Association of Periodontitis with Atherosclerotic Cardiovascular Diseases: A Nationwide Population-based Retrospective Matched Cohort Study

Min-Ji Byon 1,2, Se-Yeon Kim 1, Ji-Soo Kim 1, Han-Na Kim 3 and Jin-Bom Kim 1,2, *

1 Department of Preventive and Community Dentistry, School of Dentistry, Pusan National University, 49 Busandaehak-ro, Mulgeum-eup, Yangsan 50612, Korea; kyura2@naver.com (M.-J.B.); secan00@naver.com (S.-Y.K.); psily1@naver.com (J.-S.K.)
2 BK21 FOUR project, School of Dentistry, Pusan National University, Yangsan 50612, Korea
3 Department of Dental Hygiene, College of Health and Medical Sciences, Cheongju University, Cheongju 28503, Korea; hnkim@cju.ac.kr
*
Correspondence: jbomkim@pusan.ac.kr; Tel.: +82-51-510-8223

Received: 7 September 2020; Accepted: 2 October 2020; Published: 4 October 2020

Abstract: We investigated the association between periodontitis and atherosclerotic cardiovascular disease (ACVD) development using the National Health Insurance Service—National Sample Cohort 2.0 (NHIS-NSC2) database, which contains data for approximately 1 million nationally representative random participants. We selected 52,425 participants aged 20+ years and diagnosed with periodontitis from January to December 2003 and used propensity score matching to select an equivalent number of participants who were never diagnosed with periodontitis in the period covered by the NHIS-NSC2 database (2002–2015). The propensity scores were based on sex, age group, type of national health insurance, household income, diabetes status, and hypertension status and were used for 1:1 matching of individuals with similar propensities. A total of 104,850 participants were selected for the study. A multivariable Cox proportional hazard regression model was used to investigate the risk of ACVD development due to periodontitis from 2003 to 2015 after adjusting for sex, age, type of national health insurance, household income, hypertension status, and diabetes status. Participants with periodontitis had a higher risk of ACVD (adjusted hazard ratio: 1.09, 95% confidence interval: 1.05–1.13) than those without periodontitis. Thus, periodontitis can increase the risk of ACVD, and prevention of periodontitis may help reduce the risk of cardiovascular disease.

Keywords: atherosclerosis; cardiovascular disease; cohort study; heart disease; national health insurance service; periodontitis; risk

1. Introduction

Atherosclerotic cardiovascular diseases (ACVDs) are a group of diseases that include fatal and non-fatal coronary heart disease (angina, myocardial infarction), ischemic cerebrovascular disease (stroke/transient ischemic attack), and peripheral arterial disease [1]. Cardiovascular disease remains a leading cause of death worldwide, and the number of patients with cardiovascular disease has increased over the years [2,3]. The causes of ACVD are very complex, but ongoing studies have suggested that periodontal disease-related microorganisms may invade the cardiovascular system and promote or exacerbate atherosclerosis. For example, ApoE-null mice that received Porphyromonas gingivalis showed atherosclerosis [4]. Similarly, periodontal pathogens were detected in the tissues of patients undergoing carotid endarterectomy [5].
Periodontal disease is a chronic inflammatory disease caused by bacterial infection of the supporting tissues around the teeth [6]. In addition to causing oral cavity diseases, bacteria in the oral cavity are also reported to be closely related to the development of various systemic diseases. Poor oral health and tooth loss are significantly related to the development of coronary atherosclerotic burden [7]. Once periodontal disease is established, bacteria and their products enter the bloodstream, activating the host inflammatory response. This is known to encourage atheroma formation, maturation, and vulnerability [1].

Dietrich et al. [8] conducted a systematic review of epidemiological studies and reported that people with periodontal disease have an increased risk of developing ACVD. However, their study was limited by the inconsistent approaches used for measurement of periodontal disease and the lack of generalizability to the entire population. The National Health Insurance Service (NHIS) released a large-scale database from 2014, in which doctors’ diagnoses were reported as research data, and this made it possible to generalize the results of the research to the entire population. However, few studies have used the NHIS database to evaluate the relationship between periodontal disease and cardiovascular disease.

In this study, we investigated the association between periodontitis and ACVD development by using the National Health Insurance Service—National Sample Cohort 2.0 (NHIS-NSC2) database from 2002 to 2015 in South Korea.

2. Materials and Methods

2.1. Study Population and Design

This study used the NHIS-NSC2 database from 2002 to 2015, the data for which were released by NHIS in 2017. These data were obtained from 1,000,000 nationally representative random participants, amounting to approximately 2.2% of the entire population in the NHIS in 2006. This database included all medical claims filed from January 2002 to December 2015.

Among the 990,235 individuals who participated in the NHIS in 2003, 745,621 were aged 20 years or more. We excluded participants diagnosed with periodontitis or ACVD in 2002 to ensure that only participants with new episodes of periodontitis were included in the study population. We excluded medical-aid beneficiaries since the details of medical treatments for these individuals have been surveyed only since 2006. Thus, we selected a total of 52,425 participants diagnosed with periodontitis in the NHIS-NSC2 database from January to December 2003 for this retrospective cohort study. We then used propensity score matching (PSM) to select an equivalent number of participants who were never diagnosed with periodontitis during the period for which the NHIS-NSC2 database was active (2002–2015). The propensity scores were based on sex, age group, type of national health insurance, household income, diabetes status, hypertension status and were used for 1:1 matching with individuals with similar propensities. A total of 104,850 participants were selected for the study (Figure 1).

The Pusan National University Institutional Review Board judged this study to be exempt from review. The Board also waived the requirement for consent (IRB number PNU IRB/2019_98_HR).
2.2. Assessment of Periodontitis and ACVD

Diseases, including periodontitis and ACVD, were diagnosed using the Korean Classification of Diseases, 7th revision (KCD-7), which is a modified version of the International Classification of Disease, 10th revision (ICD-10). The NHIS uses KCD-7.

The periodontitis group included all patients diagnosed under the following KCD-7 codes one or more times in 2003: acute periodontitis (K052), chronic periodontitis (K053), periodontosis (K054), other periodontal disease (K055), and unspecified periodontal disease (K056) (Table 1). Participants newly diagnosed with periodontitis after 2004 were excluded from the study.

ACVD was defined by the following KCD-7 codes: atherosclerosis (I70), cerebral atherosclerosis (I67.2), atherosclerotic cardiovascular disease, so described (I25.0), and atherosclerotic heart disease (I25.1) (Table 1). The study included participants diagnosed with ACVD from 2003 to 2015, except those treated with the above codes in 2002. Participants diagnosed with ACVD before diagnosis of periodontitis and those diagnosed with ACVD within six months of the diagnosis of periodontitis were excluded to limit the cases to those that potentially showed ACVD development due to periodontitis (Figure 2).
Table 1. KCD-7 codes used in disease definition.

| Disease                                      | Diagnosis                                      | KCD-7 Code |
|----------------------------------------------|------------------------------------------------|------------|
| Periodontitis                                | Acute periodontitis                            | K05.2      |
|                                              | Chronic periodontitis                           | K05.3      |
|                                              | Periodontosis                                   | K05.4      |
|                                              | Other periodontal diseases                      | K05.5      |
|                                              | Periodontal disease, unspecified                | K05.6      |
| Atherosclerotic cardiovascular disease (ACVD)| Atherosclerosis                                 | I70        |
|                                              | Cerebral atherosclerosis                        | I67.2      |
|                                              | Atherosclerotic cardiovascular disease, so described | I25.0  |
|                                              | Atherosclerotic heart disease                   | I25.1      |
| Hypertension                                 | Essential (primary) hypertension                | I10        |
|                                              | Hypertensive heart disease                      | I11        |
|                                              | Hypertensive renal disease                      | I12        |
|                                              | Hypertensive heart and renal disease            | I13        |
|                                              | Secondary hypertension                          | I15        |
| Diabetes mellitus                            | Type 1 diabetes mellitus                        | E10        |
|                                              | Type 2 diabetes mellitus                        | E11        |
|                                              | Malnutrition-related diabetes mellitus          | E12        |
|                                              | Other specified diabetes mellitus               | E13        |
|                                              | Unspecified diabetes mellitus                   | E14        |

KCD-7: Korean Classification of Diseases, 7th revision.

Figure 2. Process of selecting participants diagnosed with ACVD. ACVD: atherosclerotic cardiovascular disease.
2.3. Risk Factors for ACVD

The regression models were adjusted for the participant’s sex, age (20–29, 30–39, 40–49, 50–59, ≥60 years), type of national health insurance (self-employed insured, householder of self-employed insured, employed insured, dependents of insured employee), household income, hypertension status, and diabetes status. Household income was classified in the first to fifth quintiles. The first quintile represented the lowest household income group. Hypertension was defined using the following KCD-7 codes: essential (primary) hypertension (I10), hypertensive heart disease (I11), hypertensive renal disease (I12), hypertensive heart and renal disease (I13), and secondary hypertension (I15). Diabetes mellitus was defined using the following KCD-7 codes: type 1 diabetes mellitus (E10), type 2 diabetes mellitus (E11), malnutrition-related diabetes mellitus (E12), other specified diabetes mellitus (E13), and unspecified diabetes mellitus (E14) (Table 1).

2.4. Statistical Analysis

Chi-squared tests were performed to identify the socioeconomic and systemic status of the participants. To identify the risk of ACVD development due to the prevalence of periodontitis, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated via Cox proportional hazard regression analysis. The survival rate was calculated using the Kaplan–Meier curve for the 12.5-year (150-month) follow-up period, and the log-rank test was performed to examine the differences in ACVD development between the periodontitis and non-periodontitis groups. Statistical significance was set at 0.05. Analyses were conducted with SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA) and R studio version 3.3.3 (R studio Inc., Boston, MA, USA).

3. Results

3.1. Socioeconomic Status of the Participants

Of the 104,850 study participants, 52,425 were in the periodontitis group and 52,425 in the non-periodontitis group. Both groups contained 50.3% males and 49.7% females. No significant intergroup difference was observed in sex, age group, type of national health insurance, household income, hypertension, and diabetes mellitus, since these variables had been used for propensity score matching. The prevalence of ACVD due to periodontitis was significantly different in the two groups: 11.2% in the periodontitis group and 10.5% in the non-periodontitis group (Table 2).

3.2. Risk Factors for ACVD

A Cox proportional hazard regression model was used to investigate the risk factors for ACVD development. In the univariable Cox proportional hazard regression model, the risk of ACVD in males (HR: 1.09, 95% CI: 1.05–1.13) was higher than that in females. The age-specific HR of ACVD increased with age from 3.46 (30–39 years) to 25.67 (60–69 years). With regard to the type of national health insurance, the risk of ACVD in householder of self-employed insured (HR: 1.54, 95% CI: 1.46–1.62) and in employed insured (HR: 1.58, 95% CI: 1.50–1.67) was higher than that in self-employed insured. With respect to household income, the first quintile of participants with the lowest household income showed the highest risk of ACVD (second quintile: HR: 0.77, 95% CI: 0.73–0.81; third quintile: HR: 0.74, 95% CI: 0.70–0.78; fourth quintile: HR: 0.69, 95% CI: 0.65–0.73; fifth quintile: HR: 0.81, 95% CI: 0.77–0.86). Participants with hypertension showed a higher risk of ACVD (HR: 8.16, 95% CI: 7.74–8.61), as did participants with diabetes mellitus (HR: 5.02, 95% CI: 4.81–5.25) and those with periodontitis (HR: 1.08, 95% CI: 1.04–1.12).
In the multivariable Cox proportional hazard regression model adjusted for all variables (sex, age group, type of national health insurance, household income, hypertension status, diabetes mellitus status, periodontitis status), the age-specific adjusted HR (aHR) of ACVD increased with age from 2.27 (30–39 years) to 6.29 (60–69 years). For household income, the first quintile of participants with the lowest household income showed the highest risk of ACVD (second quintile: aHR: 0.90, 95% CI: 0.86–0.95; third quintile: aHR: 0.90, 95% CI: 0.85–0.95; fourth quintile: aHR: 0.87, 95% CI: 0.82–0.92; fifth quintile: aHR: 0.93, 95% CI: 0.87–0.98). Participants with hypertension had a higher risk of ACVD (aHR: 3.64, 95% CI: 3.44–3.86), as did participants with diabetes mellitus (aHR: 2.18, 95% CI: 2.08–2.28) and those with periodontitis (aHR: 1.09, 95% CI: 1.05–1.13) (Table 3).

Table 2. Socioeconomic and systemic status of the participants by diagnosis of periodontitis.

| Variables                        | Non-periodontitis Group No. (%) | Periodontitis Group No. (%) | p-Value |
|----------------------------------|---------------------------------|----------------------------|---------|
| Total                            | 52,425 (50.0)                  | 52,425 (50.0)              |         |
| Sex                              |                                 |                            | 1.00    |
| Male                             | 26,345 (50.3)                  | 26,345 (50.3)              |         |
| Female                           | 26,080 (49.7)                  | 26,080 (49.7)              |         |
| Age group (years)                |                                 |                            | 1.00    |
| 20–29                            | 8566 (16.3)                    | 8566 (16.3)                |         |
| 30–39                            | 11,376 (21.7)                  | 11,376 (21.7)              |         |
| 40–49                            | 13,667 (26.1)                  | 13,667 (26.1)              |         |
| 50–59                            | 9578 (18.3)                    | 9578 (18.3)                |         |
| ≥60                              | 9238 (17.6)                    | 9238 (17.6)                |         |
| Type of national health insurance|                                 |                            | 1.00    |
| Self-employed insured            | 13,268 (25.3)                  | 13,268 (25.3)              |         |
| Householder of self-employed insured | 12,122 (23.1)         | 12,122 (23.1)              |         |
| Employed insured                 | 12,901 (24.6)                  | 12,901 (24.6)              |         |
| Dependents of insured employee   | 14,134 (27.0)                  | 14,134 (27.0)              |         |
| Household income (%)             |                                 |                            | 1.00    |
| First quintile (lowest)          | 14,465 (27.6)                  | 14,465 (27.6)              |         |
| Second quintile                  | 12,199 (23.3)                  | 12,199 (23.3)              |         |
| Third quintile                   | 10,970 (20.9)                  | 10,970 (20.9)              |         |
| Fourth quintile (highest)        | 7923 (15.1)                    | 7923 (15.1)                |         |
| Fifth quintile                   | 6868 (13.1)                    | 6868 (13.1)                |         |
| Hypertension                     |                                 |                            | 1.00    |
| No                               | 28,520 (54.4)                  | 28,520 (54.4)              |         |
| Yes                              | 23,905 (45.6)                  | 23,905 (45.6)              |         |
| Diabetes mellitus                |                                 |                            | 1.00    |
| No                               | 29,908 (57.1)                  | 29,908 (57.1)              |         |
| Yes                              | 22,517 (42.9)                  | 22,517 (42.9)              |         |
| ACVD                             |                                 |                            | <0.001  |
| No                               | 46,928 (89.5)                  | 46,568 (88.8)              |         |
| Yes                              | 5497 (10.5)                    | 5857 (11.2)                |         |

ACVD: atherosclerotic cardiovascular disease. p-values were obtained by chi-squared tests.
Table 3. Cox proportional hazard regression model for the risk factors of ACVD.

| Variables                        | Univariable Cox Regression | Multivariable Cox Regression * |
|----------------------------------|-----------------------------|--------------------------------|
|                                  | HR  | 95% CI      | Adjusted HR | 95% CI |
| Sex                              |     |             |             |       |
| Female (ref)                     | 1   |             | 1           |       |
| Male                             | 1.09| 1.05–1.13   | 0.99        | 0.95–1.04 |
| Age group                        |     |             |             |       |
| 20–29 (ref)                      | 1   |             | 1           |       |
| 30–39                            | 3.46| 2.94–4.07   | 2.27        | 1.93–2.68 |
| 40–49                            | 9.60| 8.24–11.18  | 3.99        | 3.41–4.66 |
| 50–59                            | 19.29| 16.59–22.43| 5.75        | 4.92–6.72 |
| ≥60                              | 25.67| 22.09–29.83| 6.29        | 5.38–7.36 |
| Type of national health insurance|     |             |             |       |
| Self-employed insured (ref)      | 1   |             | 1           |       |
| Householder of self-employed insured | 1.54| 1.46–1.62   | 0.92        | 0.91–1.03 |
| Employed insured                 | 1.58| 1.50–1.67   | 0.98        | 0.93–1.04 |
| Dependents of insured employee   | 1.02| 0.96–1.09   | 0.95        | 0.88–1.01 |
| Household income (%)             |     |             |             |       |
| First quintile (lowest) (ref)    | 1   |             | 1           |       |
| Second quintile                  | 0.77| 0.73–0.81   | 0.90        | 0.86–0.95 |
| Third quintile                   | 0.74| 0.70–0.78   | 0.90        | 0.85–0.95 |
| Fourth quintile                  | 0.69| 0.65–0.73   | 0.87        | 0.82–0.92 |
| Fifth quintile (highest)         | 0.81| 0.77–0.86   | 0.93        | 0.87–0.98 |
| Hypertension                     |     |             |             |       |
| No (ref)                         | 1   |             | 1           |       |
| Yes                              | 8.16| 7.74–8.61   | 3.64        | 3.44–3.86 |
| Diabetes mellitus                |     |             |             |       |
| No (ref)                         | 1   |             | 1           |       |
| Yes                              | 5.02| 4.81–5.25   | 2.18        | 2.08–2.28 |
| Periodontitis                    |     |             |             |       |
| No (ref)                         | 1   |             | 1           |       |
| Yes                              | 1.08| 1.04–1.12   | 1.09        | 1.05–1.13 |

ACVD: atherosclerotic cardiovascular disease. HR: hazard ratio. CI: confidence interval. * Multivariable Cox proportional hazard regression model was adjusted for sex, age group, type of national health insurance, household income, hypertension status, diabetes mellitus status, and periodontitis status.

3.3. Association of ACVD with Periodontitis

The survival rate was calculated using the Kaplan–Meier curve for the 12.5-year (150-month) follow-up period, and the log-rank test was performed to examine differences in ACVD development between the periodontitis and non-periodontitis groups. The incidence of ACVD in participants with periodontitis was higher than that in participants without periodontitis ($p < 0.001$) (Figure 3). The survival rate indicating no development of ACVD for 150 months was 88.83% in the periodontitis group and 89.17% in non-periodontitis group.
Periodontitis was associated with both subclinical atherosclerosis (adjusted odds ratio (aOR): 1.55, 95% CI: 1.07–2.24) and peripheral arterial disease (aOR: 2.03, 95% CI: 1.05–3.93) in Korean adults [14]. Periodontitis was also independently associated with ACVD (OR: 1.59, 95% CI: 1.39–1.81) in the Netherlands [15]. Similarly, patients with chronic apical periodontitis in Brazil showed a 2.79-fold higher risk of developing coronary artery disease [16].

In the retrospective cohort study using the NHIS database, the HR of peripheral arterial disease in the periodontitis group was 1.15 (95% CI: 1.07–1.23) in comparison with that in the matched group [17]. In a Danish nationwide cohort study, the incidence rate ratio (IRR) of myocardial infarction in the periodontitis group was 1.15 (95% CI: 1.07–1.23) in comparison with that in the matched group [18].
As such, this cohort study confirmed that periodontitis can be a risk factor for ACVD (aHR: 1.09, 95% CI: 1.05–1.13). Therefore, the risk of ACVD should be considered when treating or managing patients with periodontitis. Good oral hygiene is recommended to reduce cardiometabolic disease risk through the prevention of periodontitis [19]. Counselling on balanced dietary habits and avoiding smoking are recommended to improve resistance to dental caries or periodontitis, which may improve general health and possibly also improve the risk factors for cardiovascular disease [20]. Periodontitis, which is one of the causes of ACVD, should not be taken lightly, but it is easy to treat the initial gingivitis.

This study had some limitations. Most dentists working at dental clinics in Korea did not undergo calibration training to apply the same diagnostic criteria in the diagnosis of periodontitis. They do not actively diagnose and treat periodontitis since they rely on visual examinations to diagnose periodontitis. Moreover, the reimbursement of periodontitis treatment in some cases may have been rejected by the Health Insurance Review and Assessment Service related to NHIS if there were mistakes in the application process for treatment reimbursement. Therefore, it is possible that some participants were classified as “non-periodontitis”, instead of being classified as participants with periodontitis. Consequently, the aHR for the risk factor of ACVD in this study may have been underestimated.

This nationwide investigation of the association between periodontitis and ACVD is one of the largest of its kind to date. It has the advantage that it can be generalized using data from a nationwide retrospective matched cohort study with a large sample. Unlike previous studies that only confirmed the relationship between periodontitis and cardiovascular disease using cross-sectional studies, this study confirmed that periodontitis is related to ACVD development.

5. Conclusions

This study investigated the association between periodontitis and ACVD development using the National Health Insurance Service—National Sample Cohort 2.0 (NHIS-NSC2) database. The results showed that participants with periodontitis had a 9% higher risk of ACVD. Our findings confirmed that periodontitis can increase the risk of ACVD development, and it is important to prevent and manage periodontitis to improve systemic health and possibly also reduce the risk for cardiovascular disease.

Author Contributions: All authors contributed extensively to the work presented in this paper. M.-J.B. wrote the entire manuscript. S.-Y.K. and J.-B.K. provided the idea for the study. J.-S.K. performed the statistical analyses. H.-N.K. implemented the literature review. J.-B.K. conceived and coordinated the study. All authors have read and agreed to the final version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea (NRF) and the grant was funded by the Korean government (MSIT) (No. NRF-2018R1A5A2023879).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Tonetti, M.S.; Van Dyke, T.E. Working group 1 of the joint EFP/AAP workshop. Periodontitis and atherosclerotic cardiovascular disease: Consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J. Periodontol. 2013, 84 (Suppl. 4), S24–S29. [CrossRef] [PubMed]
2. Virani, S.S.; Alonso, A.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Delling, F.N.; et al. Heart disease and stroke statistics-2020 update: A report from the American Heart Association. Circulation 2020, 141, e139–e596. [CrossRef] [PubMed]
3. Shin, H. Cause-of-death statistics in 2018 in the Republic of Korea. J. Korean Med. Assoc. 2020, 63, 286–297.
4. Lalla, E.; Lamster, I.B.; Hofmann, M.A.; Bucciarelli, L.; Jerud, A.P.; Tucker, S.; Lu, Y.; Papapanou, P.N.; Schmidt, A.M. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-Null mice. Arterioscler. Thromb. Vasc. Biol. 2003, 23, 1405–1411. [CrossRef] [PubMed]
5. Fiehn, N.; Larsen, T.; Christiansen, N.; Holmstrup, P.; Schroeder, T.V. Identification of periodontal pathogens in atherosclerotic vessels. J. Periodontol. 2005, 76, 731–736. [CrossRef] [PubMed]
6. Pihlstrom, B.L.; Michalowicz, B.S.; Johnson, N.W. Periodontal diseases. Lancet 2005, 366, 1809–1820. [CrossRef]
7. Gomes, M.S.; Chagas, P.; Padilha, D.M.P.; Caramori, P.; Hugo, F.N.; Schwanke, C.H.A.; Hilgert, J.B. Association between self-reported oral health, tooth loss and atherosclerotic burden. Braz. Oral Res. 2012, 26, 436–442. [CrossRef] [PubMed]

8. Dietrich, T.; Sharma, P.; Walter, C.; Weston, P.; Beck, J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J. Periodontol. 2013, 84 (Suppl. 4), S70–S84. [CrossRef] [PubMed]

9. Van Dyke, T.E.; van Winkelhoff, A.J. Infection and inflammatory mechanisms. J. Clin. Periodontol. 2013, 40 (Suppl. 14), S1–S7. [CrossRef] [PubMed]

10. Zhang, B.; Khalaf, H.; Sirsjö, A.; Bengtsson, T. Gingipains from the periodontal pathogen Porphyromonas gingivalis play a significant role in regulation of angiopoietin 1 and angiopoietin 2 in human aortic smooth muscle cells. Infect. Immun. 2015, 83, 4256–4265. [CrossRef] [PubMed]

11. Bretz, W.A.; Weyant, R.J.; Corby, P.M.; Ren, D.; Weissfeld, L.; Kritchevsky, S.B.; Harris, T.; Kurella, M.; Satterfield, S.; Visser, M.; et al. Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population. J. Am. Geriatr. Soc. 2005, 53, 1532–1537. [CrossRef] [PubMed]

12. Liljestrand, J.M.; Paju, S.; Buhlin, K.; Persson, G.R.; Sarna, S.; Nieminen, M.S.; Sinisalo, J.; Mäntylä, P.; Pussinen, P.; Palopölysaccharide, a possible molecular mediator between periodontitis and coronary artery disease. J. Clin. Periodontol. 2017, 44, 784–792. [CrossRef] [PubMed]

13. Kozarov, E.V.; Dorn, B.R.; Shelburne, C.E.; Dunn, W.A., Jr.; Porgulskie-Fox, A. Human atherosclerotic plaque contains viable invasive Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis. Arterioscler. Thromb. Vasc. Biol. 2005, 25, e17–e18. [CrossRef] [PubMed]

14. Ahn, Y.B.; Shin, M.S.; Han, D.H.; Sukhbaatar, M.; Kim, M.S.; Shin, H.S.; Kim, H.D. Periodontitis is associated with the risk of subclinical atherosclerosis and peripheral arterial disease in Korean adults. Atherosclerosis 2016, 251, 311–318. [CrossRef] [PubMed]

15. Beukers, N.G.; van der Heijden, G.J.; van Wijk, A.J.; Loos, B.G. Periodontitis is an independent risk indicator for atherosclerotic cardiovascular diseases among 60 174 participants in a large dental school in the Netherlands. J. Epidemiol. Commun. Health 2017, 71, 37–42. [CrossRef] [PubMed]

16. Costa, T.H.; de Figueiredo Neto, J.A.; de Oliveira, A.E.; Lopes e Maia Mde, F.; de Almeida, A.L. Association between chronic apical periodontitis and coronary artery disease. J. Endod. 2014, 40, 164–167. [CrossRef] [PubMed]

17. Cho, D.H.; Song, I.S.; Choi, J.; Gwon, J.G. Risk of peripheral arterial disease in patients with periodontitis: A nationwide, population-based, matched cohort study. Atherosclerosis 2020, 297, 96–101. [CrossRef] [PubMed]

18. Hansen, G.G.; Gegeberg, A.; Holmstrup, P.; Hansen, P.R. Relation of periodontitis to risk of cardiovascular and all-cause mortality (from a Danish nationwide cohort study). Am. J. Cardiol. 2016, 118, 489–493. [CrossRef] [PubMed]

19. VanWormer, J.J.; Acharyya, A.; Greenlee, R.T.; Nieto, F.J. Oral hygiene and cardiometabolic disease risk in the survey of the health of Wisconsin. Community Dent. Oral Epidemiol. 2013, 41, 374–384. [CrossRef] [PubMed]

20. Johansson, I.; Tidehag, P.; Lundberg, V.; Hallmans, G. Dental status, diet and cardiovascular risk factors in middle-aged people in northern Sweden. Community Dent. Oral Epidemiol. 1994, 22, 431–436. [CrossRef] [PubMed]