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Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys

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Abstract. Muñoz Aguilera E, Leira Y, Miró Catalina Q, Orlandi M, Czesnikiewicz-Guzik M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F (UCL Eastman Dental Institute and Hospital, University College London, London, UK; Universitat Internacional de Catalunya, Barcelona; University of Santiago de Compostela & Medical-Surgical Dentistry (OMEQUI) Research Group, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela; Universitat Internacional de Catalunya, Barcelona, Spain; University of Glasgow Dental School, Glasgow, UK; Jagiellonian University, Krakow, Poland; University of Glasgow, Glasgow, UK; Jagiellonian University, Krakow, Poland; University College London, London, UK). Is systemic inflammation a missing link between periodontitis and hypertension? Results from two large population-based surveys. *J Intern Med* 2021; **289**: 532–546. https://doi.org/10.1111/joim.13180

Objective. The primary objective was to investigate the relationship between periodontitis and hypertension in two independent large surveys. The secondary objective was to ascertain whether systemic inflammation had a mediation effect in the association.

Methods. This cross-sectional study analysed representative samples of the US (n = 3460; NHANES 2009/10) and Korean (n = 4539; 2015 KNHANES VI-3) populations. The association between periodontitis (exposure), hypertension (outcome) and inflammatory markers [C-reactive protein (CRP) and white blood cell counts (WBC)] (mediators) was assessed using multivariate linear and logistic regression models and mediation analysis.

Results. Participants with periodontitis were more likely to have hypertension (NHANES: OR = 1.3, 95% CI: 1.0–1.6, P = 0.025; KNHANES: OR = 1.2, 95% CI: 1.0–1.4, P = 0.041) and actual systolic blood pressure ≥ 140 mmHg (NHANES: OR = 1.6, 95% CI: 1.1–2.3, P < 0.001; KNHANES: OR = 1.3, 95% CI : 1.0–1.6, P < 0.031) than those without the disease. These associations were independent of age, gender, BMI, education level, smoking, alcohol consumption, creatinine, physical activity, presence of other comorbidities and confirmed in participants not taking antihypertensive medications. Diagnosis of periodontitis was directly associated with WBC (in both surveys: NHANES: $\beta \pm SE = 0.3 \pm 0.1$, $P < 0.004$; KNHANES: $\beta \pm SE = 0.3 \pm 0.1$, $P < 0.001$) and with CRP levels (in one survey: NHANES: $\beta \pm SE = 0.1 \pm 0.03$, $P < 0.007$; KNHANES: $\beta \pm SE = 0.1 \pm 0.04$, $P > 0.213$). Mediation analyses confirmed that CRP acted as a mediator in the association between periodontitis and hypertension in both populations (mediated effect: NHANES: $\beta \pm SE = 0.010 \pm 0.003$, $P < 0.001$; KNHANES: $\beta \pm SE = 0.003 \pm 0.001$, $P = 0.015$). WBC acted as a mediator in the KNHANES (mediated effect: $\beta \pm SE = 0.004 \pm 0.001$, $P = 0.004$) whilst in the NHANES, its effect was dependent of CRP inclusion in the model (mediated effect WBC + CRP: $\beta \pm SE = 0.002 \pm 0.001$, $P = 0.001$).

Conclusions. These findings suggest that periodontitis is closely linked to hypertension and systemic inflammation is, in part, a mediator of this association.

Keywords: CRP, high blood pressure, hypertension, leucocytes, periodontitis, systemic inflammation.

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What is already known about this subject?

Consistent evidence suggests a direct relationship between periodontitis and hypertension. Poor oral health is linked to greater systemic inflammation and increased odds of hypertension. A linear association between systolic blood pressure and various oral health indices confirm these findings.

What does this study add?

Periodontitis increases the odds of hypertension by 20-60% in two large populations and systemic inflammation as assessed by peripheral levels of CRP and WBC acts as a biological mediator of this association.

How might this impact on clinical practice?

Oral health promotion could result in reduced systemic inflammation and it may represent a novel nonpharmacological intervention in hypertension management and its complications.

Introduction

Hypertension is a complex multifactorial disorder. Its prevalence exceeds 31% worldwide with more than 1.13 billion people affected [1]. Elevated blood pressure (BP) is strongly linked to cardiovascular complications, increasing morbidity and mortality [2]. Experimental and observational evidence supports a prominent role of systemic inflammation both in the initiation and in the progression of hypertension [3]. The management of this condition, however, is still a challenge and it represents an increasing burden for society.

Periodontitis is one of the most common inflammatory disorders worldwide with >46% of adults in the United States diagnosed with the disease [4]. Strong evidence supports the role of a dysbiotic dental biofilm in the development of periodontitis. Further, a cluster of modifiable risk factors is shared between periodontitis and leading noncommunicable diseases (NCDs) (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes) [5].

Patients with periodontitis exhibit not only gingival inflammation but also endothelial dysfunction, increased bacterial burden (endotoxins and exotoxins dissemination), metabolic dysregulation and systemic inflammation [6-9]. A bidirectional link has been proposed between periodontitis and other metabolic disorders such as metabolic syndrome and diabetes [10, 11].

Hypertension has been linked to periodontitis but evidence from intervention trials is limited [12]. A possible causal relationship between these two conditions has been proposed recently using Mendelian randomization. This analysis confirmed a link between genetic variants linked to periodontitis and elevated BP phenotypes in a large UK population study [13]. The exact mechanisms mediating this association remain unknown raising the question of whether inflammation or bacterial burden could play a prominent role. Given that systemic inflammatory biomarkers such as C-reactive protein (CRP) and leucocyte counts have been correlated with both periodontitis and hypertension, we hypothesized that systemic inflammation could be a mediator between the two diseases. Therefore, confirmation of this association in large independent studies with a focus on mediators needs to be unravelled prior to undertaking interventional trials investigating the treatment of periodontitis as a target nonpharmacological treatment for hypertension. Accordingly, the primary aim of this study was to investigate the association between periodontitis and hypertension using two representative surveys of the US and Korean populations. The secondary aim was to ascertain the role of systemic inflammation in mediating this association.

Material and methods

Two population-based surveys were analysed and hereby reported in compliance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Supplemental checklist).

Survey designs and study populations

Databases obtained from the US [2009/2010 National Health And Nutrition Examination Survey (NHANES)] and Korean [2015 VI-3 Korean National Health And Nutrition Examination Survey (KNHANES)] open repositories shared similar study design (stratified, multistage cluster probability sampling survey) [14, 15], and they were conducted by the statistical division of the National Centers for Disease Control and Prevention in the United States and Korea, respectively. The study

was conducted in accordance with the 1975 Declaration of Helsinki and participants provided written consent. These survey waves were selected for this study as were the first ones containing a detailed periodontal examination, measurements of average BP, serum concentrations of high-sensitivity CRP (hs-CRP) and white blood cell counts (WBC).

Exclusion criteria used in the final sample analysis were (i) age < 30 years in the NHANES ($N = 6451$) and age < 19 years in the KNHANES ($N = 1345$) as no periodontal data were collected for younger individuals; (ii) pregnancy (NHANES, $N = 23$; KNHANES, $N = 29$); (iii) lack of data on hs-CRP (NHANES, $N = 137$; KNHANES, $N = 243$); (iv) lack of data on BP (NHANES, $N = 123$; KNHANES, $N = 29$); and (v) lack of periodontal data for any other reasons (NHANES, $N = 343$, KNHANES, $N = 792$). From a total of 10 537 participants in the NHANES 2009/2010 and 6977 in the KNHANES VI-3, the final samples included in this analysis were of 3460 and 4539 participants, respectively. These populations refer to a representative sample of just over 128 millions of US and 33 millions of Korean citizens.

We extracted data on socio-demographic, healthy lifestyle behavioural factors, anthropometric measurements, medical history, oral examination, mean BP and biochemical parameters (Table S1).

Blood pressure measurements

In both cross-sectional studies, sitting BP was measured using a standardized protocol [16]. Average measurements of systolic and diastolic arterial pressure (SBP and DBP) were obtained from three consecutive readings. Participants were then categorized as normal, prehypertensive and hypertensive according to the Joint National Committee 7 guidelines [17]. Further, hypertension was defined as values of SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg or the use of antihypertensive medication [18]. The number of participants taking antihypertensive medications was also calculated.

Periodontal examination and dental exposure variables

The analysis was conducted using both established case definitions and continuous measures (full-mouth indices) of periodontitis. However, different protocols were used. In the NHANES, a full-mouth periodontal assessment was carried out at six sites per tooth and periodontitis (exposure) was defined as mild, moderate or severe [19]. Continuous aggregate dental variables (number and percentage of sites) were then created to indicate (a) the extent of periodontal lesions with probing pocket depths (PPD) of $\geq$4 mm, $\geq$5 mm, $\geq$6 mm and (b) the extent of loss of periodontal tissue attachment (AL) of $\geq$3 mm, $\geq$4 mm, $\geq$5 mm, $\geq$6 mm as previously described [20].

In the KNHANES study, participants presenting with community periodontal index (CPI) scores of 3 and 4 (at least in one sextant) were defined as having worse periodontal status, whereas those presenting scores of 0, 1 and 2 represented controls with better periodontal status. Continuous measures of periodontal lesions were then created as follows: (a) CPI cumulative score (the sum of only CPI scores of 3 or 4 of all sextants) and (b) CPI continuous score (sum of all CPI scores of all sextants) as previously described [21].

Laboratory analysis

Biochemical parameters were retrieved from both surveys including plasma glucose (mg dL^{-1}), insulin levels (uIU mL^{-1}), glycated haemoglobin [HbA1c (%)], total cholesterol (mg dL^{-1}), high- and low-density lipoprotein cholesterol levels [HDL and LDL (mg dL^{-1})], triglyceride levels (mg dL^{-1}), creatinine (mg dL^{-1}), hs-CRP (mg dL^{-1}) and WBCs (thous μL^{-1})].

Statistical analysis

Data analyses were performed with STATA version 15.0 (StataCorp, College Station, Tex, USA) and R Software (version 3.5.2). Continuous variables are reported as mean $\pm$ standard error (SE), whereas categorical variables are expressed as percentages. Simple differences between participants with or without periodontitis were assessed by independent t-test (for continuous variables) or chi-square test (for categorical variables). Normality assumptions were checked, and a logarithmic transformation of hs-CRP was used for parametric analyses. Different measures of oral disease exposure (categorical and continuous) were adopted to test the association between periodontal status and BP. Further, circulating levels of WBC and hs-CRP were used as biomarkers of systemic inflammation and possible mediators of the association between periodontal status and hypertension. Univariate analyses were performed for all continuous

variables comparing the groups of participants with periodontitis/worse periodontal status and the rest of the study sample. All those variables with statistically significant associations were then used in the multivariate models.

Multivariate logistic regression models were created to test potential associations between periodontitis case definitions or continuous measures of periodontal lesions with hypertension, SBP ≥ 140 mmHg or hs-CRP > 2mg L^{-1} as outcome variables. Multivariate linear regression models were then constructed to investigate the association between periodontal (both categorical and continuous) and arterial BP (mean SBP/DBP) variables. Similar analyses were performed with hs-CRP and WBC values (exposures) and hypertension (as categorical or continuous outcomes). Odds ratios (ORs) and 95% confidence intervals (CI) were calculated as well as β coefficient with standard errors. A fully adjusted model (Model 1) included age, gender, ethnicity, smoking, education level and chronic medical conditions as covariates (as previously reported) in both surveys [18]. In addition to these, body mass index (BMI), alcohol consumption, creatinine and physical activity were included in the multivariable models of the KNHANES survey (as they all presented univariate association with the outcome variables).

Sensitivity analyses in the subgroup of participants not taking antihypertensive medications were also performed (Model 2) (NHANES, $N = 2486$; KNHANES, $N = 3270$).

Structural equation modelling (SEM) was then used to estimate whether the association between periodontitis and hypertension was mediated by WBC or CRP using R Software [22]. Four different and prespecified routes were used as follows: direct (route 1) and indirect (route 2, 3, 4) mediation effects with their 95% CI were estimated:

Route 1: Periodontitis (exposure) → Hypertension (outcome).

Route 2: Periodontitis (exposure) → WBC (mediator) → Hypertension (outcome).

Route 3: Periodontitis (exposure) → Log CRP (mediator) → Hypertension (outcome).

Route 4: Periodontitis (exposure) → WBC (mediator) → Log CRP (mediator) → Hypertension (outcome).

Results

Characteristics of study populations

Participants with periodontitis were predominantly men (NHANES, 60%; KNHANES, 57%), older than 50 years of age, increased number of current smokers (NHANES, 52% vs 36%; KNHANES, 23% vs 15%), of lower education background and higher prevalence of diabetes (NHANES, 12% vs 6%; KNHANES, 10% vs 5%) than participants without periodontitis (Table 1). Almost a doubled prevalence of hypertension (NHANES, 42% vs 25%; KNHANES, 39% vs 19%) and antihypertensive medication (NHANES, 31% vs 19%; KNHANES, 25% vs 12%) were observed in patients with periodontitis. Similarly, participants with periodontitis had higher values of SBP (6.4 mmHg higher in NHANES and 7.3 mmHg higher in KNHANES) than survey participants without periodontitis. In the NHANES survey, Mexican and non-Hispanic black presented with the greatest prevalence of periodontitis. Lastly, when other traditional cardiovascular risk factors were assessed, patients with periodontitis exhibited greater values of glucose, triglycerides, hs-CRP and WBC in both surveys when compared to those without periodontitis, with BMI being higher in periodontitis patients only in KNHANES (all $P < 0.001$).

Logistic regression analyses

Multiple logistic regression models confirmed that amongst participants with periodontitis and worse periodontal status, the adjusted odds of hypertension were 1.3 (95%CI 1.0–1.6) in the NHANES and 1.2 (95%CI 1.0–1.4) in the KNHANES populations, respectively (Table 2). Greater odds of hypertension in patients with periodontitis and worse periodontal status (CPI 3-4) were observed in the subgroup of participants not taking antihypertensive medications (NHANES: OR = 1.4, 95%CI 1.0–1.8, $N = 2486$; KNHANES: OR = 1.3, 95%CI 0.9–1.7, $N = 3270$). Similar associations were found between diagnosis of periodontitis and worse periodontal status (CPI 3-4) and SBP ≥ 140 values in both populations (NHANES: OR = 1.6, 95%CI 1.2–2.1; KNHANES: OR = 1.3, 95%CI 1.0–1.6) with greater odds in participants with more severe periodontitis. These findings were consistent in those participants not taking antihypertensive medications (Model 2) although the estimates were smaller than those observed in the whole sample

Table 1. *Baseline characteristics of Survey participants according to Periodontal variables*

	NHANES (2009–2010)				KNHANES VI-3 (2015)			
Variables	Overall (3460)	No-Periodontitis (1799)	Periodontitis (1661)	*P*	Overall (4539)	CPI 0-2 (2996)	CPI 3-4 (1543)	*P*
Categorical % (No.)								
Gender (% female)	49 (1695)	59 (1061)	40 (664)	**<0.0001**	43 (1952)	53 (1588)	43 (664)	**<0.0001**
Smoking	43 (1488)	36 (648)	52 (864)	**<0.0001**	17 (772)	15 (449)	23 (355)	**<0.0001**
Alcohol use	28 (969)	28 (504)	29 (482)	0.5891	25 (1335)	26 (779)	22 (339)	**0.002**
Education level				**<0.0001**				**<0.0001**
School grade	6 (208)	3 (54)	9 (150)		15 (681)	11 (330)	23 (355)	
Primary school graduate	11 (380)	8 (144)	15 (249)		9 (409)	7 (210)	14 (216)	
High school graduate	22 (761)	20 (340)	24 (399)		37 (1679)	38 (1138)	35 (540)	
College or higher	60 (2076)	69 (1241)	51 (847)		39 (1770)	44 (1318)	28 (432)	
Ethnicity				**0.0021**				
Mexican American	8 (277)	5 (90)	11 (183)					
Other Hispanics	5 (175)	5 (90)	5 (83)					
Non-Hispanics white	71 (2457)	77 (1385)	64(1063)					
Non-Hispanic black	10 (346)	8 (144)	13 (216)					
Other	6 (208)	5 (90)	7 (116)					
Diabetes	9 (311)	6 (108)	12 (199)	**0.0004**	6 (272)	5 (150)	10 (154)	**<0.00001**
Hypertension	33 (1142)	25 (450)	42 (698)	**<0.0001**	25 (1135)	19 (569)	39 (602)	**<0.0001**
Normal BP	40 (1384)	48 (864)	31 (515)		51 (2315)	56 (1678)	38 (586)	
Prehypertension	27 (934)	27 (486)	28 (465)		24 (1089)	25 (749)	23 (355)	
Antihypertension medication	25 (865)	19 (342)	31 (515)	**<0.0001**	16 (726)	12 (360)	25 (386)	**<0.0001**
Mean SBP ≥ 140 mmHg	13 (450)	8 (144)	18 (299)	**<0.0001**	9 (409)	7 (210)	15 (231)	**<0.0001**
Chronic medical conditions	52 (1799)	48 (864)	56 (930)	**0.0021**	6 (272)	5 (150)	9 (139)	**<0.0001**

Table 1 (*Continued*)

Variables	NHANES (2009–2010) Overall (3460)	No-Periodontitis (1799)	Periodontitis (1661)	*P*	KNHANES VI-3 (2015) Overall (4539)	CPI 0-2 (2996)	CPI 3-4 (1543)	*P*
Continuous (mean ± SE)								
Age (years)	51 ± 0.4	47 ± 0.4	55 ± 0.5	**<0.0001**	45.9 ± 0.4	42.3 ± 0.4	54.2 ± 0.6	**<0.0001**
BMI (kg m^{-2})	29 ± 0.1	28.8 ± 0.2	29.3 ± 0.2	0.067	23.9 ± 0.1	23.6 ± 0.1	24.6 ± 0.1	**<0.0001**
SBP (mmHg)	121.6 ± 0.5	118.5 ± 0.4	124.9 ± 0.5	**<0.0001**	117.1 ± 0.3	114.9 ± 0.3	122.2 ± 0.6	**<0.0001**
DBP (mmHg)	71.0 ± 0.6	71.4 ± 0.6	70.6 ± 0.7	**0.043**	75.5 ± 0.2	74.7 ± 0.3	77.2 ± 0.3	**<0.0001**
Physical activity[a]	3.4 ± 0.1	3.3 ± 0.1	3.5 ± 0.1	0.182	7.6 ± 0.03	7.6 ± 0.03	7.7 ± 0.04	**0.015**
Glucose (mg dL^{-1}) (NHANES: $N = 1690$)	104.2 ± 0.9	102.4 ± 1.4	108.2 ± 1.0	**<0.001**	99.6 ± 0.5	96.5 ± 0.4	106.8 ± 1.0	**<0.0001**
Insulin (uIU mL^{-1})	13.5 ± 0.3	12.8 ± 0.4	14.3 ± 0.5	**0.028**	8.5 ± 0.1	8.3 ± 0.2	8.8 ± 0.3	0.181
HbA1C (%)	5.7 ± 0.01	5.6 ± 0.01	5.8 ± 0.01	**<0.0001**	5.6 ± 0.02	5.5 ± 0.1	5.8 ± 0.1	**<0.0001**
Total cholesterol (mg dL^{-1})	201.7 ± 1.2	202.4 ± 1.3	200.9 ± 1.4	0.292	189.8 ± 0.6	188.3 ± 0.7	193.3 ± 1.1	**<0.0001**
HDL (mg dL^{-1})	53.3 ± 0.5	54.9 ± 0.6	51.6 ± 0.6	**<0.0001**	51.2 ± 0.2	54.5 ± 0.3	48.3 ± 0.4	**<0.0001**
LDL (mg dL^{-1}) (NHANES: $N = 1654$)	119.8 ± 1.1	119.7 ± 1.6	120.0 ± 1.1	0.895	113.4 ± 0.6	112.3 ± 0.6	115.8 ± 1.0	**0.003**
Triglycerides (mg dL^{-1}) (NHANES: $N = 1683$)	129.5 ± 2.3	120.7 ± 3.6	138.9 ± 3.1	**<0.0001**	138.8 ± 2.4	127.7 ± 2.6	164.7 ± 4.6	**0.0001**
Hs-CRP(mg L^{-1})	1.7 ± 1.01	1.5 ± 1.11	1.8 ± 1.01	**<0.0001**	1.2 ± 0.04	1.1 ± 0.04	1.3 ± 0.07	**0.005**
WBC (thous μL^{-1})	7.0 ± 0.04	6.9 ± 0.1	7.1 ± 0.1	**0.004**	6.5 ± 0.03	6.4 ± 0.03	6.8 ± 0.1	**<0.0001**
Creatinine[b]	118.5 ± 1.2	120.2 ± 1.9	116.7 ± 1.4	**0.113**	0.85 ± 0.01	0.8 ± 0.01	0.9 ± 0.02	**0.031**

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HbA1c, glycohaemoglobin A1c; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; KNHANES, Korea National Health and Nutrition Examination Survey; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; WBC, white blood cell counts. Bold values highlighting statistically significant results (i.e. $P < 0.05$).

[a]Physical activity *(NHANES = days/week); (KNHANES = days/month).

[b]Creatinine *(NHANES: Urine (μmol L^{-1}); KNHANES: serum mg dL^{-1}.

Table 2. *Multiple logistic regression models of hypertension and SBP ≥ 140 mmHg according to periodontal variables or systemic inflammation (hs-CRP/ WBC levels)*

		Hypertension		SBP ≥ 140 mmHg	
Survey	Exposure: Periodontal variables	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
NHANES	Periodontitis	**1.3 (1.0–1.6)***	**1.4 (1.0–1.8)***	**1.6 (1.2–2.1)****	**1.6 (1.1–2.3)***
	Mild	1.4 (0.8–2.2)	1.1 (0.5–2.6)	1.1 (0.6–2.0)	1.1 (0.4–2.8)
	Moderate	1.2 (1.0–1.6)	1.4 (1.0–2.0)	**1.5 (1.1–2.0)***	**1.6 (1.0–2.4)***
	Severe	1.3 (0.9–1.7)	**1.6 (1.2–2.4)****	**2.5 (1.7–3.6)*****	**2.3 (1.4–3.6)****
KNHANES	CPI 3–4 vs CPI 0–2	**1.2 (1.0–1.4)***	1.3 (0.9–1.7)	**1.3 (1.0–1.6)***	**1.4 (1.0–1.9)***
	CPI continuous	1.03 (0.9–1.1)	1.1 (0.9–1.2)	**1.1 (1.0–1.2)***	**1.1 (1.0–1.2)***
	CPI cumulative	0.9 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)
	Exposure: Systemic inflammation				
NHANES	Hs-CRP (log)	**1.4 (1.3–1.5)*****	**1.3 (1.1–1.4)****	**1.2 (1.1–1.3)****	1.2 (1.0–1.4)
	WBC	**1.1 (1.0–1.1)****	1.1 (1.0–1.2)	1.0 (1.0–1.1)	1.0 (0.9–1.1)
KNHANES	Hs-CRP (log)	1.1 (1.0–1.2)	1.1 (0.9–1.3)	1.1 (0.9–1.2)	1.0 (0.9–1.2)
	WBC	**1.1 (1.02–1.1)****	**1.1 (1.01–1.2)***	1.0(1.0–1.1)	1.0 (0.9–1.1)

CI, confidence interval; CPI, Community Periodontal Index; Hs-CRP, high-sensitivity c-reactive protein (logarithm); KNHANES, Korea National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SBP, systolic blood pressure; WBC, white blood cell counts.
Model 1 (population sample: 3460 NHANES; 4539 KNHANES): (NHANES): Age, gender, ethnicity, smoking, education level, chronic medical condition; (KNHANES): age, gender, BMI, education level, smoking, diabetes, alcohol consumption, creatinine, physical activity, chronic medical conditions.
Model 2 (population sample: 2486 NHANES; 3270 KNHANES): Not taking antihypertensive medication.
Bold values highlighting statistically significant results.
***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

(Table 2). Indeed, NHANES participants with severe periodontitis also presented with more than twice increased likelihood of SBP ≥ 140 mmHg in model 1 (OR = 2.5 95%CI 1.7–3.6) and model 2 (OR = 2.3 95%CI 1.4–3.6), respectively (Table 2).

When hs-CRP or WBC was introduced as independent exposure variables, the odds of hypertension and SBP ≥ 140 mmHg ranged from 1.0 to 1.4 in the US and from 1.0 to 1.1 in the Korean survey. Only some continuous measurements of periodontitis (mean PPD and mean CAL) were associated with greater odds of hypertension, SBP ≥ 140 mmHg and of hs-CRP ≥ 2 mg L^{-1} in the fully adjusted model and in those participants not taking antihypertensive medications (Figure 1).

Linear regression analyses

Linear regression analyses confirmed that periodontitis (assessed both as categorical and as continuous variables) was associated with mean SBP. These findings were confirmed in the subgroup of participants not taking antihypertensive medications in the US survey (Table 3). In the Korean survey, the cumulative CPI score was consistently associated with SBP and DBP and this was also confirmed in participants not taking BP medications. Higher WBC counts were associated with mean SBP in both surveys, whilst higher hs-CRP levels were associated with SBP and DBP only in the US study (Table 3). Further, we observed a negative association between DBP and the number or percentage of gingival sites with attachment loss of ≥3 mm and of sites with probing depth ≥ 6 mm in the NHANES (model 2) and with the cumulative CPI score in the KNANES (models 1 and 2) (Table 3). Lastly, both US and Korean participants with severe periodontitis or worse periodontal status (CPI 3-4) exhibited greater systemic inflammation as assessed by hs-CRP serum levels and by WBC when compared to those without periodontitis or better periodontal status (CPI 0-2) and this difference was independent of other common confounders (Table 4).

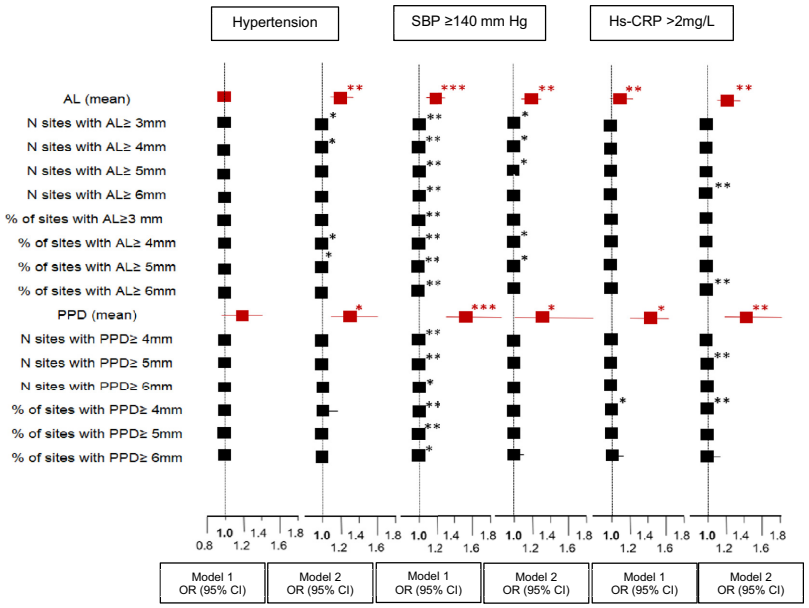

Fig. 1 *Multiple logistic regression model of hypertension, SBP ≥ 140 mmHg and hs-CRP > 2 mg L^{-1} according to continuous periodontal variables (NHANES database only). NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; hs-CRP, high-sensitivity C-reactive protein (logarithm); N, number; AL, attachment level; PPD, probing pocket depth. Model 1 (population sample: 3460 NHANES): Age, gender, ethnicity, smoking, education level, chronic medical condition. Model 2 (population sample: 2486 NHANES): Not taking antihypertensive medication.* ***P < *0.001;* **P < *0.01;* *P < *0.05.*

Mediation analyses

The association between periodontitis and hypertension (categorical) was mediated by CRP (β ± SE = 0.010 ± 0.003; $P < 0.001$) in the NHANES dataset, whilst WBC (β ± SE = 0.001 ± 0.001; $P = 0.221$) was only an indirect mediator of the association (indirect route linked to hs-CRP) (Model A, unadjusted) (Fig. 2a and Table S2). When repeating the same analysis in the KNHANES database, both hs-CRP (β ± SE = 0.003 ± 0.001; $P = 0.015$) and WBC (β ± SE = 0.004 ± 0.001; $P = 0.004$) acted as mediators of the association between worse periodontal status and hypertension (Fig. 2b and Table S2). Models B, D, C replicated these results when the analyses applied for continuous periodontal (PPD, CAL in NHANES and CPI continuous in KNANES) and BP (SBP) variables, in both adjusted and unadjusted models (Table S2).

Discussion

The analysis of two of the largest population surveys with available dental and general health data demonstrated that both categorical and continuous measures of periodontitis were consistently associated with hypertension and SBP independent of other common cardiovascular risk factors. Participants in the United States with severe periodontitis had higher odds for SBP ≥ 140 mmHg when compared to participants without periodontitis and all findings were confirmed in participants not taking antihypertensive medications. Systemic inflammation defined by two commonly measured biomarkers (hs-CRP and WBC) was not only associated independently with periodontitis, SBP and diagnosis of hypertension but acted as a modest mediator of these associations.

This analysis confirmed that participants with periodontitis have a 20-60% greater chance of presenting also a concomitant diagnosis of hypertension and a 10% to 2.5 times greater chance of SBP ≥ 140 mmHg. This is consistent with previous studies reporting that patients with periodontitis have on average 4.5 higher mean SBP (95% CI: 2.88–6.11) than participants without periodontitis [12]. In the present study, a higher mean SBP of 6.4 mmHg (NHANES, 95%CI 5.3–7.4) and of 7.2 mmHg (KNHANES, 95%CI 6.1–8.4) were observed when participants with periodontitis were

Table 3. *Linear regression models of SBP and DBP according to periodontal variables or systemic inflammation (hs-CRP or WBC levels)*

Survey	Exposure: Periodontal variables	SBP Model 1 ß ± SE	SBP Model 2 ß ± SE	DBP Model 1 ß ± SE	DBP Model 2 ß ± SE
NHANES	Case Definition (vs non perio)				
	Periodontitis	**1.7 ± 0.7***	**1.5 ± 0.7***	−0.1 ± 0.4	−0.5 ± 0.4
	Mild	−0.2 ± 1.0	−0.4 ± 1.2	0.7 ± 0.6	0.6 ± 0.7
	Moderate	**1.7 ± 0.6****	**1.6 ± 0.7***	−0.4 ± 0.4	−1.0 ± 0.5
	Severe	**4.9 ± 1.3****	**4.7 ± 1.6***	−0.2 ± 0.7	−0.5 ± 0.8
	Continuous variable				
	AL (mean)	**1.3 ± 0.4****	**1.6 ± 0.5****	−0.1 ± 0.2	−0.2 ± 0.3
	N sites with AL ≥ 3 mm	**0.1 ± 0.04****	**0.03 ± 0.01***	−0.01 ± 0.01	**−0.01 ± 0.0***
	N sites with AL ≥ 4 mm	**0.1 ± 0.1****	**0.1 ± 0.02****	−0.02 ± 0.02	−0.02 ± 0.02
	N sites with AL ≥ 5 mm	**0.1 ± 0.03***	**0.1 ± 0.03***	0.01 ± 0.01	−0.01 ± 0.01
	N sites with AL ≥ 6 mm	**0.1 ± 0.1***	**0.1 ± 0.1***	0.02 ± 0.02	0.02 ± 0.02
	% of sites with AL ≥ 3 mm	**7.7 ± 2.5****	**5.6 ± 2.0***	−1.8 ± 1.4	**−3.8 ± 1.5***
	% of sites with AL ≥ 4 mm	**11.5 ± 3.5****	**9.6 ± 2.9****	−1.7 ± 1.6	−3.1 ± 2.0
	% of sites with AL ≥ 5 mm	**16.0 ± 5.4***	**13.1 ± 5.4***	0.8 ± 2.2	−1.5 ± 2.9
	% of sites with AL ≥ 6 mm	**23.8 ± 8.5***	**19.5 ± 8.9***	4.5 ± 3.7	0.8 ± 4.5
	PPD (mean)	**2.3 ± 0.6****	1.1 ± 0.7	0.01 ± 0.4	−0.6 ± 0.4
	N sites with PPD ≥ 4 mm	**0.1 ± 0.01****	0.01 ± 0.01	0.01 ± 0.02	−0.01 ± 0.01
	N sites with PPD ≥ 5 mm	**0.2 ± 0.1****	0.1 ± 0.1	0.01 ± 0.02	−0.1 ± 0.02
	N sites with PPD ≥ 6 mm	0.3 ± 0.1	0.1 ± 0.1	−0.01 ± 0.02	**−0.1 ± 0.02***
	% of sites with PPD ≥ 4 mm	**16.3 ± 4.0****	7.0 ± 3.7	0.9 ± 2.9	−4.4 ± 2.3
	% of sites with PPD ≥ 5 mm	**32.0 ± 9.1****	**17.6 ± 8.5***	0.7 ± 4.7	−8.6 ± 4.5
	% of sites with PPD ≥ 6 mm	44.2 ± 22.6	21.3 ± 21.7	−1.5 ± 5.7	**−16.5 ± 6.7***
KNHANES	CPI 3–4 vs CPI 0–2	0.7 ± 0.5	0.4 ± 0.6	0.7 ± 0.4	0.2 ± 0.5
	CPI continuous	0.3 ± 0.2	0.2 ± 0.2	0.2 ± 0.1	0.1 ± 0.1
	CPI cumulative	**0.1 ± 0.03***	**0.1 ± 0.04***	**−0.1 ± 0.1****	**−0.1 ± 0.1***
	Exposure: Systemic Inflammation				
NHANES	hs-CRP (log)	**1.2 ± 0.2*****	**1.3 ± 0.3*****	**0.7 ± 0.2****	**0.7 ± 0.2***
	WBC	**0.5 ± 0.1****	**0.6 ± 0.2****	−0.03 ± 0.1	0.1 ± 0.2
KNHANES	hs-CRP (log)	0.4 ± 0.2	0.4 ± 0.3	0.1 ± 0.2	0.1 ± 0.2
	WBC	**0.5 ± 0.1*****	**0.7 ± 0.2*****	**0.3 ± 0.1****	**0.5 ± 0.1*****

AL, attachment loss; CPI, Community Periodontal Index; DBP, diastolic blood pressure; hs-CRP, high-sensitivity c-reactive protein (logarithm); KNHANES, Korea National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey; PPD, probing pocket depth; SBP, systolic blood pressure; SE, standard error; WBC, white blood cell counts.

Model 1 (Population sample: 3460 NHANES; 4539 KNHANES): (NHANES): Age, gender, ethnicity, smoking, education level, chronic medical condition; (KNHANES): Age, gender, BMI, education level, smoking, diabetes, alcohol consumption, creatinine, physical activity, chronic medical conditions.

Model 2 (population sample: 2486 NHANES; 3270 KNHANES): Not taking antihypertensive medication.

Bold values highlighting statisticaly significant results.

***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

Table 4. *Linear regression model of CRP and WBC according to periodontal variables*

Survey	Exposure: Periodontal variables	Unadjusted ß ± SE	Model 1 ß ± SE
hs-CRP (log)			
NHANES	Periodontitis	**0.2 ± 0.01*****	**0.1 ± 0.03****
	Mild	**0.3 ± 0.1****	0.1 ± 0.1
	Moderate	**0.2 ± 0.1****	0.1 ± 0.02
	Severe	**0.3 ± 0.1****	**0.3 ± 0.1****
KNHANES	CPI 3-4 vs CPI 0-2	**0.3 ± 0.04*****	0.1 ± 0.04
	CPI continuous	**0.1 ± 0.01*****	**0.03 ± 0.01***
	CPI cumulative	**0.02 ± 0.01*****	**0.01 ± 0.01*****
WBC			
NHANES	Periodontitis	**0.3 ± 0.1****	**0.3 ± 0.1****
	Mild	**0.4 ± 0.1***	**0.3 ± 0.1***
	Moderate	0.1 ± 0.1	0.1 ± 0.1
	Severe	**0.8 ± 0.2****	**0.7 ± 0.1*****
KNHANES	CPI 3-4 vs CPI 0-2	**0.4 ± 0.1*****	**0.3 ± 0.1*****
	CPI continuous	**0.2 ± 0.02*****	**0.1 ± 0.03*****
	CPI cumulative	**0.02 ± 0.01*****	**0.02 ± 0.01*****

CPI, Community Periodontal Index; Hs-CRP, high-sensitivity C-reactive protein (logarithm); KNHANES, Korea National Health and Nutrition; Examination Survey; NHANES, National Health and Nutrition Examination Survey; SE, Standard Error; WBC, White Blood Cell Counts.
Model 1 (population sample: 3460 NHANES; 4539 KNHANES): (NHANES): Age, gender, ethnicity, smoking, education level, chronic medical condition; (KNHANES): Age, gender, BMI, education level, smoking, diabetes, alcohol consumption, creatinine, physical activity, chronic medical conditions.
Bold values highlighting statistically significant results.
***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

compared to those without the disease. The magnitude of this association could have important public health implications if we consider that high sodium intake with the diet is linked to a 6.0mmHg higher average SBP [23]. Further, SBP is a strong independent risk predictor for coronary heart disease events, stroke, heart failure and end-stage renal disease [24, 25].

Negligible associations of measures of periodontitis with DBP have been reported [20, 26]. Interestingly, we observed a negative linear association between two measures of continuous disease and DBP in both datasets. This observation has not been reported previously, and it seems to be in contrast with the findings related to SBP. At this stage, it is speculative to suggest a biological explanation of these findings. Authors consider important the role of residual confounding from other traditional risk factors variables (i.e. age, gender, ethnicity) as the estimates of association between DBP and some of the continuous measures of periodontitis tended to be greater in multivariate fully adjusted models. DBP is not considered on its own as a strong predictor for CVD events [27, 28], and the role of inflammation on affecting this measure of blood pressure is unclear. Further research should be conducted to ascertain the degree of association between diastolic pressure and periodontal inflammation as well as investigate potential biological mechanisms linking them.

When comparing the findings between the two surveys, a stronger association of categorical and continuous variables of periodontitis and gingival inflammation with hypertension and SBP was observed in the US dataset when compared with the Korean data survey. Similar findings were found for the association between biomarkers of inflammation (CRP and leucocytes counts) with measures of arterial blood pressure. Whilst the two sample populations present ethnic and socio-economic differences including a higher proportion of current smokers, adiposity and chronic medical

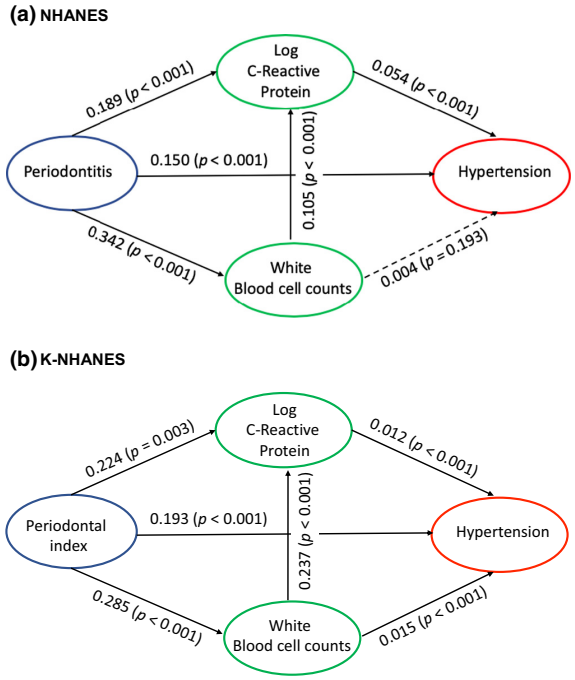

Fig. 2 *Mediation analysis model. (a) NHANES. Mediation models of periodontitis, inflammation and hypertension (unadjusted) in NHANES (*N *= 3460): Route 1: Direct effect (0.150;* P *< 0.001) of periodontitis (exposure) towards hypertension (outcome). Route 2: Indirect effect (0.342;* P *< 0.001) of periodontitis (exposure) towards WBC (mediator) is shown, but no effect (0.004;* P *= 0.193) is observed in the last step of the model from WBC (mediator) towards hypertension (outcome). Route 3: Indirect effect (0.18;* P *< 0.001), of periodontitis (exposure) is observed towards Log CRP (mediator) and an effect (0.054;* P *< 0.001), from Log CRP (mediator) towards hypertension (outcome). Route 4: Indirect effect (0.342;* P *< 0.001) of periodontitis (exposure) towards WBC (mediator) and an effect (0.105;* P *< 0.001) from WBC towards Log CRP (mediator) and an effect (0.054;* P *< 0.001) from the Log CRP (mediator) towards hypertension (outcome). (b) K-NHANES. Mediation models of periodontitis, inflammation and hypertension (unadjusted) in K-NHANES (*N *= 4539): Route 1: Direct effect (0.193;* P *< 0.001) of periodontal index (exposure) towards hypertension (outcome). Route 2: Indirect effect (0.285;* P *< 0.001) of periodontal index (exposure) towards WBC (mediator), and an effect (0.015;* P *< 0.001) from WBC (mediator) towards hypertension (outcome). Route 3: Indirect effect (0.224;* P *= 0.003), of periodontal index (exposure) is observed towards Log CRP (mediator) and an effect (0.012;* P *< 0.001), from Log CRP (mediator) towards Hypertension (outcome). Route 4: Indirect effect (0.285;* P *< 0.001) of periodontal index (exposure) towards WBC (mediator) and an effect (0.237;* P *< 0.001) from WBC towards Log CRP (mediator) and an effect (0.012;* P *< 0.001) from the Log CRP (mediator) towards hypertension (outcome).*

conditions in the US population, authors believe that the different clinical measures of periodontitis recorded in the surveys could influence the results of the analyses.

A recent intervention study assessing the impact of periodontitis treatment on arterial blood pressure confirmed a substantial reduction of SBP after 2 months (mean difference of 11.1 mmHg) [13]. This preliminary evidence suggests that periodontal treatment could represent a novel nonpharmacological intervention for hypertension of similar magnitude of other lifestyles adjustments (weight loss, increasing physical activity, salt or alcohol intake reduction or smoking cessation) with an average reduction of SBP ranging from 4.6 to 6.4 mmHg [29-31]. However, larger and longer RCTs are needed.

Several lines of evidence now implicate inflammation in the development and progression of vascular diseases. For the last 3 decades, inflammation has been recognized as a common denominator of early vascular dysfunction, leading onto the development of atheroma and vascular complications [32]. Recent proof-of-concept evidence suggests that targeting upstream inflammation by selective drugs results in reduced morbidity and mortality [33]. This could also be applicable in hypertension. Experimental and human studies have documented several pathways by which elevated inflammatory markers such as CRP and circulating leucocytes are associated with an increased risk of incident hypertension including a derangement of the renin–angiotensin system, increased oxidative stress and downregulation of nitric oxide leading to increased endothelial stiffness and dysfunction [34]. A recent review identified a number of potential sources of extravascular inflammation including periodontitis as a potential factor influencing vascular risk [32]. It is now well documented that patients with periodontitis have elevated levels of CRP and WBC [7, 35].

In the mediation analysis, our findings suggest that CRP and WBC mediate partly the association between periodontitis and hypertension, although the effect is rather modest in nature (only 2% of the association explained by the model for the Korean survey whilst up to 7% in the US survey). Similar findings were recently reported for CRP (5.4%), WBC (4.2%) and ferritin (10.2%) as mediators of the total association between a continuous measure of periodontitis and high/uncontrolled BP

(≥130/80 mmHg) [36]. An alternative pathway implicated in hypertension and cardiovascular injury relates to the activation of innate and adaptive immune cells such as monocyte/macrophages, and B and T lymphocytes [37]. Damage-activated molecular patterns from the vasculature and pathogen-activated molecular patterns from opportunistic diseases such as periodontitis can exacerbate the inflammatory cascade by activation of Th1 and Th17 lymphocytes, with kidneys and vasculature injuries aggravating a pro-hypertensive status, which results in progressive raised BP [38, 39].

Our analyses point perhaps towards a more prominent role of the gut and oral microbiome and their dysbiosis on hypertension [40]. Periodontal pathogens may well play a role influencing the gut microbiome as well as exerting a direct vascular effect. Swallowing Gram-negative oral bacteria or their end-products may trigger metabolic endotoxemia and systemic inflammation contributing to cardio-metabolic disorders [41]. Lastly, experimental studies confirmed that periodontal bacteria can cause lower nitric oxide bioavailability and vascular dysfunction [42] and patients with periodontitis exhibit less nitrate-reducing bacteria [43]. These novel mechanistic hypotheses warrant further investigation.

Cross-sectional designs preclude any inference on a possible temporal and/or causal association between periodontitis and hypertension. In the attempt of mitigating this limitation, we performed the analysis in two large surveys as to identify common patterns of association and minimizing spurious findings. Two different periodontal assessments and case definitions were adopted in each survey which could be considered a limitation but could also show that the association remains significant irrespectively. Whilst in the NHANES, a recognized case definition was used [19], in the Korean survey a simplified clinical index (CPI) was selected, which is known to have risks of overestimation of the extent but underestimation of the prevalence of periodontitis [44]. In the attempt to overcome some of these limitations, we included a panel of measures of periodontal lesions to detect whether simple categorical associations were replicated when using other exposure variables. Another limitation to consider is the effect of antihypertensive medications on gingival inflammation and increased probing depths as well as on the overall association between periodontitis and hypertension [45]. Sensitivity analyses were therefore performed by repeating the models in the group of participants not taking antihypertensive medications. We cannot, however, exclude that our analyses missed some common risk determinants for hypertension (abdominal obesity, salt intake, use of anti-inflammatory drugs, hormone treatments and stress) as well as unmeasured confounders associated with both periodontitis and hypertension (residual confounding). Future mechanistic and clinical studies should investigate further the role of periodontal-driven systemic inflammation and microbial burden as a risk factor for the development and management of hypertension and its complications.

Conclusion

Periodontitis is closely linked to hypertension and low-grade systemic inflammation could be a key mediator in the association. Further interventional studies are needed to ascertain whether the treatment of periodontitis, leading to a decrease in systemic inflammation, may represent a novel nonpharmacologic intervention in hypertension management.

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Author contribution

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Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Conflict of interest statement

None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Variables description for Korean and American databases.

Table S2. (Models A, B, C, D): Mediation analyses.

