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Associations between periodontal disease and cardiovascular surrogate measures among Indigenous Australians ☆

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ABSTRACT

Background/objectives: Inflammation is a key pathogenetic factor in atherogenesis. Periodontitis is a chronic inflammatory source which can have systemic impacts. Indigenous Australians have a higher prevalence of periodontal disease and experience cardiovascular disease earlier than non-Indigenous Australians. The aim was to describe the association between severity of periodontal inflammatory disease and measures of arterial structure and function.

Methods: Periodontal disease in a convenience sample of Indigenous Australians was assessed clinically; for those with periodontal disease, the extent of periodontal pockets ≥4 mm was stratified into quartiles. Vascular health was measured non-invasively via carotid-dorsalis pedis pulse-wave velocity (PWV), and via B-mode ultrasound of the common carotid intima-media (IMT). Non-fasting blood samples were collected for lipid and inflammatory marker evaluation. Linear regression models were constructed to determine the associations between extent of periodontal pocketing and vascular health, adjusting for traditional cardiovascular common risk factors.

Results: 273 Indigenous Australian adults were recruited and complete data was available for 269 participants (154 males), median age 39 years. Arterial stiffness (PWV) significantly increased with increasing extent of periodontal pocketing (p trend = 0.001). By contrast, carotid IMT did not differ across quartiles.

Conclusions: Periodontal pocketing was associated with central arterial stiffness, a marker of presymptomatic arterial dysfunction, in Indigenous Australian adults with periodontal disease.

1. Introduction

Periodontitis is characterised by chronic low-grade inflammation of the periodontal tissues which results in the destruction of the alveolar bone and formation of pathological pockets around diseased teeth that can lead to tooth loss [1].

Inflammation is a core component of the arterial wall disturbances leading to atherosclerosis [2]. The source of inflammation, however, does not necessarily have to arise from within the artery [3]. Long-term systemic inflammatory events such as those observed in periodontitis may contribute to atherosclerosis. The various mechanisms in which this may occur have recently been reviewed [4].

Periodontitis and cardiovascular disease (CVD) share common risk factors. For example, both occur more frequently among those with a history of cigarette smoking, people with diabetes and both are also associated with ageing. It is currently unclear whether periodontitis contributes to the initiation and/or progression of atherosclerosis, and if so, to what extent. It remains possible that no causal relationship

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exists, but rather, that periodontal and cardiovascular diseases are associated simply due to both developing over the same timeframe [5].

Periodontal disease has been linked with increased pulse wave velocity (PWV) of peripheral arteries [6–8]. Associations of PWV at different sites and atherosclerosis have suggested that peripheral arterial PWV may not be comparable to the assessment of central arterial stiffness made when measuring carotid-femoral PWV to determine CVD risk [9]. Little is known about the relationship between periodontitis and central arterial stiffness [7].

Life expectancy of Indigenous Australians is estimated to be 10–12 years lower than non-Indigenous Australians due to high rates of chronic diseases including CVD [10,11]. The occurrence of coronary heart disease is much earlier among Indigenous Australians compared to their non-Indigenous counterparts [12].

We hypothesised that increased severity of periodontal disease would correspond with increased levels of CVD risk markers and surrogate measures of vascular health. Accordingly, we sought to: 1) determine the associations between periodontal pocketing, measures of inflammation and vascular health in Indigenous Australian adults with periodontitis; and 2) determine if the association corresponds to a dose–response relationship between periodontal disease, IMT and PWV.

2. Materials and methods

A convenience sample of Indigenous Australian adults residing in Darwin, Katherine and Alice Springs in Australia's Northern Territory was recruited from community medical and dental health clinics, Aboriginal medical services and correctional facilities in the first instance. The "snowballing method" was also utilised by seeking to recruit friends and family of those already recruited as a secondary approach. The resultant sample was recruited for the purposes of a randomised controlled trial investigating the effect of periodontal therapy on surrogate markers of cardiovascular disease [13]. This study uses baseline data from the over-arching trial to investigate the present study aims. Study participants were examined by two dental clinicians to verify periodontitis case status defined as the presence of at least 2 interproximal sites with clinical attachment loss (CAL) ≥4 mm, or at least two interproximal sites with probing depth (PD) ≥5 mm [14]. Eligibility for inclusion was further determined via combination of oral interview and medical history. To be eligible, participants had to be aged 18 years or older and have a minimum of five natural teeth. Individuals having received periodontal treatment in the preceding six months, those with a history of any cardiovascular condition (with the exception of angina pectoris), rheumatic fever or any other cardiac or medical conditions which require preventive antibiotic prophylaxis, pregnant women, or people with clinically visible endodontic or orofacial infections were excluded from participation.

2.1. Oral assessment

Clinical oral assessments were conducted to obtain information on tooth presence, gingival bleeding and periodontal destruction. Probing depth and gingival recession were measured at 4 sites at every tooth excluding third molars. The sites included mesio-buccal, mid-buccal, disto-buccal and disto-lingual. A single gingival bleeding value was recorded for each tooth periodontally assessed. The scoring system of the Gingival Index (values 2 & 3) [15] was used to indicate the number of teeth with positive gingival bleeding. Dental armamentarium included disposable mirrors (Mirrorlite™ Defend, Hauppauge, New York, U.S.A.) and a periodontal probe with 2 mm markings (Hu-Friedy, Chicago, USA, product number PCP2).

2.2. Common carotid intima-media thickness imaging

Participants rested in a supine position for 10 min prior to bilateral ultrasound of the carotid arteries with a portable ultrasound and L38e 10–5 MHz linear transducer (Sonosite Micromaxx, Bothell, USA). Carotid intima-media thickness (IMT) was assessed as previously described [13]. In brief, the carotid artery was imaged in longitudinal section, focusing on the distal wall of the common carotid artery (CCA) just proximal to the bulb. Images were stored for later analysis by an observer blinded to participant characteristics using semi-automated and validated software (Carotid Analyzer, Medical Imaging Applications, USA). The average IMT over a 10 mm long segment of distal wall of the carotid artery was measured twice from each carotid artery. A third measure was obtained if the first two measures differed by more than 10%. Inter-observer variability for mean IMT was excellent (ICC = 0.993), as derived from a second independent observer in a random sample of 20 participants.

2.3. Arterial stiffness

Carotid-dorsalis pedis (DP) pulse wave velocity (PWV) was measured via applanation tonometry using a Millar transducer and SphygmoCor-PVMx device (AtCor Medical, Sydney, Australia) [16] after participants had rested in a supine position for at least 10 min. The distance from each site to the suprasternal notch was measured, and the path length determined using the subtraction method [17]. The PWV score was calculated using the 'foot-to-foot' method. Two trained examiners were calibrated prior to commencement of the study. Inter-observer repeatability was tested throughout the study and was rated as 'good' (intra-class correlation = 0.72). Intra-observer repeatability was equally comparable between the two examiners; examiner 1 = 0.86 and examiner 2 = 0.83.

2.4. Blood and urine sampling

Non-fasting venous blood samples were collected via the antecubital vein. Samples were transported to a local commercial pathology clinic for analysis of lipid profile: total cholesterol (TC) and high-density lipoprotein (HDL). Serum and plasma were stored at −80 °C until batch analysis for high-sensitivity C-reactive protein (hsCRP) and apolipoproteins A1 and B from serum, and interleukin-6 (IL-6), arginine and asymmetric dimethyl-arginine (ADMA) from plasma. Urine samples were collected to examine renal function measured via the albumin to creatinine ratio (ACR) at the same pathology laboratory.

Direct methods were used to determine lipid profile and ACR using an ADVIA 2400 Chemistry System (Siemens, Tarrytown, USA). Apolipoproteins A1 and B were measured on an auto-analyser using an immunoturibidimetric assay. Plasma asymetric dimethylarginine was assessed using high-performance liquid chromatography with simultaneous UV and fluorescence detection as previously described [18]. Serum high sensitivity CRP was measured via particle-enhanced immunonephelometry using the BN II system. Plasma IL-6 was measured via commercial ELISA assay (Human IL-6 Quantikine kit, R&D Systems Inc., Minneapolis, USA).

2.5. Anthropometric measurements

Participant height was recorded to the nearest 0.1 cm using a metric stadiometer. A portable weight scale (Tanita model HD-351, Arlington Heights, USA) was used to measure weight to the nearest 0.1 kg. Body Mass Index (BMI) was calculated as weight (kg) divided by the square of height (metres).Waist circumference of the abdomen was horizontally measured at the centre-point between the iliac crest and vertebro-costal margin while hip circumference was measured at its widest point of the buttocks using a metric tape (Model W606PM Lufkin, USA). Three blood pressure (BP) measurements were obtained using an automated device (Welch Allen, Medical Products, Skaneateles Falls, USA) at three-minute intervals while the participant was sitting upright in a chair. The final two sitting recordings were used to calculate the mean BP measurements.

2.6. Self-reported questionnaire

A questionnaire to obtain information relating to socio-demographic characteristics, tobacco smoking status and self-reported health was administered to study participants. Lifetime exposure to smoking was quantified as the number of 'pack years' [19]. Diabetes status was determined via self-report where study participants responded 'yes' to the question: "Has a doctor told you that you have diabetes". To account for potential undiagnosed diabetes, those with HbA1c ≥47.5 mmol/mol were included as having diabetes for this study.

2.7. Ethical approval

All participants provided informed consent and completed a medical history via interview prior to commencement. The PerioCardio study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, the Central Australian Human Research Ethics Committee, Northern Territory Correctional Services Research Committee, University of Adelaide Human Research Ethics Committee, and the Aboriginal Health Council of South Australia. Study participants gave informed consent before participating. Research was conducted in accordance with the World Medical Association Declaration of Helsinki (version VII, 2008).

2.8. Statistical methods

Extent of PD and CAL was calculated as the percentage of sites examined based on the methods of Carlos and colleagues [20]. Quartiles of extent PD ≥4 mm were calculated to stratify participants as a proxy for periodontitis exposure on cardiovascular risk factors. Mean carotid IMT, calculated as the average from the left and right carotid arteries, was used for analysis. Categorical variables were assessed using Chi-squared test. Continuous variables were assessed using various methods. For heavily skewed data, medians across quartiles were assessed using the Kruskal–Wallis test. For age and extent PD ≥4 mm, ANOVA using Scheffe's post-hoc tests for means was conducted (supplementary table). Least squares means across quartiles and respective standard errors were derived from ordinary least squares regression models after centering median age (39 years) and including modified Gingival Index and pack-years as covariates. A trend analysis was conducted to describe the type of relationship between extent PD ≥4 mm and PWV. The relationship between periodontal disease and IMT was assessed in two ways: firstly, comparisons of least squares means of extent PD ≥4 mm across quartiles, and secondly as a post-hoc