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ORIGINAL ARTICLE

Association between periodontitis and heart failure in the general population

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Abstract

Aims Data on the association between periodontitis and preclinical cardiac alterations remain scarce. The aim of the current study is to determine if periodontitis is associated with morphological and functional cardiac changes measured by transthoracic echocardiography as well as different heart failure (HF) phenotypes.

Methods Participants from the population-based Hamburg City Health Study [ClinicalTrial.gov (NCT03934957)], who underwent transthoracic echocardiography and periodontal screening were included. Periodontitis was classified according to Eke and Page (none/mild, moderate, severe). The 2021 ESC HF guidelines were applied and HF was classified into HF with preserved ejection fraction (HFpEF, ejection fraction ≥50%), HF with mid-range and reduced ejection fraction [HF(m)rEF, ejection fraction <50%], and HF in general [HFpEF and HF(m)rEF]. Due to limited size, all subjects with LVEF <50% and symptoms or signs of HF were classified as HF with reduced and mildly reduced ejection fraction [HF(m)rEF].

Results Within 6209 participants with full periodontal examination, we identified an overlap of n = 167 participants with periodontitis and HF. Participants with severe periodontitis showed a higher burden of cardiovascular risk factors (men at advanced age, diabetes mellitus, hypertension) when compared with participants with none/mild periodontitis. After adjustment for age, sex, body mass index, smoking, diabetes, hypertension, atrial fibrillation, and coronary artery disease, severe periodontitis was significantly associated with HF(m)rEF (odds ratio: 3.16; 95% CI: 1.21, 8.22; P = 0.019), although no association was found for HFpEF and HF in general.

Conclusions The current study demonstrated that severe periodontitis was significantly associated with HF(m)rEF, although no relevant associations were found with HFpEF and HF in general as well as echocardiographic variables. The results implicate a potential target group, who need special attention from cooperating physicians and dentists. Future studies are warranted to verify whether systemic inflammation could be the link between the two diseases.

Keywords Heart failure; Cardiovascular diseases; Risk factors; Periodontitis; DMFT; Gingival recession

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Introduction

Severe periodontitis affects 796 million people worldwide with a peak of prevalence in adults aged >60 years.[1] Poor oral hygiene enables excessive biofilm accumulation in the gingival pocket. This highly complex 'micro-ecosystem' can, under certain environmental conditions, experience a shift towards the outgrowth of periodontal pathogen bacteria and their virulence factors.[2] The consequences are manifold: destruction of the periodontal tissue until tooth loss (clinical phenotype of periodontitis), relocation of pathogenic bacteria into the bloodstream,[3] and production of

pro-inflammatory cytokines that add to the overall inflammatory pool.[4]

Heart failure (HF) is a progressive syndrome characterized by structural and functional cardiac changes resulting in typical symptoms as exertional dyspnoea, ankle swelling, and fatigue.[5] With a prevalence estimated up to be up to 10% in subjects aged 70 years or older, HF is a disease of pandemic outreach,[6] especially affecting the older population. HF can be stratified by left ventricular systolic function in heart failure with preserved ejection fraction (HFpEF), with mildly reduced ejection fraction (HFmrEF), and with reduced ejection fraction (HFrEF).[7]

Several studies propose an association of HF with low-grade systemic inflammation, expressed by elevated levels of circulating pro-inflammatory cytokines.[8–10] Subjects suffering from periodontitis exhibit raised levels of monocytes, endotoxins, and cytokines as an expression of systemic inflammation.[11,12] *Porphyromonas gingivalis (Pg)*, a major periodontal pathogen in periodontitis, produces a large set of different virulence factors.[13] A recent published cross-sectional study detected higher *Pg* antibody levels in participants with HF.[14] In line with this, HF patients showed a higher prevalence of severe periodontitis compared with the general population.[15] Nevertheless, data on the association between periodontitis and cardiac alterations measured by cardiac ultrasound as well as the different HF entities remain scarce.

Thus, the aim of the current study is to determine if periodontitis is associated with morphological and functional cardiac changes measured by transthoracic echocardiography (TTE) as well as different HF phenotypes in a representative sample of the general population.

Material and methods

Subjects, study design, and setting

The Hamburg City Health Study is a prospective, long-term, population-based, cohort study in Germany evaluating the interaction of socio-economic risk factors, modern imaging techniques, physiological measurements, and clinical variables.[16] The study population derived from a sample of the first 10 000 participants was included between 2016 and 2018. All measurements were conducted during a 1-day baseline visit at the HCHS study centre Hamburg-Eppendorf, Germany, according to the published protocol.[16] Exclusion criteria were missing full periodontal examination (n = 3791). Consequently, 6209 subjects with complete periodontal data were included in the study. All participants gave their informed consent prior to their inclusion in the study. The study protocol (PV5131) was approved by the local ethics committee of the Medical Association of Hamburg and registered at ClinicalTrial.gov (NCT03934957). This manuscript was written according to the STROBE guidelines.[17]

Assessment of dental variables

All participants underwent a comprehensive oral examination performed by certified study nurses supervised by dentists. Periodontal screening included probing depth (in mm), gingival recession (in mm), bleeding on probing (yes/no), and plaque index (yes/no). Subsequently clinical attachment loss (CAL; in mm) and DMFT (Decayed, Missing, Filled, Teeth, scores 1–32) was calculated. Periodontitis grading was in line with the classification introduced by Eke and Page (none/mild, moderate, severe),[18] which is currently confirmed as gold standard in reporting periodontitis in epidemiological studies.[19]

Echocardiographic data

TTE was performed and analysed by cardiologists and sonographers (technicians) on dedicated ultrasound machines (Siemens Acuson SC2000 Prime, Siemens Healthineers, Erlangen, Germany) following standard operating procedures. All TTE standard views were assessed. Qualitative and quantitative image analyses were performed using an off-line workstation (Siemens syngo SC 2000 Version 4.0, Siemens Healthineers, Erlangen, Germany) in agreement with the current guidelines of the American Society of Echocardiography and the European Association of cardiovascular imaging.[9,10] Left-sided volumes and ejection fraction (LVEF) were calculated biplane from the apical four-chamber and two-chamber view using the method of disk summation. Left-sided diameters were measured in parasternal long-axis view. Mitral inflow pattern was assessed in apical four-chamber view by placing pulsed-wave (PW) Doppler sample volume between mitral leaflet tips. Pulsed-wave tissue Doppler imaging e' velocity was measured in apical four-chamber view by placing the sample volume at the lateral and septal basal regions. Tricuspid annular plane systolic excursion (TAPSE) was obtained by M-mode echocardiography in the apical four-chamber view. Left atrial global peak strain was measured in apical four-chamber view by velocity vector imaging averaging global peak strain of all segments of the left atrium.

HF classification based on 2021 ESC guidelines

For the classification of subjects (not) having HF, the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF were applied and modified as follows.[5]

HF was considered present if subjects showed a combination of symptoms/signs, self-reported history of HF, HF medication, laboratory data, or echocardiographic criteria as

previously described by our group.[20] Symptoms or signs were dyspnoea (NYHA class ≥II) and oedema of the lower extremities. If no symptoms or signs were detectable, alternatively a self-reported history of HF and/or the following medication was seen as equivalent. Medication included for HF(m)rEF: beta-blockers, ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI) mineralocorticoid receptor antagonists (MRA), sodium-glucose co-transporter-2 (SGLT2) inhibitors, and loop diuretics, whereas for HFpEF only loop diuretics were defined as medication. Oedema were evaluated by physical examination by medical professionals following a standardized protocol. Dyspnoea, history of HF, and medication were assessed by standardized self-reported questionnaires. NT-proBNP samples were measured from fasting blood samples withdrawn at the day of examination using an immunoassay (Alere NT-proBNP for ARCHITECT, Abbott Diagnostics) with a measurement ranges between 8.2 and 35 000 ng/L.

Due to limited size, all subjects with LVEF <50% and symptoms or signs of HF were classified as HF with reduced and mildly reduced ejection fraction [HF(m)rEF], instead of differentiating between heart failure with mildly reduced ejection fraction (HFmrEF LVEF 41–49%) and heart failure with reduced ejection fraction (HFrEF, LVEF <40%). Subjects were classified as having HFpEF if they presented with preserved LVEF (LVEF ≥50%), symptoms or signs of HF, and either at least two or more echocardiographic signs of cardiac structural of functional abnormalities or the combination of NT-proBNP levels exceeding 125 pg/mL (sinus rhythm) or 365 pg/mL [atrial fibrillation (AF)] and at least one or more echocardiographic signs of cardiac structural of functional abnormalities. Echocardiographic signs of cardiac structural or functional abnormalities were defined as left ventricular hypertrophy: LV mass indexed to BSA ≥ 95 g/m^2 for women, ≥115 g/m^2 for men, left atrial enlargement: left atrial volume index (LAVI) > 34 mL/m2 (sinus rhythm) and >40 mL/m2 (AF), E/e' ratio >9, and tricuspid regurgitation velocity (Vmax) > 2.8 m/s. HF in general describes all subjects with either HF(m)rEF or HFpEF. Subjects with LVEF <50%, but no symptoms or signs of HF were considered to have asymptomatic left ventricular systolic dysfunction (ALVSD). In addition, HF was classified based on the 2016 ESC HF guidelines (*Supporting Information*).

Assessment of additional variables

At the baseline visit the following variables were assessed: sex, age (in years), education (International Standard Classification of Education[21]), body mass index (BMI in kg/m^2), smoking (yes/no), diabetes (positive self-disclosure, taking medication of the A10 group (ATC Code), fasting glucose >126 mg/dL, not fasting glucose >200 mg/dL), systolic and diastolic blood pressure (blood pressure was measured twice on the right arm with a 5-min resting period in between the measurements, the average of two measurements of the systolic and diastolic blood pressure was taken), and coronary artery disease (CAD = defined as suffering from one or more of the following conditions: status post myocardial infarction, percutaneous coronary intervention or history of coronary bypass surgery assessed by questionnaire). Furthermore, blood plasma was analysed for biomarkers: high-sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6). Dental parameters included DMFT Index (Decayed, Missing, Filled, Teeth), BOP Index (Bleeding on Probing), and plaque index.

Statistical analyses

In descriptive analyses, absolute numbers and proportions (%) are listed for categorical variables and median (interquartile ranges) are shown for continuous variables. Differences within periodontitis groups (none/mild, moderate, and severe) were tested for continuous variables using the Kruskal–Wallis test and for categorical variables using the chi-square test. Descriptive analyses were presented for all variables stratified by the grading of periodontitis (none/mild, moderate, and severe). Multivariable linear and logistic regression models and multinomial regression models were calculated (outcome variable: HF, HF subtypes and echocardiographic variables; exposure: periodontitis severity). Based on prior research and also based on theoretical considerations, adjustments for relevant confounders (age, sex, BMI, smoking, diabetes, hypertension, AF, and coronary artery disease) were applied. More precisely, an association between various known cardiovascular risk factors and HF has been shown. For example, age and sex are highly associated with HF,[22] and an adverse association (the 'obesity paradox') is documented for the association between the BMI and HF.[23] Also smoking,[24] diabetes,[25] and AF[26] are known risk factors for HF, and the association between coronary artery disease and HF has been recently reviewed in detail here.[27]

A *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using R software, version 4.0.3.

Results

Baseline characteristics

From a total of 10 000 participants, a subset of 6209 participants presented full periodontal examination. We identified an overlap of *n* = 167 participants with periodontitis and HF. Participants with severe periodontitis were more often men (60.9 vs. 39.6%), of older age (66 vs. 59 years) and lower educational level (4.1 vs. 2.7%), were more frequently smokers (25.1 vs. 16.2%), were diabetic (11.3 vs. 6.2%), were

affected by arterial hypertension (72.5 vs. 54.8%), and were more likely to have AF (6.9 vs. 4.3%) and coronary artery disease (9.3 vs. 6.1%) when compared with participants with none/mild periodontitis. Furthermore, participants with severe periodontitis differed in their current medication (beta-blockers: 18.7 vs. 13.2%) and angiotensin-converting-enzyme inhibitors/angiotensin II receptor blocker (ACEi/ARBs: 23.2 vs. 17.3%) when compared with participants with none/mild periodontitis. Laboratory biomarkers of inflammation as well as NT-proBNP showed higher median values in participants presenting with severe vs. none/mild periodontitis (IL-6 = 1.77 vs. 1.45 ng/mL; $P < 0.001$, hs-CR$P = 0.13$ vs. 0.10 mg/dL; $P < 0.001$, NT-proBNP 71 vs. 89 ng/L; $P < 0.001$) (*Table 1*). Baseline characteristics of the cohort with absent dental examination are displayed in *Table S1*.

HF showed an increase from none/mild over moderate to severe periodontitis (2.5%, 3.8%, 6.0%; $P = 0.001$). This trend was also depictable for the HF(m)rEF (1.0%, 1.9%, 3.3%; $P = 0.006$) and HFpEF phenotype (1.4%, 1.8%, 2.6%; $P = 0.006$). Although no significant intergroup changes for echocardiographic parameters of left and right ventricular systolic function were detected, left ventricular mass index (LVMI) and E/e' ratio showed the highest values in the severe periodontitis group compared with those with no/mild periodontitis (*Table 2*).

Regression analysis

In multivariable linear regression analysis adjusted for age, sex, BMI, smoking, diabetes, hypertension, AF, and CAD, moderate and severe periodontitis were associated with reduced LV volumes, indicated by a β of −6.57 (95% CI: −9.16, −3.97, $P < 0.001$) and −5.15 (95% CI: −8.62, −1.67, $P = 0.004$) for LVEDV, respectively. No significant associations were found for periodontitis with biventricular systolic function, represented by LVEF and TAPSE, as well as markers of diastolic function, represented by E/e' and TR Vmax (*Table 3*).

Applying the 2021 ESC HF guidelines, in multinomial logistic regression analysis adjusted for age, sex, BMI, smoking, diabetes, hypertension, AF, and CAD, severe periodontitis was significantly associated with HF(m)rEF (OR: 3.16; 95% CI: 1.21, 8.22; $P = 0.019$) (*Table 4*). No significant associations

Table 1 Baseline characteristics stratified by periodontitis severity

	Total cohort $n = 10\,000$	No/mild periodontitis $n = 1453$	Moderate periodontitis $n = 3580$	Severe periodontitis $n = 1176$	
		$n = 6209$			*P* for trend
	Demographics				
Female sex	5108 (51.1)	878 (60.4)	1814 (50.7)	460 (39.1)	<0.001
Age	63.00 [55.00, 70.00]	59.00 [52.00, 66.00]	63.00 [55.00, 69.00]	66.00 [59.00, 71.00]	<0.001
Educational level (high)	4163 (44.1)	650 (47.6)	1521 (45.6)	431 (39.8)	0.001
BMI	26.13 [23.53, 29.21]	25.56 [23.01, 28.67]	26.02 [23.55, 29.01]	26.44 [24.11, 29.65]	<0.001
Smoking	1978 (19.9)	235 (16.2)	608 (17.1)	293 (25.1)	<0.001
	Co-morbidities				
Diabetes	794 (8.6)	85 (6.2)	242 (7.4)	122 (11.3)	<0.001
Hypertension	6301 (66.1)	768 (54.8)	2266 (66.3)	810 (72.5)	<0.001
Atrial fibrillation	561 (6.2)	57 (4.3)	181 (5.5)	75 (6.9)	0.019
Asthma or COPD	861 (9.5)	131 (9.7)	298 (9.0)	85 (7.9)	0.327
	Medication				
Aldosterone antagonists	67 (0.7)	5 (0.4)	18 (0.5)	5 (0.4)	0.715
Loop diuretics	201 (2.1)	17 (1.2)	56 (1.6)	23 (2.1)	0.226
Beta-blockers	1661 (17.4)	188 (13.2)	552 (16.2)	209 (18.7)	0.001
ACEis/ARBs	2030 (21.3)	246 (17.3)	698 (20.5)	259 (23.2)	0.001
ARNIs	6 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)	0.476
SGLT inhibitors	15 (0.2)	1 (0.1)	7 (0.2)	2 (0.2)	0.579
	Laboratories				
Leukocyte count, 10^9/l	6.00 [5.00, 7.10]	5.80 [4.90, 6.70]	5.90 [4.90, 7.00]	6.20 [5.27, 7.40]	<0.001
IL-6, pg/mL	1.62 [1.17, 2.31]	1.45 [1.01, 2.04]	1.55 [1.15, 2.16]	1.77 [1.33, 2.63]	<0.001
hs-CRP, mg/dL	0.12 [0.06, 0.26]	0.10 [0.06, 0.23]	0.11 [0.06, 0.25]	0.13 [0.07, 0.30]	<0.001
NT-proBNP, ng/L	81.00 [44.00,148.00]	71.00 [42.00,128.00]	79.00 [42.75,141.00]	89.00 [48.00,158.00]	<0.001
	Dental variables				
DMFT Index	20.00 [16.00, 23.00]	17.00 [14.00, 21.00]	19.00 [16.00, 23.00]	21.00 [17.00, 24.25]	<0.001
BOP Index	7.69 [1.92, 20.37]	2.08 [0.00, 7.14]	8.33 [2.17, 19.23]	21.05 [9.26, 41.67]	<0.001
Plaque Index	8.70 [0.00, 29.17]	0.00 [0.00, 10.71]	8.93 [0.00, 27.78]	22.00 [5.77, 54.76]	<0.001

ACEi/ARBs, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blocker; BMI, body mass index; BOP Index, Bleeding on Probing Index; COPD, chronic obstructive pulmonary disease; DMFT, Decayed, Missing, Filled, Teeth; Hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; NT-ProBNP, N-terminal pro-B-type natriuretic peptide.
Continuous variables are presented as median and interquartile range (95% CI), and categorical variables are presented as absolute numbers and percentages.

Table 2 Heart failure entities and echocardiographic findings stratified by periodontitis severity

	Overall cohort $n = 10\,000$	No/mild periodontitis $n = 1453$	Moderate periodontitis $n = 3580$	Severe periodontitis $n = 1176$	
		$n = 6209$			*P* for trend
	Heart failure				
HF = overall	342 (4.9)	26 (2.5)	93 (3.8)	48 (6.0)	<0.007
HF(m)rEF	187 (2.6)	11 (1.0)	48 (1.9)	27 (3.3)	0.006
HFpEF	155 (2.2)	15 (1.4)	45 (1.8)	21 (2.6)	0.006
ALVSD	79 (1.1)	18 (1.7)	28 (1.1)	11 (1.4)	0.006
	Echocardiographic data				
LVEF, %	58.43 [55.50, 61.79]	58.44 [55.72, 61.82]	58.58 [55.72, 61.84]	58.17 [55.37, 61.42]	0.124
LVMI, g/m²	82.35 [71.57, 96.53]	79.45 [70.05, 92.11]	81.95 [71.28, 95.25]	85.89 [74.03, 100.42]	<0.001
LVEDV, mL	109.87 [91.96, 132.59]	111.58 [94.47, 133.57]	108.99 [90.54, 131.56]	111.49 [93.80, 134.07]	0.014
LAVI, mL	26.40 [21.81, 31.96]	26.63 [22.55, 31.68]	26.06 [21.31, 31.75]	26.94 [22.15, 33.36]	0.009
TAPSE, mm	24.00 [21.33, 27.02]	24.42 [21.80, 27.20]	24.00 [21.33, 27.17]	24.18 [21.34, 27.20]	0.260
TR Vmax, m/s	2.33 [2.21, 2.52]	2.32 [2.19, 2.49]	2.32 [2.21, 2.51]	2.32 [2.22, 2.52]	0.555
E/e'	7.33 [6.22, 8.72]	7.13 [6.12, 8.45]	7.28 [6.14, 8.62]	7.42 [6.35, 9.08]	<0.001
LA strain, %	37.70 [29.77, 47.71]	37.89 [30.32, 47.91]	38.07 [30.00, 47.83]	38.26 [29.57, 48.23]	0.968

ALVSD, asymptomatic left ventricular systolic dysfunction; HF, heart failure; HF(m)rEF, heart failure with mildly and reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA strain, left atrial strain; LAVI, left atrial systolic volume indexed to body surface area; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation.
Continuous variables are presented as median and interquartile range, and categorical variables are presented as absolute numbers and percentages.

Table 3 Multivariable linear regression analysis for the association of moderate/severe periodontitis and echocardiographic variables

	Moderate periodontitis		Severe periodontitis	
	Beta (95% CI)	*P* value	Beta (95% CI)	*P* value
Echocardiographic data				
LVEF, %	0.24 [−0.23, 0.70]	0.321	0.17 [−0.43, 0.78]	0.576
LVMI, g/m²	−1.25 [−2.94, 0.43]	0.145	0.51 [−1.70,2.72]	0.653
LVEDV, mL	−6.57 [−9.16, −3.97]	<0.001	−5.15 [−8.62, −1.67]	0.004
LAVI, mL	−1.43 [−2.24, −0.62]	<0.001	−0.31 [−1.39, 0.77]	0.571
TAPSE, mm	−0.17 [−0.61, 0.27]	0.453	−0.23 [−0.83, 0.37]	0.457
TR Vmax, m/s	0.00 [−0.04, 0.04]	0.960	0.01 [−0.04, 0.06]	0.755
E/e'	−0.09 [−0.26, 0.08]	0.313	0.04 [−0.18, 0.27]	0.702
LA strain, %	0.81 [−0.75, 2.37]	0.308	0.24 [−1.84, 2.32]	0.818

Adjustment was performed for age, sex, body mass index, smoking, diabetes, hypertension, atrial fibrillation, and coronary artery disease. Abbreviations as in *Table 2*.

Table 4 Logistic regression analysis for the association of moderate/severe periodontitis and heart failure classified by the 2021 ESC guidelines

	Heart failure		
	OR	95% CI	*P* value
Periodontitis moderate	1.03	0.59, 1.81	0.917
Periodontitis severe	1.64	0.88, 3.06	0.122
Age	1.04	1.01, 1.07	0.015
Female sex	0.94	0.60, 1.46	0.776
Smoking	1.64	0.95, 2.80	0.074
BMI	1.06	1.01, 1.10	0.017
Hypertension	6.41	2.53, 16.24	<0.001
Diabetes	1.58	0.88, 2.82	0.123
CAD	3.63	2.23, 5.92	<0.001
Atrial fibrillation	2.99	1.77, 5.03	<0.001

Adjustment was performed for age, female sex, body mass index (BMI), smoking, diabetes, hypertension, atrial fibrillation, and coronary artery disease (CAD). Abbreviations as in *Table 2*.

were found for HFpEF (OR: 1.21; 95% CI: 0.53, 2.75; *P* = 0.657) and HF in general (OR: 1.64; 95% CI: 0.88, 3.06; *P* = 0.122) (*Tables 4* and *5*). However, when applying the 2016 ESC HF guidelines, severe periodontitis was significantly associated with both HF phenotypes: HF(m)rEF (OR: 3.85; 95% CI: 0.99, 14.91; *P* = 0.051), HFpEF (OR: 3.76; 95% CI: 1.36, 10.40; *P* = 0.011), and HF in general (OR: 2.92; 95% CI: 1.24, 6.86; *P* = 0.014) (*Tables S1* and *S2*).

Discussion

Based on a contemporary, well-characterized sample from the general population, the present study provides new data on the association of periodontitis and HF. Severe periodontitis

Table 5 Multinominal regression analysis for the association of moderate/severe periodontitis and heart failure subtypes classified by the 2021 ESC guidelines

	HFpEF OR (95% CI), *P* value	HF(m)rEF OR (95% CI), *P* value
Periodontitis moderate	0.740 (0.361, 1.515) 0.410	1.784 (0.727, 4.379) 0.207
Periodontitis severe	1.205 (0.529, 2.747) 0.657	3.156 (1.212, 8.218) 0.019
Age	1.065 (1.021, 1.109) 0.003	1.042 (1.002, 1.083) 0.039
Female sex	1.646 (0.899, 3.014) 0.106	0.526 (0.278, 0.996) 0.049
Smoking	2.006 (0.976, 4.122) 0.058	1.376 (0.660, 2.869) 0.395
Diabetes	2.521 (1.227, 5.180) 0.012	1.071 (0.425, 2.699) 0.885
CAD	4.626 (2.318, 9.233) <0.001	4.485 (2.378, 8.458) <0.001
BMI	1.098 (1.038, 1.161) 0.001	1.024 (0.959, 1.092) 0.482
Atrial fibrillation	3.221 (1.551, 6.686) 0.002	3.356 (1.695, 6.644) 0.001

Adjustment was performed for age, female sex, body mass index (BMI), smoking, diabetes, atrial fibrillation, and coronary artery disease (CAD). Abbreviations as in *Table 2*. No adjustment for hypertension, because of multicollinearity with HF(m)rEF.

was significantly associated with HF(m)rEF, in contrast to HFpEF and HF in general, even after adjustment for cardiovascular risk factors and prevalent cardiovascular diseases.

All investigated echocardiographic variables, except the LVEDD, were not associated with moderate or severe periodontitis, which is partially in line with the literature. In a cross-sectional study from the University of Hong Kong, LVMI, E/e', and left ventricular global longitudinal strain were associated with periodontitis.[28] However, in contrast to our study, only patients with diabetes mellitus were included, proposing a diabetes-induced effect on myocardial morphology and function. Furthermore, in the mentioned study, no intergroup differences were detected for LVEF in subjects with or without periodontitis. Regarding LVMI, conflicting results have been reported. Although a study by Angeli *et al*. identified LVMI as a predictor for the severity of chronic periodontitis, this finding was not reproducible in other studies.[29,30] Both studies included solely subjects with essential hypertension, which further limits their applicability to the general population. Because we could not detect any associations of periodontitis with the above-mentioned variables, but solely with LVEDD, we interpret this as a result of limited sample size as the LVEDD subjects to significant fluctuations based on the volume status during ultrasound examination.

Severe periodontitis was significantly associated with HF(m)rEF, but not with HFpEF and HF in general. Up to now, only few studies investigated the association of periodontitis and HF.[14,15,31] Comparing our findings with the so far published studies is challenging due to differing study populations as well as various periodontitis and HF classification protocols. Notably, in the present study, we documented periodontitis using the current gold standard to report periodontal disease in epidemiological approaches.[19] Furthermore, HF and its entities were classified following the current 2021 ESC HF guidelines.[7] In line with our results, data from the National Health Insurance System–National Health Screening Cohort (NHIS-HEALS) showed that a higher number of missing teeth was significantly associated with HF during a median follow-up of 10.5 years.[31] Nevertheless, the investigated study population was rather young (median age 52.5 years) with male predominance (61.2% males). In comparison with our data, fewer participants suffered from hypertension (38.9%), whereas a similar prevalence of diabetes mellitus was documented (9.0%).

Non-cardiac co-morbidities drive HF progression, as data from 31 344 participants revealed up to eight co-morbidities in patients with HFpEF or HF(m)rEF (mean: 2.9 or 2.4).[32] We see a similar accumulation of non-cardiac co-morbidities for periodontitis, particularly in the elderly population, for example, type 2 diabetes, hypertension, rheumatoid arthritis, and psoriasis.[33] A major part of those conditions share inflammatory pathways, which most likely also display the link between periodontitis and HF, rather than a causal relationship.[33] Periodontitis itself nurtures the production of cytokines and endotoxins and thereby further aggravates a systemic inflammatory state. Current literature proposes endothelial dysfunction as contributor to HF.[34] Periodontitis induces endothelial dysfunction via two possible mechanisms: (i) Vascular inflammation via increased levels of monocytes, which adhere to endothelial cells, activate NF-κB and the expression of VCAM-1, and thus initiate a local TNF-α cascade.[11] (ii) The virulence factor 'Gingipains' of *P. gingivalis* degrades platelet endothelial cell adhesion molecule (PECAM1) and vascular endothelial cadherin (VE-cadherin) and thus increases vascular permeability.[12] Furthermore, it is suspected that the translocation of periodontal bacteria into the bloodstream can cause autoimmunization against muscarinic (MR-Aabs) and beta1-adrenergic receptors (β1AR-Aabs), which are a potential risk factor for chronic HF.[35]

In the Atherosclerosis Risk in Communities Study (ARIC) with 6707 participants with a median follow-up time of 13 years, periodontal disease was associated with increased risk for HFpEF and HF(m)rEF.[36] In the current study, severe periodontitis was solely associated with HF(m)rEF and not with HFpEF. However, when applying the 2016 ESC HF guidelines, severe periodontitis was significantly associated with both HFpEF and HF(m)rEF. Because HF phenotypes in the ARIC study derived from hospitalization records between

2005 and 2018, the 2021 ESC HF guidelines were not applied. Notably, the 2021 ESC HF guidelines propose a revised algorithm for diagnosing HF with preserved ejection fraction including raised NT-proBNP and LAVI cut-offs for subjects with AF as well as new criteria for diastolic dysfunction. These changes might be explanatory for the lost association with periodontitis compared to the 2016 ESC HF guidelines as they lead to a numerical decrease of the HFpEF population, possibly reflecting a more accurate HFpEF definition.

For the consistent association of severe periodontitis with HFrEF, no matter which of the ESC classifications is applied, we propose the following explanation: Whereas HFrEF primarily originates from direct myocardial injury, HFpEF seems to be the result of impaired left ventricular relaxation, abnormal volume regulation, and disrupted ventricular-arterial interplay.[37] As described above, periodontitis mediates vascular inflammation and increased vascular permeability leading to endothelial dysfunction. Endothelial dysfunction itself can result in myocardial ischaemia with direct myocardial damage, potentially accounting for the association of severe periodontitis and HF(m)rEF.

Limitations

Our study cohort originates from the population of Hamburg. Hence, most study participants were of Caucasian descent, and the functional translation of our findings into other populations is limited. Further validation in other ethnic groups is needed.

The classification of subjects as having HF was based on echocardiographic, laboratory, and anamnestic following current ESC HF guidelines. These were modified, as HFrEF and HFmrEF were not evaluated individually, but as the joint HF(m)rEF group. Further prospective studies, with a high amount of subjects suffering from HF, making a distinction of HFrEF and HFmrEF feasible, are needed to evaluate the role of periodontitis in the genesis or aggravation of HF. Furthermore, dyspnoea, the leading symptom of HFpEF, was assessed by a validated questionnaire without clinical testing. Finally, our study setting is cross sectional.

Our dataset does not provide information on the duration of periodontitis. Consequently, a potential correlation of the duration of periodontitis and the risk of heart failure cannot be addressed and should be part of future studies. No conclusions can be drawn concerning the cause and effect of periodontitis and HF.

Conclusion

The current study demonstrated that severe periodontitis was significantly associated with HF(m)rEF, although no relevant associations were found with HFpEF and HF in general as well as echocardiographic variables. The results implicate a potential target group, who need special attention from cooperating physicians and dentists. Future prospective studies are warranted to verify the direction of association and whether systemic inflammation could be the link between the two diseases.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supporting information

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

Table S1. Baseline characteristics stratified by gender.
Table S2. Multinominal regression analysis for the association of moderate/severe periodontitis and heart failure phenotypes classified by the 2016 ESC Guidelines.
Table S3. Logistic regression analysis for the association of moderate/severe periodontitis and heart failure classified by the 2016 ESC heart failure Guidelines.

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