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Abdominal obesity modifies long-term associations between periodontitis and markers of systemic inflammation

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ABSTRACT

Objective: Periodontitis is considered to promote atherosclerosis and cardiovascular diseases through increased low-grade systemic inflammation. However, there is no information on the long-term impact of periodontitis on systemic inflammation from cohort studies. Thus, this study aims to assess the impact of periodontitis on systemic inflammation (fibrinogen and white blood cells (WBC)) in a population-based longitudinal survey in north-eastern Germany.
Methods: The study sample comprised 2622 subjects from the Study of Health in Pomerania with complete 5- and 11-year follow-ups. Periodontitis was assessed by probing depth and clinical attachment level. Multilevel regression analyses were applied to evaluate associations between periodontitis measures and i) fibrinogen/WBC count using 11-year follow-up data and ii) respective *z*-scores of fibrinogen/WBC count using 5- and 11-year follow-up data. We adjusted for common cardiovascular risk factors and stratified analyses by abdominal obesity (P for interaction <0.10).
Results: In lean subjects, beta-coefficients of mean probing depth were $B = 0.13$ (0.08–0.019; $P < 0.001$) for fibrinogen and $B = 0.50$ (0.37–0.64; $P < 0.001$) for WBC count using 11-year follow-up data only. For lean subjects, models using *z*-scores confirmed that increased mean probing depths were associated with increased fibrinogen *z*-scores ($B = 0.14$ (0.09–0.18; $P < 0.001$)) and increased WBC *z*-scores ($B = 0.16$ (0.11–0.20; $P < 0.001$)). Consistent results were found for mean clinical attachment levels. For abdominally obese subjects, relations between periodontitis measures and levels of inflammation markers were less pronounced or non-significant.
Conclusion: Modified by abdominal obesity, periodontitis affected systemic inflammation in a significant dose-dependent manner. Results contribute to the discussion on how periodontitis is linked to atherosclerosis and cardiovascular diseases.

1. Introduction

Cardiovascular diseases (CVD) rank among the leading causes of deaths worldwide. [1] Over the past decade, the global number of people succumbing to ischaemic heart disease and stroke increased from 11.9 million in 2000 to 13.2 million in 2011; which refers to 21.9% of the total number of deaths [1].

Periodontitis is a highly prevalent [2] bacterially induced inflammatory disease affecting the supporting tissues of the teeth. There is increasing evidence that periodontitis might be associated with a higher risk of cardiovascular events [3–6], but the potential pathways linking periodontitis and CVD are manifold and not entirely known yet [7–9]. One putative pathway involves systemic inflammatory host responses to oral bacteraemia [7,9]. It is widely accepted that periodontitis promotes transient bacteraemia while tooth brushing, chewing or dental procedures [10,11] because the ulcerated periodontal pocket epithelium provides an entrance for oral pathogens. These bacteria are thought to provoke an immune

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system response and thereby cause low-grade systemic inflammation [8,9] and promote the formation of atheromatous plaques [12].

Numerous studies [8,13–17] consistently observed significantly elevated levels of inflammation markers in periodontitis patients as compared to healthy controls, reflecting also the severity of the periodontal destruction [14,16]. Moreover, periodontal treatment studies [18–20] and recent meta-analyses [21–23] indicate that periodontal therapy reduces serum levels of inflammation markers. However, current evidence from cohort studies regarding the association between periodontitis and progression of systemic inflammation is missing. Therefore, our aim was to assess the long-term impact of periodontitis on changes in serum levels of fibrinogen and white blood cell (WBC) counts using data from the population-based Study of Health in Pomerania (SHIP) over an 11-year period.

2. Material and methods

2.1. Study population

SHIP is a population-based longitudinal survey in West Pomerania, the northeast region of Germany. Further details on the SHIP study design and recruitment can be found elsewhere [24–26]. Briefly, a two-stage stratified cluster design was implemented. First, three cities and 12 larger towns were selected and 17 surrounding villages were randomly drawn. Second, a sample of Caucasian subjects, stratified according to age and gender, was drawn from population registries proportional to each municipality size. In total, 7006 adults aged 20–79 years were invited, whereof 4308 finally participated (1553 refused to participate, 615 migrated, 126 deceased, 404 did not attend scheduled appointments) in the baseline examinations from 1997 to 2001 (SHIP-0). The first follow-up examinations (SHIP-1) were conducted about five years later, from 2002 to 2006 and comprised 3300 subjects (58 did not answer, 541 refused to participate, 127 migrated, 579 deceased, 89 did not attend scheduled appointments). The second follow-up examinations (SHIP-2) were performed on 2252 subjects another six years later, from 2008 to 2012. In SHIP-2, all SHIP-0 participants were reinvited and thus, the sample was composed of 2146 of those 3300 subjects who participated in SHIP-0 and SHIP-1 before (175 did not answer, 579 refused to participate, 9 migrated, 246 deceased, 145 did not attend scheduled appointments) and of 106 of those 1008 subjects who participated in SHIP-0 before but not in SHIP-1 (184 did not answer, 354 refused to participate, 7 migrated, 326 deceased, 31 did not meet appointment). The SHIP protocol was approved by the Ethical Review Board of the University of Greifswald.

Among 4308 baseline participants, 26 had missing fibrinogen or WBC data, 251 lacked at least one confounder and 73 were excluded because of pregnancy (20) or cancer (53). Another 440 subjects were edentulous and 13 refused dental examination. Data on probing depth (PD) and clinical attachment level (CAL) were missing for 43 and 276 subjects, respectively. In total, with respect to PD (CAL), 3462 (3299) subjects completed SHIP-0. Of these, 2472 (2340) and 1758 (1674) subjects had complete data and met inclusion criteria at SHIP-1 and SHIP-2, respectively. The study sample comprised 2622 (2483) subjects with complete data at SHIP-0 and at least one follow-up.

2.2. Covariates

Baseline data comprised socioeconomic and behavioural risk factors assessed by computer-assisted personal interviews, but also laboratory and somatometric variables. School education was defined as <10, 10 and >10 years. Smoking status was assessed as never, former and current smoking. Participants who reported to exercise physically for at least 1 h per week during summer or winter were classified as being physically active. Average daily alcohol consumption in grams of pure ethanol was assessed using an additive beverage-specific measure by multiplying standard ethanol contents with drinking frequencies and consumed quantities [27]. Risky alcohol consumption was defined as at least 20 g per day for women and 30 g per day for men [27]. Waist circumference (WC) was measured to the nearest 0.1 cm using an inelastic tape. Men with a WC of ≥102 cm and women with a WC of ≥88 cm were classified as abdominally obese [28].

Diabetes mellitus was defined as self-reported physician's diagnosis, treatment with insulin or antidiabetic agents (Anatomical Therapeutic Chemical Classification System (ATC) code A10) or non-fasting glucose levels ≥11.1 mmol/l or glycated haemoglobin (HbA1c) concentrations of ≥48 mmol/mol (6.5%) as an indicator of undiagnosed diabetes [29].

2.3. Laboratory measurements

Non-fasting blood samples were drawn from the cubital vein in the supine position. Total cholesterol, low (LDL-C) and high density lipoprotein cholesterol (HDL-C) were measured photometrically (Hitachi 704; Roche, Mannheim, Germany). Dyslipidaemia was defined as total cholesterol ≥ 6.2 mmol/l, LDL-C ≥ 4.1 mmol/l, HDL-C < 1.04 mmol/l or the use of lipid-modifying drugs (ATC code C10). HbA1c was measured by HPLC (ClinRep HbA1C, Recipe Chemicals + Instruments GmbH, Munich, Germany). WBC levels were determined using a Coulter MaxM analyser (Coulter Electronics, Miami, Florida, USA) in SHIP-0 and SHIP-1 as well as XT 2000 and XE 5000 haematology analysers (Sysmex Corporation, Kobe, Japan) in SHIP-2. Plasma fibrinogen concentrations were assayed according to Clauss with an Electra 1600 analyser (Instrumentation Laboratory, Barcelona, Spain) in SHIP-0, with an Amax analyser (Trinity Biotech, Bray, Ireland) in SHIP-1 and with a BCS-XP analyser (Siemens Healthcare Diagnostics, Eschborn, Germany) in SHIP-2. A Behring Nephelometer II (Dade Behring Inc., Eschborn, Germany) was used to determine serum levels of high-sensitivity C-reactive protein (hs-CRP) in SHIP-0 and SHIP-1. For SHIP-2, hs-CRP data were not available.

2.4. Periodontal assessments

At baseline and follow-up examinations, identical recording protocols were used. PD and CAL were measured according to the half-mouth method at four sites per tooth (distobuccal, mesiobuccal, midbuccal, midlingual/midpalatal), alternating on the right or left side, using a periodontal probe (SHIP-0: PCP11, SHIP-1: PCP2, SHIP-2: PCP11, Hu-Friedy, Chicago, IL, USA). Third molars were excluded. PD represents the distance from the gingival margin to the base of the periodontal pocket and CAL represents the distance from the cemento-enamel junction to the bottom of the periodontal pocket. In case of an indistinct determination of the cemento-enamel junction (e.g. wedge-shaped defects, fillings or crown margins), CAL was not recorded. Mean values of PD and CAL were calculated on subject-level. The percentage of sites with PD/CAL ≥3 mm was also considered because this threshold was shown to correlate most strongly with fibrinogen levels [30].

Examiners were initially trained and calibrated dentists. For SHIP-0 and SHIP-1 the initial training was performed by a periodontist. In the course of all surveys, calibration exercises were performed every 6–12 months on persons not connected to the study. In SHIP-0, an intra-class correlation of 0.82–0.91 per examiner (SHIP-1: 0.70–0.89, SHIP-2: 0.76–0.88) and an inter-class correlation of 0.84 (SHIP-1: 0.90, SHIP-2: 0.74) were achieved relative to CAL [25,31,32]. The use of different periodontal probes at