Atherosclerosis 251 (2016) 311–318

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Periodontitis is associated with the risk of subclinical atherosclerosis and peripheral arterial disease in Korean adults

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ARTICLE INFO

Article history:
Received 13 June 2016
Received in revised form
6 July 2016
Accepted 12 July 2016
Available online 14 July 2016

Keywords:
Periodontitis
Subclinical atherosclerosis
Intima-media thickness
Peripheral arterial disease
Ankle-brachial index
Epidemiology

ABSTRACT

Background and aims: We aimed to evaluate the association of periodontitis with the development of early atherosclerotic vascular disease in Korean adults.
Methods: In this cross-sectional study, a total of 1343 adults aged over 40 years were recruited from a community-based cohort of Yangpyeong county, Korea, during the period 2010–2014. Only dentate individuals were included in the study. Subclinical atherosclerosis (SA) was defined as carotid intima-media thickness (cIMT)≥0.754 mm, as assessed bilaterally by B-mode ultrasound. Peripheral arterial disease (PAD) was defined as ankle-brachial index (ABI)≤1.0, as measured by Doppler. History of periodontitis was assessed by measuring the radiographic alveolar bone loss (RABL) on a digital dental panorama and was classified into three groups: normal, moderate and severe periodontitis (≥2 non-adjacent interproximal sites with RABL ≥ 4 mm and 6 mm, respectively). The associations of periodontitis with SA and PAD were evaluated by multivariable logistic regression analysis and analysis of covariance, adjusted for age, sex, education level, tooth loss, smoking, drinking, exercise, obesity, triglycerides, HDL, LDL, hs-CRP, diabetes and hypertension. Stratified analyses were performed to identify specific risk groups.
Results: After controlling for confounders, severe periodontitis was associated with SA [adjusted odds ratio (aOR) = 1.55; 95% confidence interval (CI): 1.07–2.24] and PAD (aOR = 2.03; 95% CI: 1.05–3.93). These associations were highlighted in never-smokers. For increasing severity of periodontitis, the adjusted mean cIMT increased ($p = 0.011$) while that of ABI decreased ($p = 0.033$).
Conclusions: Our data showed that periodontitis is a substantially important risk factor for atherosclerotic vascular disease among Korean adults.

1. Introduction

Atherosclerotic vascular disease (ASVD) is a major public health burden for the global population [1]. As the leading cause of mortality worldwide, the two most prevalent ASVDs, namely ischemic heart disease and stroke, are responsible for more deaths than total cancers, accounting for 25.1% of all-cause mortality [2]. Atherosclerosis is one of the major causes of these ASVDs, a condition characterized by thickening of the arterial wall due to chronic inflammation and lipid and metabolic alterations of vessel walls [3]. For the last few decades, growing evidence has suggested that a chronic low-grade inflammatory process of periodontal disease contributes to the pathogenesis of atherosclerosis and subsequently, ischemic heart disease and stroke [4]. Recently, a consensus report concluded that the current state of the evidence supports a positive and significant association between periodontitis and ASVD [5].

Periodontal disease is a chronic inflammatory disease characterized by the destruction of the tooth-supporting connective tissues in response to subgingival infection with various periodontal pathogens [6]. The biological plausibility of periodontal inflammation-associated atherosclerotic process is supported by experimental studies on transient bacteremia and elevated

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http://dx.doi.org/10.1016/j.atherosclerosis.2016.07.898
0021-9150/

inflammatory markers in patients with periodontitis [7]. Such a periodontal infection-mediated systemic bacteremia can induce upregulation of local and systemic cytokines and other inflammatory mediators, which can subsequently lead to endothelial dysfunction and plaque formation [8,9].

Epidemiological evidence on this link, however, is not yet conclusively established. Previous studies have presented inconsistent results on the association between periodontal disease and surrogate markers of atherosclerosis, including such subclinical morphological changes as increased carotid intima-media thickness (cIMT) and low ankle-brachial index (ABI). Abnormally increased cIMT and a low ABI represent a state of subclinical atherosclerosis (SA) and peripheral arterial disease (PAD), respectively [10]. Large cross-sectional studies conducted among Americans reported that increased cIMT is associated with periodontitis [11,12] and periodontopathogenic bacterial dominance [13]. A cross-sectional study among Japanese [14] and a cohort study among Swedish people [15] also reported that periodontitis is an independent predictor of an increased cIMT. On the other hand, case-control studies among Finnish [16] and Spanish [17] people found no consistent association between periodontitis and cIMT. In the Korean population, a recent cross-sectional study reported that periodontitis was not associated with increased cIMT [18]. A few epidemiological studies explored the link between periodontitis and ABI-defined PAD. The Health Professionals Follow-up Study reported that periodontitis was associated with low ABI [19]. A cross-sectional analysis of the NHANES data also showed a positive association between low ABI and periodontitis [20]. A Japanese study found an increased risk of ABI-defined PAD among periodontitis patients [21]. However, in an Indian case-control study, the mean ABI was found to be rather higher among periodontitis cases compared to gingivitis cases [22].

Hitherto, no study has reported the association between periodontitis and the two markers of early ASVD, namely cIMT and ABI. In the absence of conclusive evidence on the association of periodontitis with early atherosclerosis development, the authors explored this potential link in Korean adults in the Korean Genome and Epidemiology Study (KoGES) Cardiovascular disease Association Study (CAVAS). Thus, the aim of this study was to test the hypothesis that periodontitis is associated with SA and PAD.

2. Materials and methods

2.1. Ethical consideration

This study was approved by the Institutional Review Board of Seoul National University, School of Dentistry (IRB No: S-D20100006, S-D20130005). After receiving a full explanation of study details, all subjects provided written informed consent. The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Study design and subjects

We enrolled 1854 subjects aged 40 years or more, who participated in the Korean Genome and Epidemiology Study Cardiovascular disease association study (KoGES_CAVAS) in 2010, 2012–2014 for an oral assessment conducted in Yangpyeong county, Korea. The KoGES_CAVAS is a community-based cohort which provides a health examination follow-up program for individuals aged 40 years or more, directed by the Korea Centers for Disease Control and Prevention (KCDC). A detailed description of the sampling methods and survey contents is provided in the cohort profile paper [23]. To overcome the limitations of multiyear study, a standardized protocol was employed to train all interviewers and examiners for questionnaires and examination procedure. Standardization training preceded each annual survey. Out of the 1854 participants of the study, only dentate individuals with complete data sets were included in the analysis, which constituted a total of 1343 individuals (501 males and 843 females) (Table 1).

2.3. Assessment of ASVD risk markers

The surrogate markers of atherosclerosis used for this study are cIMT and ABI, known as strong predictors of ASVD, such as stroke and myocardial infarction [24]. IMT of left and right common carotid artery was evaluated using an ultrasound equipment, as previously described [25]. The average of IMT values was used for analysis. SA was regarded as a binary variable with the threshold value set at cIMT $\geq$ 0.754 mm, considering it as the critical value of increased cardiovascular risk in Koreans [26]. The sonographer was blinded of the periodontal status of participants. PAD was evaluated by using ABI. The blood pressure in the upper and lower extremities was measured using a portable Doppler system Minidop Es-100Vx (Hadeco, Inc. Arima, Miyamae-ku, Kawasaki, Japan), applying the probe at the posterior tibial artery at an angle approximately 60° to the direction of blood flow. ABI was calculated separately by dividing the higher of the two systolic pressures in the ankle by the higher of the two systolic pressures in the arm. PAD was considered if ABI was lower than 1.0, adopting the threshold value of increasing PAD-related mortality as suggested by the ABI Collaboration [27]. Although individuals with a high ABI >1.4 are also known to be at increased risk, these individuals were not separately considered in our study due to the very small number of cases. The threshold values for cIMT and ABI used to define SA and PAD in our study are lower than the conventionally used criteria of 1 mm and 0.9. This was due to the very small number of SA and PAD cases when the conventional criteria were applied, as study participants were predominantly healthy individuals. Thus, our definition of SA and PAD should be considered as an indicator of early vascular disease for the prevention and control of ASVD, rather than a diagnostic criterion to delineate cases for treatment.

2.4. Assessment of history of periodontitis

History of periodontitis of participants was assessed by dentists using panoramic radiographs taken by a digital panoramic tomography machine (Pax-Primo, Vatech Global, Seoul, Korea). The radiographic alveolar bone loss (RABL), defined as the vertical distance between the cemento-enamel junction (CEJ) and the deepest point of alveolar bone crest, was measured on the mesial and distal side of all teeth. When CEJ was not clearly visible for technical reasons (overlapping teeth or prosthesis), arbitrary CEJ was applied by referring to the CEJ of the adjacent teeth. Training and calibration procedure preceded each annual survey. Classification of periodontitis status followed the Centers for Disease Control/American Association of Periodontology (CDC/AAP) guidelines [28] using RABL as the surrogate of clinical attachment loss. For the purpose of this analysis, periodontitis was categorized into 3 groups: normal (no or mild periodontitis; RABL < 4 mm), moderate (RABL $\geq$ 4 mm at two or more interproximal sites, not on the same tooth) and severe periodontitis (RABL $\geq$ 6 mm at two or more interproximal sites, not on the same tooth).

2.5. Assessment of potential confounders

We considered the following as potential confounders on ASVD: age, sex, education level, tooth loss, smoking, drinking, exercise, central obesity, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), C-reactive protein (hs-CRP), diabetes