



Left ventricular geometry and periodontitis in patients with the metabolic syndrome

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Abstract

Objective The presence of periodontal disease (PD) in subjects affected by the metabolic syndrome (MetS) may affect their risk of developing cardiovascular disease. The aim of this cross-sectional study was to investigate the systemic impact of PD in MetS, by assessing measures of sub-clinical atherosclerosis and left ventricular mass and geometry.

Materials and methods A total of 103 patients undergoing treatment for MetS were examined for confirmation of diagnosis, blood sampling, and measures of pulse wave velocity (PWV), carotid intima-media thickness (c-IMT), left ventricular mass index (LVM), and relative wall thickness (RWT). All subjects underwent a detailed dental assessment, including measurements of DMFT (decayed-missing-filled teeth) and periodontal parameters.

Results Ten patients (10%) were diagnosed with healthy-mild periodontitis, 38 patients (37%) were diagnosed in the moderate periodontitis group, and 55 (53%) had severe periodontitis. A total of 37% of subjects were affected by dental caries. Linear regression analysis revealed that patients with severe PD had increased average ventricular RWT (adjusted $p = 0.032$). Average full mouth probing pocket depth (PPD) was also associated with RWT (adjusted $p = 0.006$). No associations between PD and c-IMT, PWV, and LVM were detected after adjusted analyses.

Conclusion This study suggests that periodontitis may be associated with concentric left ventricular remodeling, a predictive index of cardiovascular events.

Clinical relevance The presence of periodontitis in patients with MetS might have an effect on left ventricular geometry. These findings stress the importance of prevention, diagnosis, and management of periodontitis in patients with MetS.

Trail registration NCT03297749

Keywords Metabolic syndrome · Periodontitis · Periodontal medicine · Cardiovascular disease

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Introduction

Epidemiological evidence accumulated over the last two decades suggests that periodontitis is associated with dyslipidemia, glucose intolerance, a low-grade systemic inflammatory state, and systemic diseases such as cardiovascular disease and diabetes [1, 2].

Obesity, insulin resistance, hypertension, and dyslipidemia often cluster in the same group of individuals and are described as part of a condition termed metabolic syndrome (MetS), associated with increased risk of developing diabetes and cardiovascular events [3]. A recent systematic review concluded that MetS is associated with the presence of periodontitis (OR = 1.71; 95% CI = 1.42 to 2.03) and suggested that periodontal diagnostic procedures should be routinely carried out in MetS patients [4]. The association between MetS and periodontitis may be mediated by predisposing genetic variants (common susceptibility), microbially driven inflammatory reactions facilitated by pro-inflammatory cytokines, abdominal obesity, and oxidative stress [5–7].

Cardiovascular disease-predisposing data of arterial thickness and dysfunction and arterial stiffness have been reported in patients with periodontitis [8–12]. Also, MetS is associated with arterial stiffness, and monitoring of arterial pulse wave velocity in patients with MetS was found to be helpful in identifying patients at high risk for sub-clinical atherosclerosis [13]. Another important prognostic factor for cardiovascular events is altered left ventricular geometry. In particular, left ventricular hypertrophy (LVH) is caused by an increase in mass of the left ventricle and can be secondary to an increase in cavity size, in wall thickness, or both. While some studies reported a positive association between increased left ventricular mass (LVM) and chronic periodontitis [11–14], not much is known about relationships between left ventricular relative wall thickness (RWT) and periodontitis. No data are available, to our knowledge, on arterial stiffness and ventricular geometry in patients affected by both MetS and PD and on how the latter may act as a modifier of the systemic impact of MetS.

Therefore, the aim of this study was to investigate the systemic impact of periodontitis in patients with MetS, by assessing measures of sub-clinical atherosclerosis and cardiac remodeling, namely carotid intima-media thickness (c-IMT), arterial stiffness (carotid-femoral and carotid-radial pulse wave velocity (PWV)), left ventricular mass (LVM), and geometry (RWT).

Material and methods

The null hypothesis of this cross-sectional study was that there were no differences in cardiovascular event predictors (PWT, c-IMT, LVM, and RWT) in patients with MetS with and without periodontitis. PWV was chosen as the primary outcome of

the study. The STROBE checklist (attached as supplementary material 1) was followed during the conduct and reporting of the study.

Study population

One hundred twelve patients with metabolic syndrome were identified as suitable from 200 consecutive subjects attending the Department of Internal Medicine (Ospedale Cannizzaro and Ospedale Garibaldi), University of Catania, for outpatient examination. A total of 103 subjects agreed to undergo all the necessary examinations as part of the study and were included from July 2015 to July 2017. Ethics approval was obtained by the sponsor institution, University College London (reference 4242/01), and, separately, by the clinical center (reference 1497/Cs). All patients signed informed consents to take part in the study. The study was registered on clinicaltrials.gov (identifier NCT03297749).

Inclusion criteria

- Caucasian ethnicity
- Age 25–75
- Diagnosis of metabolic syndrome as defined by the revised NCEP ATP III (e.g., the presence of at least 3 of the following factors) [15]:

Waist circumference: > 102 cm for men and > 88 cm for women

High triglycerides: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality

Low HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality

High blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension

High fasting plasma glucose: FPG ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

- Presence of at least 12 teeth

Exclusion criteria

- Pregnancy
- Presence of infectious diseases such as hepatitis and HIV
- Antibiotic pre-medication required for the performance of periodontal examination
- Previous periodontal therapy within 6 months of the study visit

Medical assessment and blood sampling

The medical history of the patients was recorded. Smoking was defined as self-reported former, current (at least 1 cigarette/day), and never, and packs/years were recorded. Body mass index (BMI), waist circumference, and office blood pressure readings (by Omron 907 semi-automated device) were measured and recorded. All subjects were required to fast for at least 12 h prior to blood sampling, taken from the antecubital vein. Within 1 h of collection, vacutainer for serum and plasma separation were centrifuged at 3000 rpm for 15 min. The serum and plasma collected were then placed into aliquots of 1 mL in plastic cryovials and stored in a $-80\text{ }^{\circ}\text{C}$ freezer until analysis. Routine hematological analysis included analysis of white cell count (WCC) and differential, red cell count (RCC), high-sensitivity C-reactive protein (CRP), fasting glucose, insulinemia, and lipid levels. The HOMA index was calculated as previously described [16].

Ultrasound assessment

B-mode real-time ultrasound was performed in blind, evaluating the arterial wall thickness in the carotid arteries. Patients were examined in the supine position, and each carotid wall or segment was examined to identify the thickest intimal-medial site as previously described [17]. Three segments were identified and measured in antero- and posterior-planes on each side: the distal 1.0 cm of the common carotid proximal to the bifurcation, the bifurcation itself, and the proximal 1.0 cm of the internal carotid artery. At each of these sites, the presence of any possible plaque was detected and the intima-media thickness (c-IMT) was determined as the distance between the echogenic line representing the intima blood interface and the outer echogenic line representing the adventitia junction.

Arterial stiffness

Assessment of aortic pulse wave velocity, augmentation index, and pressure was done by a tonometer, with the patient lying in supine position, after a 10-min rest [18]. Tonometry was carried out by Pulse Pen on the carotid, radial, and femoral arteries. Distance between carotid and both radial femoral arteries was measured and given to the instrument software to calculate pulse wave velocity (PWV), augmentation index, and pressure. Based on the fact that both elastic and muscular arterial components could be affected by inflammation [19], both carotid-femoral (cf) and carotid-radial (cr) PWV were calculated.

Echocardiography

Echocardiographic data were measured by MyLab 25 instrument (Esaote S.P.A., Genoa, Italy) according to the recommendations of the American Society of Echocardiography by an observer unaware of other study outcomes. LVM was calculated according to the Devereux formula and indexed to height^{2.7} (LVMi) [20] in order to minimize any potential distortion attributable to extracellular volume expansion [21]. LVH was defined by a LVMi $>47\text{ g m}^{-2.7}$ in women or $>50\text{ g m}^{-2.7}$ in men. RWT was calculated as follows: $2 \times \text{posterior wall thickness} / \text{left ventricular end diastolic diameter}$, as an index of the left ventricular geometric pattern. Values indicative of concentric and eccentric left ventricular geometry were established on the basis of age-specific reference standards [22].

Dental examination

Patients' dental history was investigated, including family history of periodontal disease, frequency of dental appointments, date of last appointment and previous treatment, reasons for tooth loss and frequency, and type of tooth brushing. The following clinical parameters were assessed by a single calibrated examiner at six sites/tooth: dichotomous full mouth plaque scores (FMPS) [23], full mouth probing pocket depth (PPD), recession (REC) of the gingival margin from the cemento-enamel junction, bleeding on probing (FMBS) [23], tooth mobility, and furcation involvement. Clinical attachment level (CAL) was calculated as $\text{PPD} + \text{REC}$. Clinical parameters were assessed by probing with a UNC-15 periodontal probe and a Nabers probe for furcation involvement. Furthermore, the examiner recorded the DMFT (decayed-missing-filled teeth) index for each patient, which represents an estimation of the total number of teeth in the mouth which have experienced carious lesions [24]. Decays and fillings were sought clinically in the occlusal, buccal, lingual, and interproximal surfaces by visualization and with the help of a standard probe. Saliva, gingival crevicular fluid, and subgingival plaque samples were collected and stored for future analyses.

Definition of periodontitis

Patients were classified as having periodontitis according to the criteria below [25]:

- Healthy/mild periodontitis: <2 sites on different teeth with $\text{CAL} \geq 4\text{ mm}$ or no sites with $\text{PPD} \geq 4\text{ mm}$
- Moderate periodontitis: ≥ 2 sites on different teeth with $\text{CAL} \geq 4\text{ mm}$ or one site with $\text{PPD} \geq 4\text{ mm}$
- Severe periodontitis: ≥ 2 sites on different teeth with $\text{CAL} \geq 6\text{ mm}$ and ≥ 1 site with $\text{PPD} \geq 4\text{ mm}$

Examiner calibration

Laboratory, ultrasonic, and statistical analyses were performed masked to the dental classification of subjects. Digitized ultrasonic images from 10 non-study subjects were used for the examiners' calibration of ultrasound assessments. The designated examiners measured PWV, c-IMT, and echocardiographic parameters twice on the same day (minimum of 15-min separation) for intra-examiner calibration. Reproducibility was calculated by intraclass correlation coefficient (ICC) as 0.93, 0.92, and 0.92 for PWV, c-IMT, and RWT. The periodontal clinical examiner had been calibrated before the start of the study by carrying out double measurements in a total of five non-study subjects with minimum of 15-min separation. The ICC was 0.93 for PPD and 0.91 for CAL.

Sample size calculation

The sample size calculation was based on a previous systematic review [12] showing a PWV mean difference 0.85 m/s (95% confidence interval, 0.53–1.16) between patients with and without periodontitis. A sample size of 102 patients was required with a power of 0.8, standard deviation of 2.5, and sampling ratio of 2 (www.powerandsamplesizes.com).

Statistical analysis/power calculation

Data were entered in a computer as an Excel file and proofed for entry errors. The resulting database was locked and loaded in SPSS Version 23.0. Continuous, normally distributed variables are reported as means \pm standard deviations (SD). Comparisons of continuous and categorical data between groups were analyzed with ANOVA and chi-square test, respectively. The α value was set at 0.05. Given the expected high prevalence of periodontitis in this patient cohort, a dichotomous variable "severe periodontitis" was given according to the criteria described above: no/mild/moderate periodontitis vs. severe periodontitis [25]. Data relative to all **three** groups (healthy-mild, moderate, and severe) are also reported. Associations between presence of periodontitis and cardiovascular parameters were sought by linear regression analyses adjusted for confounders.

Results

Demographic and clinical characteristics of the 103 included subjects are reported in Table 1. Patients were on average 58 years old, with a majority of males, and had an average BMI of nearly 32.

Dental history and diagnoses

The great majority of included subjects were not regular dental attenders: 77% said they only attended the dentist in case of problems, and two of them had never had a dental visit in their life. Although most patients reported brushing their teeth 2/day, six subjects reported brushing 1–2/week, and one said he never brushed his teeth. Only a small proportion (13%) ever used interdental cleaning tools. Table 2 reports dental clinical parameters assessed in all subjects. An average of nearly 23 teeth were present, excluding third molars. The average DMFT score was 12.58, and caries was found in 38 subjects (37%). Periodontal examination revealed high plaque scores (average 72%) and bleeding on probing score just below 24%. The majority of PPDs (93.17%) were in the 1–4-mm range, with only around 1% exceeding 6 mm. Overall, 10 subjects were classified as no-mild periodontitis, 38 as moderate periodontitis, and 55 as severe periodontitis [25]. All the subjects in the no-mild periodontitis showed minimal gingival inflammation, with FMBS < 15%.

Metabolic syndrome and cardiovascular diagnosis

A total of 40 subjects had five metabolic syndrome components diagnosed, while 39 and 24 subjects had four or three positive components, respectively. The most common component detected was decreased HDL (88%), followed by increased waist circumference (86%), hypertension (84%), increased triglycerides (83%), and increased glycemic levels (74%). A total of 73 subjects (70%) were diagnosed with diabetes. Fourteen subjects reported previous cardiovascular events.

Associations between dental status and metabolic and cardiovascular parameters

Figure 1 shows respectively c-IMT, cf-PWV, and cr-PWV for patients divided by periodontal disease severity (no-moderate vs. severe periodontitis). Figure 2 reports LVMi and RWT for patients divided by periodontal severity. Table 3 reports non-adjusted analyses of associations between periodontal diagnosis (no-moderate vs. severe periodontitis) and number of MetS components, previous cardiovascular disease (CVD) events, c-IMT, and PWV. Both cf- and cr-PWV did not show any association with periodontal status. Age was associated with both cf-PWV ($p = 0.019$) and cr-PWV ($p = 0.048$); c-IMT showed a borderline association with periodontal diagnosis ($p = 0.042$), but the significance disappeared ($p = 0.175$) after adjustment for confounders (age, gender, systolic blood pressure, smoking, and HOMA index). Age and gender were associated with c-IMT ($p = 0.005$ and $p = 0.004$, respectively).

No association was detected between LVMi and periodontal status. By contrast, RWT was higher in patients with severe

Table 1 Demographics and dental history of included cases

		Average
Age		58.12 ± 9.89
BMI		31.88 ± 4.37
		Frequency
Gender	Male	65 (63.1%)
	Female	38 (36.9%)
Smoking status	Non-smoker	67 (65.0%)
	Current smoker	28 (27.2%)
	Former smoker	8 (7.8%)
Frequency of dental visits	Never been	2 (1.9%)
	Only in case of problems	79 (76.7%)
	1/year	12 (11.7%)
	> 1/year	10 (9.7%)
Previous periodontal treatment	Yes	3 (2.9%)
	No	100 (97.1%)
Last dental visit	Never been	2 (1.9%)
	> 10 years ago	7 (6.8%)
	1–10 years ago	60 (58.3%)
	< 1 year ago	34 (33.0%)
Tooth brushing frequency	< 1/day	6 (5.9%)
	1/day	34 (33.0%)
	At least 2/day	63 (61.1%)
Type of toothbrush	None	1 (1.0%)
	Manual	92 (89.3%)
	Electric	10 (9.7%)
Use of interdental cleaning tools	Daily-weekly	14 (13.6%)
	Never	89 (86.4%)

BMI body mass index

Table 2 Dental clinical parameters in all included subjects

	Average	Number
Number of teeth (excluding third molars)	22.77 ± 4.19	2345
DMFT	12.58 ± 6.07	–
Decayed teeth	0.63 ± 0.96	65
Patients with caries detected	–	38 (36.89%)
FMPS	72.11 ± 22.51	–
FMBS	23.92 ± 19.62	–
Average PPD	2.44 ± 0.73	–
Average CAL	3.05 ± 1.12	–
% PPDs 1–4 mm	93.17 ± 0.88%	–
% PPDs 5–6 mm	5.92 ± 0.75%	–
% of PPDs > 6 mm	0.94 ± 0.23%	–
No-mild periodontitis	–	10 (9.7%)
Moderate periodontitis	–	38 (36.9%)
Severe periodontitis	–	55 (53.3%)

DMFT, decayed missing filled teeth; FMPS, full mouth plaque score; FMBS, full mouth bleeding score; PPD, probing pocket depth; CAL, clinical attachment level

periodontitis compared with subjects with no-moderate periodontitis ($p = 0.025$ adjusted for age, gender, systolic blood pressure, smoking, HOMA index, and number of teeth) (see Table 4 for linear regression model). Exploring this further, average PPD was also associated with RWT ($p = 0.006$ adjusted for age, gender, systolic blood pressure, smoking, HOMA index, and number of teeth), while no association was detected between bleeding on probing score (FMBS) and RWT ($p = 0.707$).

Discussion

Parameters of sub-clinical atherosclerosis and cardiac remodeling were assessed in a group of 103 subjects with MetS according to periodontal diagnosis (divided into 48 with no-moderate periodontitis and 55 with severe periodontitis). In particular, arterial stiffness (measured by PWV), c-IMT, LVMI, and RWT were investigated. This is the first study, to our knowledge, to report an association between severity of periodontitis and RWT in patients with the metabolic syndrome.

A strong epidemiological association between periodontitis and MetS has been widely reported and suspected to be mediated by shared genetic susceptibility, by environmental and behavioral factors, and by bi-directional effects of dyslipidemia, reduced glucose tolerance, oxidative stress, molecular mimicry, and dysbiosis [4]. Both patients with MetS and patients with periodontitis have been found to have an increased risk in surrogate CVD markers and also in cardiovascular mortality [3, 26]. In particular, indexes of arterial thickness and dysfunction (including c-IMT), increased left ventricular mass and blood pressure have been reported in patients with periodontitis [10, 11, 27]. A recent systematic review showed that patients with severe periodontitis have increased arterial stiffness (measured as higher PWV) compared with patients without periodontitis or with gingivitis/mild periodontitis [12]. Both c-IMT and PWV have, in turn, been associated with mortality for CVD [28–30].

The finding of an association between RWT and periodontitis suggests that periodontal pathology might contribute to abnormal left ventricular geometry. This is further corroborated by an association between continuous measures of periodontal disease severity (average PPD) and RWT, while no association was detected between bleeding on probing and RWT. Previous studies observed increased left ventricular mass in periodontitis patients with essential hypertension [11, 31] and diabetes [14]. It is well recognized that, although LVM has been widely used to assess left ventricular hypertrophy as a consequence of arterial hypertension, RWT increase can be often found without increased LVM [32], thus indicating a concentric ventricular remodeling, predictive of stroke risk independently of LVM [32, 33].

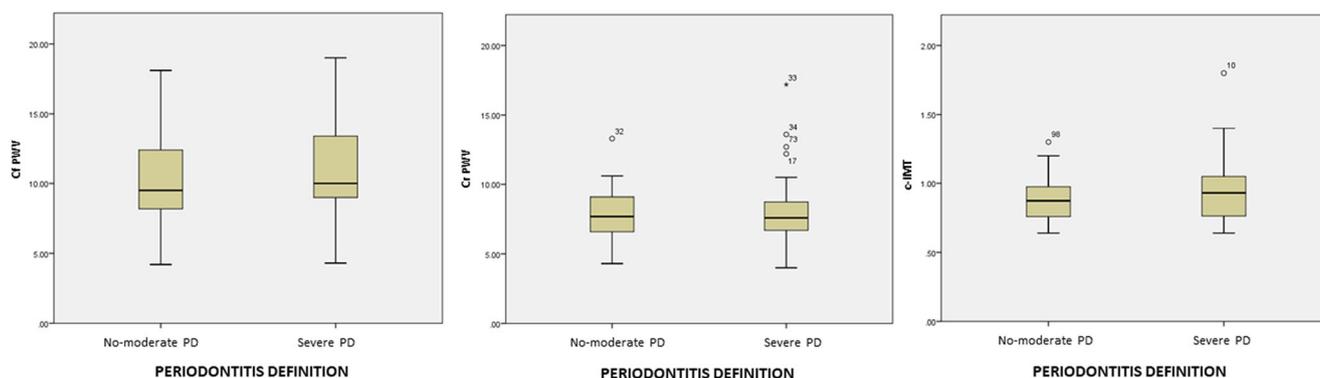


Fig. 1 Carotid intima-media thickness (c-IMT), carotid-femoral pulse wave velocity (PWV), and carotid-radial PWV in patients divided by periodontal diagnosis (no-moderate periodontitis vs. severe periodontitis). Periodontal definition used: Page and Eke [25]

Of note, concentric hypertrophy, in parallel with LVM, has been shown to be associated with a marked increase in adverse CVD events in adults free of prevalent CVD [34]. In the current study, while no association was detected between left ventricular mass and periodontitis, RWT showed an increase in patients with severe periodontitis, independently of other risk factors such as age, gender, smoking, hypertension, and insulin resistance.

Among other CVD predictors, although c-IMT was found higher in patients with MetS affected by severe periodontitis, no statistically significant differences were detected after adjusted analysis. Furthermore, no differences by periodontal diagnosis were detected for cf- and cr-PWV. The findings of borderline-increased c-IMT in patients with severe periodontitis largely corroborate previous data in the literature, although this was not statistically significant in the present study after adjusting for confounders. The difference in c-IMT detected in the current study between no-moderate and severe periodontitis (0.88 mm vs. 0.96) was of the same magnitude of the average difference in c-IMT in a recent meta-analysis (increased c-IMT for PD vs. controls, with a difference of

0.08 mm) [29]. Interestingly, a study in a Chinese cohort of 59 patients with chronic periodontitis, 26 of whom also had MetS, showed increased c-IMT for patients with both MetS and periodontitis compared with patients with periodontitis and no MetS. However, no associations were detected between severity of periodontitis and c-IMT [13].

One of the possible reasons for the lack of associations between arterial stiffness and periodontitis in this study is that comorbidities (such as hypertension, dyslipidemia, and impaired glucose metabolism) may act as confounders, so masking the association between periodontitis and PWV. In support of this, in populations with comorbidities (e.g., hypertension, diabetes), less marked differences in PWV were detected between patients with and without periodontitis [12]. It is also important to notice that the patients included in the study were not treatment-naïve, but were under pharmacological therapy for the MetS, which could have masked potential associations.

The population described here included subjects with overall poor dental care, measured as irregular dental attendance, irregular tooth brushing, and almost complete absence of

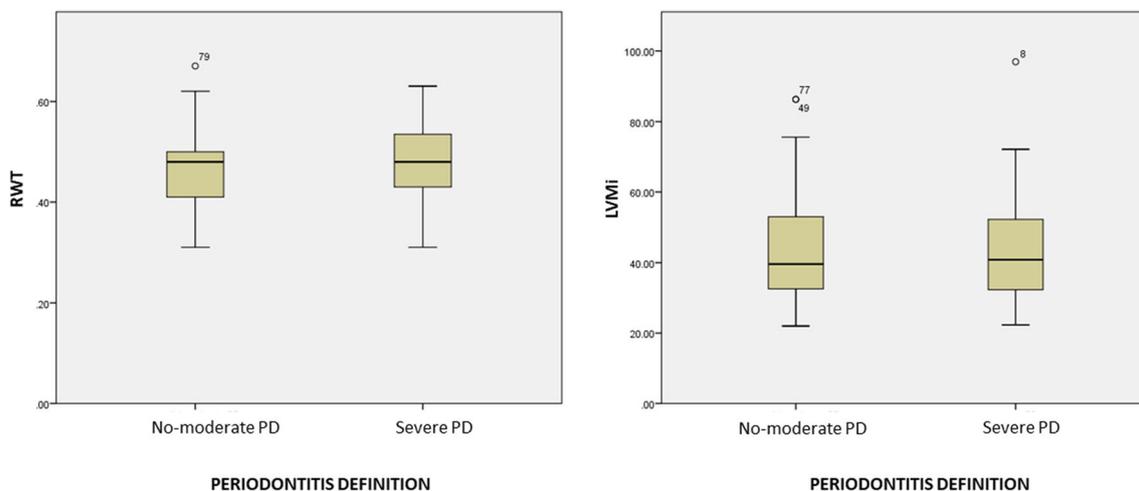


Fig. 2 Left ventricular mass index (LVMi) and relative wall thickness (RWT) in patients divided by periodontal diagnosis (no-moderate periodontitis vs. severe periodontitis). Periodontal definition used: Page and Eke [25]

Table 3 Selected metabolic and cardiovascular parameters for subjects divided by periodontal diagnosis. Comparisons of continuous and categorical data between groups were analyzed with ANOVA and chi-square test, respectively

	No-moderate PD (<i>n</i> = 48)	Severe PD (<i>n</i> = 55)	Comparison <i>p</i>
Age (year)	56.65 ± 11.79	59.40 ± 7.75	0.160
Male gender	30 (62.5%)	35 (63.6%)	0.534
Current smoking	9 (18.8%)	19 (34.5%)	0.012
BMI (Kg/h ²)	31.92 ± 4.47	4.33 ± 0.58	0.925
MetS components			0.234
	3	13 (27.1%)	11 (20.0%)
	4	14 (29.2%)	25 (45.5%)
	5	21 (43.8%)	19 (34.5%)
Previous CVD events	5 (10.4%)	9 (16.4%)	0.279
c-IMT (mm)	0.88 ± 0.19	0.96 ± 0.24	0.042
cf-PWV (m/s)	10.54 ± 3.48	10.90 ± 3.36	0.629
cr-PWV (m/s)	7.81 ± 1.83	7.97 ± 2.42	0.729
cf-cr PWV ratio (m/s)	1.35 ± 0.53	1.51 ± 0.78	0.265
LVMi (g/h ^{-2.7})	43.38 ± 15.27	43.37 ± 14.02	0.998
RWT	0.46 ± 0.08	0.49 ± 0.07	0.139
CRP (mg/dL)	0.50 ± 1.04	0.34 ± 0.29	0.332
Neutrophils (× 10 ⁹ /L)	4.23 ± 1.40	4.70 ± 1.50	0.109
Total cholesterol (mg/dL)	192.19 ± 43.81	187.72 ± 42.34	0.602
HDL (mg/dL)	42.17 ± 11.31	44.41 ± 12.12	0.338
LDL (mg/dL)	110.25 ± 42.21	112.06 ± 38.33	0.821
Triglycerides (mg/dL)	178.50 ± 131.01	157.09 ± 80.90	0.317
HOMA index	8.56 ± 13.70	9.01 ± 15.65	0.881

Comparisons by chi-square and ANOVA for categorical and continuous variables, respectively

BMI, body mass index; *MetS*, metabolic syndrome; *CVD*, cardiovascular disease; *CRP*, C-reactive protein; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *HbA1c*, glycated hemoglobin; *C-IMT*, carotid intima-media thickness; *CF*, carotid-femoral; *CR*, carotid-radial; *PWV*, pulse-wave velocity; *HOMA*, homeostasis model assessment

interdental brushing; all reflected in high plaque scores. It is somewhat surprising that, despite this and the MetS diagnosis, “severe periodontitis” [25] was not widespread, and even within it, only 1.7% of PPDs were > 6 mm, with an average PPD of 2.89 mm.

Strengths of this study are the ethnic homogeneity of the included subjects, the consistency of full mouth periodontal examinations carried out by a single calibrated examiner, and the analysis of a wealth of CVD parameters in a population well-characterized periodontally. Limitations of the study are

Table 4 Results of linear regression analysis for association between severe periodontitis and RWT (relative wall thickness)

Coefficients ^a		Unstandardized coefficients		Standardized coefficients		Sig.
Model		<i>B</i>	Std. error	Beta	<i>t</i>	
1	(Constant)	.550	.094		5.852	.000
	Severe periodontitis (Page and Eke [25])	.040	.018	.261	2.277	.025
	Age	-.001	.001	-.139	-1.225	.224
	Gender	-.020	.017	-.127	-1.150	.254
	Smoking	-.019	.013	-.161	-1.405	.180
	Systolic blood pressure	.000	.000	-.051	-.471	.639
	HOMA index	.000	.001	-.053	-.488	.648
	Number of teeth	-.001	.002	-.050	-.458	0.648

^a Dependent variable: RWT

the fact that patients were already receiving treatment for MetS and the absence of controls without the metabolic syndrome. Only internal controls with MetS and no periodontitis were included, as the aim was to assess if periodontitis might add to the systemic burden of patients with MetS. Furthermore, the inclusion of subjects with at least 12 remaining teeth may have introduced bias by excluding the subjects with MetS with the highest predisposition to periodontal disease, who may have already been edentulous. The definition of periodontitis employed, previously applied to other studies on periodontitis and MetS [35, 36], may have affected the study results, and different outcomes of association may have been seen if other definitions had been adopted.

Overall, this study suggests that severe periodontitis may be associated with altered left ventricular geometry in patients with MetS, suggesting that periodontal disease may be an emerging co-factor in increasing cardiovascular risk in patients under treatment for the metabolic syndrome. The absence of association between periodontitis and both c-IMT and PWV also suggests, in agreement with what was found by previous studies [12, 13], that any effect of periodontal disease on sub-clinical atherosclerosis may be diluted by the presence of other comorbidities (such as in MetS) and by concomitant pharmacological treatment. However, the different effects on the arterial vessels and the heart would underscore that the heart seems to be more sensitive to the association of metabolic syndrome and periodontitis. Further studies in larger cohorts should be performed to investigate associations between periodontitis and left ventricular geometry, in populations with and without systemic comorbidities.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and 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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References

1. Mealey BL, Oates TW (2006) Diabetes mellitus and periodontal diseases. *J Periodontol* 77:1289–1303
2. Kerschbaum M, Demmer RT, Papapanou PN (2010) “Gum Bug, Leave My Heart Alone!” -epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. *J Dent Res* 89: 879–902
3. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ (2010) The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol* 56:1113–1132
4. Nibali L, Tatarakis N, Needleman I, Tu YK, D’Aiuto F, Rizzo M, Donos N (2013) Clinical review: association between metabolic syndrome and periodontitis: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 98:913–920
5. Han DH, Shin HS, Kim MS, Paek D, Kim HD (2012) Group of serum inflammatory markers and periodontitis-metabolic syndrome coexistence in Koreans. *J Periodontol* 83:612–620
6. Andriankaja OM, Sreenivasa S, Dunford R, DeNardin E (2010) Association between metabolic syndrome and periodontal disease. *Aust Dent J* 55:252–259
7. Ohnishi T, Bandow K, Kakimoto K, Machigashira M, Matsuyama T, Matsuguchi T (2009) Oxidative stress causes alveolar bone loss in metabolic syndrome model mice with type 2 diabetes. *J Periodontol Res* 44:43–51
8. Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S (2001) Relationship of periodontal disease to carotid artery intima-media wall thickness - the atherosclerosis risk in communities (ARIC) study. *Arterioscler Thromb Vasc Biol* 21:1816–1822
9. Amar S, Gokce N, Morgan S, Loukidelis M, Van Dyke TE, Vita JA (2003) Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol* 23:1245–1249
10. Tonetti MS, D’Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J (2007) Treatment of periodontitis and endothelial function. *N Engl J Med* 356:911–920
11. Franek E, Klameczynska E, Ganowicz E, Blach A, Budlewski T, Gorska R (2009) Association of chronic periodontitis with left ventricular mass and central blood pressure in treated patients with essential hypertension. *Am J Hypertens* 22:203–207
12. Schmitt A, Carra MC, Boutouyrie P, Bouchard P (2015) Periodontitis and arterial stiffness: a systematic review and meta-analysis. *J Clin Periodontol* 42:977–987
13. Li P, Zhang DK, Zhang JR, Chen L (2011) Detection of the parameters for early atherosclerosis in patients with metabolic syndrome and periodontitis. *Beijing da Xue Xue Bao Yi Xue Ban/Journal Peking Univ Health Sci* 43:34–39
14. Sarda T, Rathod S, Kolte A, Bodhare G, Modak A (2016) Expression of periodontal inflammation into left ventricular hypertrophy in type 2 diabetes mellitus: a cross-sectional study. *Contemp Clin Dent* 7:343–348
15. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C (2004) Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 109: 433–438
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419

17. Rizzo M, Corrado E, Coppola G, Muratori I, Novo G, Novo S (2008) Prediction of cardio- and cerebro-vascular events in patients with subclinical carotid atherosclerosis and low HDL-cholesterol. *Atherosclerosis* 200:389–395
18. Kim YJ, Kim YJ, Cho BM, Lee S (2010) Metabolic syndrome and arterial pulse wave velocity. *Acta Cardiol* 65:315–321
19. Zanolli L, Lentini P, Boutouyrie P, Fatuzzo P, Granata A, Corrao S et al (2018) Pulse wave velocity differs between ulcerative colitis and chronic kidney disease. *Eur J Intern Med* 47:36–42
20. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH (1992) Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 20:1251–1260
21. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giaccone G, Cataliotti A, Seminara G, Stancanelli B, Malatino LS, CREED Investigators (2001) Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J Am Soc Nephrol* 12:2768–2774
22. Ganau A, Saba PS, Roman MJ, de Simone G, Realdi G, Devereux RB (1995) Ageing induces left ventricular concentric remodelling in normotensive subjects. *J Hypertens* 13(12 Pt 2):1818–1822
23. Guerrero A, Griffiths GS, Nibali L, Suvan J, Moles DR, Laurell L, Tonetti MS (2005) Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: a randomized placebo-controlled clinical trial. *J Clin Periodontol* 32:1096–1107
24. Tomita NE, Chinellato LE, Lauris JR, Kussano CM, Mendes HJ, Cardoso MT (2005) Oral health of building construction workers: an epidemiological approach. *J Appl Oral Sci* 13:24–27
25. Page RC, Eke PI (2007) Case definitions for use in population-based surveillance of periodontitis. *J Periodontol* 78(7 Suppl): 1387–1399
26. Söder B, Jin LJ, Klinge B, Söder PO (2007) Periodontitis and premature death: a 16-year longitudinal study in a Swedish urban population. *J Periodontol* 42:361–366
27. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A et al (2014) Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. *Atherosclerosis* 236:39–46
28. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA (2003) The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 42: 1149–1160
29. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 115:459–467
30. Sethi S, Rivera O, Oliveros R, Chilton R (2014) Aortic stiffness: pathophysiology, clinical implications, and approach to treatment. *Integr Blood Pressure Control* 23:29–34
31. Angeli F, Verdecchia P, Pellegrino C, Pellegrino RG, Pellegrino G, Prosciutti L, Giannoni C, Cianetti S, Bentivoglio M (2003) Association between periodontal disease and left ventricle mass in essential hypertension. *Hypertension* 41:488–492
32. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S (2003) Left ventricular mass and geometry and the risk of ischemic stroke. *Stroke* 34:2380–2384
33. Eguchi K, Ishikawa J, Hoshida S, Ishikawa S, Pickering TG, Schwartz JE et al (2007) Differential impact of left ventricular mass and relative wall thickness on cardiovascular prognosis in diabetic and no diabetic hypertensive subjects. *Am Heart J* 154(79):e9–e15
34. Tsao CW, Gona PN, Salton CJ, Chuang ML, Levy D, Manning WJ et al (2015) Left ventricular structure and risk of cardiovascular events: a Framingham Heart Study Cardiac Magnetic Resonance Study. *J Am Heart Assoc* 4:e002188
35. D'Aiuto F, Sabbah W, Netuveli G, Donos N, Hingorani AD, Deanfield J, Tsakos G (2008) Association of the metabolic syndrome with severe periodontitis in a large US population-based survey. *J Clin Endocrinol Metab* 93:3989–3994
36. Benguigui C, Bongard V, Ruidavets JB, Chamontin B, Sixou M, Ferrières J, Amar J (2010) Metabolic syndrome, insulin resistance, and periodontitis: a cross-sectional study in a middle-aged French population. *J Clin Periodontol* 37:601–608