–54	862	705 (81.8%)	120 (13.9%)	37 (4.3%)	
≥ 55	424	300 (70.8%)	84 (19.8%)	40 (9.4%)	
Occupation					< 0.001
White collar	2225	2028 (91.2%)	165 (7.5%)	32 (1.4%)	
Blue collar	2016	1745 (86.6%)	208 (10.3%)	63 (3.1%)	
Country of origin					0.065
Spain	3656	3252 (89.0%)	319 (8.7%)	85 (2.3%)	
Others	436	400 (91.7%)	30 (6.9%)	6 (1.4%)	
Education					< 0.001
Primary school	1041	868 (83.4%)	124 (11.9%)	49 (4.7%)	
Secondary school	1705	1543 (90.5%)	130 (7.6%)	32 (1.9%)	
University	1345	1245 (92.6%)	90 (6.7%)	10 (0.7%)	
Net income (monthly)					0.312
< 1200 €	1184	1055 (89.1%)	100 (8.5%)	29 (2.5%)	
1201–3600 €	2138	1919 (89.8%)	179 (8.4%)	40 (1.9%)	
> 3600€	436	396 (90.83%)	32 (7.34%)	8 (1.83%)	
Smoking Status					0.020
Non smoker	2017	1834 (90.9%)	157 (7.8%)	26 (1.3%)	
Former smoker	593	487 (82.1%)	77 (13.0%)	29 (4.9%)	
Smoker	1360	1208 (88.8%)	118 (8.7%)	34 (2.5%)	
BMI (kg/m^2)					< 0.001
Normal	1908	1803 (94.5%)	94 (4.9%)	11 (0.6%)	
Overweight	1617	1407 (87.0%)	168 (10.4%)	42 (2.6%)	
Obese	687	537 (78.2%)	109 (15.9%)	41 (6.0%)	
Waist circumference (cm)					< 0.001
Normal	2270	2102 (92.6%)	143 (6.3%)	25 (1.1%)	
High	996	885 (88.9%)	91 (9.1%)	20 (2.0%)	
Very high	975	786 (80.6%)	139 (14.3%)	50 (5.1%)	
Triglycerides (mg/dl)	4225	100.77 (69.92)	131.87 (124.63)	170.92 (114.87)	< 0.001
Total cholesterol (mg/dl)	4212	194.42 (37.40)	211.67 (38.64)	212.72 (41.49)	< 0.001
Systolic blood pressure (mmHg)	3943	119.31 (15.67)	131.09 (18.95)	139.01 (20.69)	< 0.001
Diastolic blood pressure (mmHg)	3943	74.39 (10.69)	70.63 (11.58)	83.18 (11.18)	< 0.001

BMI, body mass index

In Table 2, the associations between the subject's oral/periodontal condition and glucose control were depicted. Subjects with poorer glycemic control tended to present a greater extent of attachment loss and a higher value of CPI ($p < 0.01$). Also, the number of missing teeth or the frequency of dental attendance was associated with altered glucose metabolism ($p < 0.01$).

In unadjusted logistic regression models (Table 3, model 1), subjects with IFG or diabetes were significantly more likely to have a CAL ≥ 6 mm and a CPI 4. A lower number of teeth (≤ 12 teeth) also significantly correlated with abnormal glucose regulation. When using age-sex-adjusted models (model 2), these significant associations between periodontitis and prediabetes and diabetes expressed diminished odds ratios (ORs). In fact, prediabetes was not significantly associated with periodontal destruction, defined either by CAL or CPI. IFG was only significantly associated with presenting ≥ 16 missing teeth (OR = 1.91; 95% confidence interval (CI) 1.08–3.35). In fully adjusted models (model 3; adjusted for age, sex, occupation, education, smoking, BMI, waist circumference, triglycerides, total cholesterol, systolic/diastolic blood pressure, and frequency of dental attendance), the resulting ORs were further reduced for both prediabetes and diabetes. In fact, the association between diabetes and CAL ≥ 6 mm (OR = 0.95; 95% CI 0.52–1.72) and the presence of a lower number of teeth (OR = 1.57; 95% CI 0.62–3.97) was not significant. Only the association between diabetes and CPI 4 (OR = 1.86; 95% CI 1.13–3.07) remained statistically significant.

After stratifying by sex and age (Table 4) and adjusting for all potential confounders, subjects with CPI 4 were significantly more likely to have diabetes in the < 45 years group (OR = 3.97; 95% CI 1.24–12.68) than in the ≥ 45 years (OR = 1.69; 95% CI 0.99–2.90). In females, the presence of deep periodontal pockets (CPI 4) was not significantly associated with altered glucose levels. In males, the severity of periodontitis (CPI 4) increased in subjects with diabetes (OR = 1.88; 95% CI 1.12–3.16), but significant association was not found for IFG.

Discussion

In this epidemiological survey of the Spanish employed population (WORALTH), diabetes mellitus was significantly associated with severe periodontitis (CPI 4) (OR = 1.86; 95% CI 1.13–3.07). Conversely, the association between prediabetes (as defined by IFG) and periodontitis (assessed by CPI and CAL) was not statistically significant.

Although some studies have reported a significant association between periodontitis and prediabetes [19–22, 24], others did not demonstrate a significant association, such as the study of Health in Pomerania (SHIP) [25] using the

Table 2 Risk distribution for periodontal condition based on fasting glucose levels

	Periodontal condition											
	Maximum CPI			Maximum CAL			Missing teeth				Regular dental visit	
	($n = 4222$)			($n = 4222$)			($n = 4241$)				($n = 4054$)	
	Codes 0–2	Code 3	Code 4	0–3 mm	4–5 mm	≥ 6 mm	0	1–15	16–19	≥ 20	Yes	No
Normal glucose level[a]	2368 (62.95%)	1053 (27.99%)	341 (9.06%)	3043 (80.89%)	479 (12.73%)	240 (6.38%)	1578 (41.82%)	2141 (56.75%)	23 (0.61%)	31 (0.82%)	1907 (52.62%)	1717 (47.38%)
Prediabetes	253 (58.58%)	108 (29.43%)	44 (11.99%)	253 (68.94%)	108 (19.07%)	44 (11.99%)	103 (27.61%)	252 (67.56%)	8 (2.14%)	10 (2.68%)	164 (47.67%)	180 (52.33%)
Diabetes	30 (32.26%)	33 (35.48%)*	30 (32.26%)*	53 (56.99%)	22 (23.66%)*	18 (19.35%)*	13 (13.68%)	75 (78.95%)	1 (1.05%)	6 (6.32%)*	32 (37.21%)	54 (62.79%)*

CPI, Community Periodontal Index; *CAL*, clinical attachment level

[a] Reference category

*Statistically significant difference when comparing with the reference category ($p < 0.01$)

Table 3 Odds ratios (OR) and 95% confidence intervals (95% CI) for different measures of periodontitis and tooth loss by categories of glucose regulation

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
CPI code 4			
Diabetes mellitus	4.73 (3.02–7.42)	1.93 (1.20–3.09)	1.86 (1.13–3.07)
Prediabetes	1.40 (1.00–1.96)	0.79 (0.56–1.12)	0.78 (0.54–1.13)
Normal glucose regulation	1	1	1
CAL ≥ 6 mm			
Diabetes mellitus	3.53 (2.07–6.01)	1.13 (0.65–1.96)	0.95 (0.52–1.72)
Prediabetes	1.99 (1.41–2.80)	1.03 (0.71–1.47)	0.93 (0.63–1.38)
Normal glucose regulation	1	1	1
Missing teeth (≤ 15 vs ≥ 16)			
Diabetes mellitus	5.15 (2.27–11.67)	2.02 (0.87–4.69)	1.57 (0.62–3.97)
Prediabetes	3.43 (1.99–5.90)	1.91 (1.08–3.35)	1.81 (0.98–3.35)
Normal glucose regulation	1	1	1

OR, odds ratio; *CI*, confidence interval; *CPI*, Community Periodontal Index; *CAL*, clinical attachment level

Model 1: crude ORs, no adjustment

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, occupation, education, smoking, BMI, waist circumference, triglycerides, total cholesterol, and systolic/diastolic blood pressure

European Workshop in Periodontitis case definition [37] and other measures of periodontitis (mean probing pocket depth (PPD) and percentage of sites with CAL ≥ 4 mm). Also, in agreement with the results from this investigation, Noack et al. [23] in a cohort of 100 patients in Germany did not find significant differences between the periodontal condition of subjects with IGT and normal metabolic status.

Other cross-sectional and nationally representative surveys, such as the National Health and Nutrition Examination Survey (NHANES) in the USA or the KNHANES in South Korea depicted inconclusive results. While data from NHANES III (1988–1994) positively correlated IFG with periodontitis measured by CAL and PPD [20], more recent data derived from NHANES 2009–2010 and NHANES 2009–2012 failed to prove that periodontitis, as defined by the Center for Disease Control/American Academy of Periodontology (CDC/AAP) case definitions [38], was more likely in people with IFG [24, 26]. On the contrary, data from KNHANES 2012–2013 identified IFG as a risk indicator of periodontitis (defined by a CPI ≥ 3), although just in its higher range (111–125 mg/dl) [22]. Recently, a subgroup analysis of a multi-center randomized controlled trial suggested that non-surgical periodontal treatment may reduce HbA1c among people with prediabetes [39]. However, other studies evaluating the effect of scaling and root planing on the glycemic control of patients with prediabetes reported inconsistent results [40, 41].

The present study demonstrated a significant association between diabetes and periodontal condition (CPI 4), which is in accordance with most of the published studies reporting a significantly higher prevalence of severe periodontitis in people with diabetes [42, 43]. Specifically, approximately 30% of people with diabetes had severe forms of periodontitis [26]. Other studies also using CPI have reported similar results, with subjects with diabetes being approximately 1.5-fold more likely to suffer from severe periodontitis, after the adjusted logistic regression analysis [22]. Other studies have evaluated the effect of glycemic control on the odds for having periodontitis, with most of these studies reporting significant associations between periodontitis and diabetes only in people with uncontrolled diabetes [25, 26, 44]. In the present study, it was not possible to evaluate the effect of glycemic control as A1c data was not available, and single FPG measurements are

Table 4 Sex and age-stratified Odds Ratios (ORs) and 95% confidence intervals (95% CI) for subjects with Community Periodontal Index (CPI) code 4 by categories of glucose regulation

	Subjects with CPI = 4 OR (95%CI)	
	Prediabetes	Diabetes
Sex		
Female	1.04 (0.45–2.40)	1.24 (0.13–11.61)
Male	0.74 (0.49–1.11)	1.88 (1.12–3.16)
Age		
< 45 years	0.68 (0.29–1.59)	3.97 (1.24–12.68)
≥ 45 years	0.80 (0.53–1.22)	1.69 (0.99–2.90)

Logistic regressions were adjusted for age, sex, occupation, education, smoking, body mass index (BMI), waist circumference, triglycerides, total cholesterol, and systolic/diastolic blood pressure. Normal Glucose Level served as reference category (OR = 1.00)

not adequate to evaluate the metabolic control in diabetes patients.

The strength of the associations between periodontal condition and diabetes also varied among the published studies. In the present investigation, the reported degree was weak (after adjusting for confounders, there was a significant association for CPI, but not for mean CAL or lower number of teeth). This may be due to the low prevalence of diabetes in this sample (2.24%), lower than the prevalence reported in other population-based studies, such as NHANES 2009–2012 in the USA (12.6%) or SHIP-Trend in Germany (11.8%) [25, 26]. The present study is restricted to the employed population, with a mean age (38.8 years) and range (16–65 years) relatively young, which may account for this low prevalence of diabetes, since this disease prevalence significantly increases with age. Indeed, diabetes prevalence in the entire Spanish population is sixfold higher than the one presented in this sample comprising just a working population.

Another possible explanation for the absence of an association between periodontitis and CAL or lower number of teeth underlies on the biological plausibility of the relationship. Both the direct (bacteremia) and indirect (pro-inflammatory cytokines) mechanisms proposed require the presence of an ulcerated pocket epithelium. While CPI is related with the probing pocket depth component, mean CAL and the number of missing teeth could represent gingival recession or past disease, without any impact on the periodontal inflamed surface area (PISA) [45].

This study has also reported differences by sex and age, with periodontitis being significantly associated with diabetes in men, but not in women. Again, these results may have been influenced by the low number of cases of females with diabetes. Similar findings have been reported in NHANES 2009–2012 [26]. Also, when different phenotypes of periodontitis have been proposed based on gingival tissue transcriptomic data, gender was an important independent risk factor for the extent and severity of periodontitis [46]. In terms of age, this study reported a stronger association between diabetes and CPI 4 in adults < 45 years, which may imply a higher aggressiveness of the chronic inflammation secondary to periodontitis or diabetes.

The present study is not free of limitations. The study design is cross-sectional and, therefore, does not allow for a causal or temporal relationship. The included population was limited to employed subjects and did not include older adults, which may reflect the quite low diabetes prevalence in the study. What is more, a single fasting glucose test was performed, while current standards for the diagnosis of diabetes mellitus advise for repeated testing in absence of unequivocal hyperglycemia [36]. As discussed previously, one limitation of this study could emanate from the partial recording protocol used [11]. CPI is not the gold standard in periodontal epidemiology and has several limitations, although this method is highly sensitive for prevalence estimates in presence of 4–6 mm probing pocket levels (≥ 90%) [47].

The major strength of the study was the large, representative sample of the Spanish employed population since periodontal and FPG data were available from 4222 subjects.

In conclusion, this epidemiological survey has found a significant association between severe periodontitis (CPI 4) and diabetes mellitus, especially in men and younger adults (< 45 years). Conversely, there was no significant association between the periodontal health status and prediabetes (assessed by IFG). The present findings highlight the importance of providing oral health education as well as regular periodontal examinations to patients with diabetes. These recommendations are in agreement with the guidelines proposed in the recent workshop on periodontal diseases and diabetes organized by the International Diabetes Federation (IDF) and the European Federation of Periodontology [48].

Funding This study was supported by *Cualtis*, previously named *Sociedad de Prevención de Ibermutuamur,* a company that focuses specifically on preventing diseases and accidents, by monitoring and promoting workers' health. The authors were fully independent in preparing the protocol, conducting the research, interpreting the results and preparing the manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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