Association between periodontal disease and non-communicable diseases
A 12-year longitudinal health-examinee cohort study in South Korea
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Abstract
The National Health Insurance Service–Health Examinee Cohort during 2002 to 2013 was used to investigate the associations between periodontal disease (PD) and the following non-communicable diseases (NCDs): hypertension, diabetes mellitus, osteoporosis, cerebral infarction, angina pectoris, myocardial infarction, and obesity.

Univariate and multivariate logistic regression analyses adjusting for potential confounders during the follow-up period—including age, sex, household income, insurance status, residence area, health status, and comorbidities—were used to estimated odds ratios (ORs) with 95% confidence intervals (CIs) in order to assess the associations between PD and NCDs.

We enrolled 200,026 patients with PD and 154,924 subjects with a healthy oral status. Statistically, significant associations were found between PD and the investigated NCDs except for cerebral and myocardial infarction after adjusting for sociodemographic and comorbidity factors (P < .05). In particular, obesity (OR = 1.30, 95% CI = 1.04–1.63, P = .022), osteoporosis (OR = 1.22, 95% CI = 1.18–1.27, P < .001), and angina pectoris (OR = 1.22, 95% CI = 1.17–1.27, P < .001) were significantly and positively associated with PD.

This longitudinal cohort study has provided evidence that patients with PD are at increased risk of NCDs. Further studies are required to confirm the reliability of this association and elucidate the role of the inflammatory pathway in periodontitis pathogenesis as a triggering and mediating mechanism.

Abbreviations: HIRA = health insurance review and assessment service, NCDs = non-communicable diseases, NHIS = National Health Insurance Service, NHIS-HEC = National Health Insurance Service–Health Examinee Cohort, NHIS-NSC = National Health Insurance Service–National Sample Cohort, PD = periodontal disease.

Keywords: cohort analysis, non-communicable diseases, periodontal disease, retrospective study

1. Introduction
Acute and chronic periodontal diseases (PDs) are considered the most common cause of loss of teeth and periodontal tissues such as the cementum, periodontal ligament, and supporting alveolar bone in adults. In 2015, the Health Insurance Review and Assessment Service (HIRA) reported that PD is the most costly health condition (about US$ 900 million) and second-most-frequent disease (about 26.3% [13 million] of the Korean population) among outpatients in South Korea. Many recent studies have demonstrated significant positive correlations between PD and various systemic disease processes. Preventing and treating PD, therefore, influences the quality of life of many people.

Interest in non-communicable diseases (NCDs) is increasing, and the WHO reported that NCDs cause over 38 million deaths worldwide in 2012. NCDs including cardiovascular disease, cancer, chronic respiratory disease, diabetes, Alzheimer’s disease, and osteoporosis are chronic and noninfectious disorders that are likely to progress slowly over many years. The National Statistical Office reported that the mean life expectancy of the Korean population in 2014 was 82.4 years. This is higher than the mean in most other countries of the Organization for Economic Cooperation and Development, and is increasing continuously. In contrast, the health life expectancy decreased to below 66 years (65.4 years) in 2012. The gap of 17 years between...
the mean life expectancy and healthy life expectancy may be at least partially attributable to physical damage, but NCDs have also been reported to be major causes of this discrepancy. The prevalence of NCDs has increased steadily due to increases in smoking and alcohol consumption, lack of physical activity and exercise, and poor dietary habits, and NCDs accounted for 77.4% of the direct causes of deaths among the Korean population in 2012.[9]

PD and NCDs are worldwide representative chronic disorders that share many risk factors such as older age, active smoking, stress, and uncontrolled blood pressure and glucose level.[9] The mechanisms underlying diverse systemic diseases including PD and NCDs have been identified and reported through systematic reviews of the experimental and epidemiological evidence.[10,11]

Despite PD being a chronic bacterial infectious disease, a new strategy aimed at preventing and treating PD is associated with a strategy intending to prevent NCDs that are currently suspected to be involved in oral diseases.

There is only single study based on the database for the National Health Insurance Service-National Sample Cohort (NHIS–NSC) in South Korea that has identified associations between PD and lifestyle-related comorbidities including cardiovascular disease, hypertension, diabetes mellitus, rheumatoid arthritis, erectile dysfunction, osteoporosis, and obesity; no previous research has used the database for the National Health Insurance Service–Health Examinee Cohort (NHIS–HEC) study released in 2016.[12,13] The purpose of the present study was, therefore, to determine the incidence of PD and its associations with major NCDs including hypertension, diabetes mellitus, osteoporosis, cerebral infarction, angina pectoris, myocardial infarction, and obesity using the database for the nationwide population-based NHIS–HEC.

2. Methods

2.1. Study design and data collection

More than 97% of the Korean population was covered by National Health Insurance (NHI) in 2013. Those eligible for NHI are directed by the NHIS to undergo regular health checkup examinations in order to maintain and promote their health and thereby reduce their respective long-term insurance payouts. These regular health checkup examinations are classified into general health examinations (primary and secondary), health examinations of the life-span transition period (primary and secondary, for people aged 40 years and 66 years), cancer examinations (gastric, breast, colorectal, cervical, and liver cancer), and infant/child health examinations. Individuals who qualify as being insured for medical aid are directed by the NHIS to undergo regular health checkup examinations in order to maintain and promote their health and thereby reduce their respective long-term insurance payouts. These parameters were collected for 12 years (2002–2013) and rearranged to prevent the identification of individuals for the cohort study.

This study conformed to the STROBE guidelines for reporting observational studies (www.strobe-statement.org) and was approved by the Institutional Review Board, Daejeon Dental Hospital, Wonkwang University (approval no. W1611/001-001).

2.2. Identification of non-communicable diseases

Principal and subprincipal diagnostic and prescription codes were collected for each patient based on the databases of the NHIS and HIRA. The following NCDs were diagnosed by physicians or other medical professionals during visits to out- or in-patient clinics from 2002 to 2013: hypertension (Korean Classification of Diseases, 6th revision [KCD-6], codes I10 and I15; corresponding to the International Classification of Disease, 10th revision [ICD-10], codes I10 and I15), diabetes mellitus (KCD-6 codes E10–E14, corresponding to ICD-10 codes E10–E14), osteoporosis (KCD-6 codes M08–M82, corresponding to ICD-10 codes M08–M82), cerebral infarction (KCD-6 codes I63–I66, corresponding to ICD-10 codes I63–I66), angina pectoris (KCD-6 code I20, corresponding to ICD-10 code I20), myocardial infarction (KCD-6 code I21–I22, corresponding to ICD-10 code I21–I22), and obesity (KCD-6 code E66, corresponding to ICD-10 code E66). The date of the initial NHIS and HIRA claims related to NCDs was assigned as the index date in the analysis, and we excluded patients who had already experienced NCDs based on their responses to a self-reported questionnaire in the health checkup examination. To increase the validity of the assessment of NCD diagnoses, we only included patients who had been diagnosed at least twice with a specific NCD-related disorder from 2002 through 2013.

2.3. Identification of patients with periodontal disease

In order to improve diagnostic accuracy of PD in patients, oral examination data has been used besides diagnostic code (KCD-6 codes K05.2–K05.6, corresponding to ICD-10 codes K05.2–K05.6) which has been confirmed before index date. PD was diagnosed clinically in oral checkup examinations based on assessments of missing teeth, gingival/periodontal inflammation (swelling and redness), and the deposition of calculus in accordance with criteria of the Centers for Disease Control and Prevention/American Academy of Periodontology by a general dentist or a periodontist in the biannual NHIS programme.[14]

2.4. Parameters in the health checkup examinations

The health checkup examinations in the NHIS–HEC included a self-reported questionnaire, anthropometric measurements, and blood laboratory measurements. Subjects who responded in self-reported questionnaires that they were currently not smoking, or had smoked fewer than 100 cigarettes were classified as nonsmokers, while the other subjects were classified as smokers. Weight and height were measured without shoes. BMI was calculated by dividing the weight by height squared. SBP and DBP were measured by medical personnel or with an automatic oscillometry device. FBG, TC, hemoglobin, AST, ALT, and r-GTP levels were assessed in blood samples drawn from the subjects. Subjects with SBP < 60 mmHg and > 400 mmHg, DBP
<30 mmHg and >250 mmHg, FBG <25 mg/dL and >999 mg/dL, TC <40 mg/dL and >999 mg/dL, hemoglobin >25.0 g/dL, and AST, ALT, and r-GTP levels >999 IU/L were assumed to be either unknown or missing values, and, therefore, were excluded from the study sample.

2.5. Definition of sociodemographic factors

The sociodemographic factors were collected from the NHIS–HEC and categorized as follows using random stratified analysis by the NHIS Big Data Steering Department: sex (2 groups), age (8 groups classified into those aged 40–69 years in 10-year intervals, and those >70 years old), monthly household income (41 groups classified into quintiles: MAP beneficiaries were in the first-quintile group), insurance status (2 groups: self-employed and employees), residence area (2 groups based on metropolitan [≥1,000,000 residents] or not metropolitan [<1,000,000 residents] living), health status (3 groups classified into healthy, minor disability, and major disability based on the Handicapped Welfare Law), and smoking status.

2.6. Statistical analysis

We used chi-squared, univariate, and multivariate logistic regression analyses to determine the incidence of PD and its associations with major NCDs for the entire enrolled population. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and a P value of less than .05 was considered to be statistically significant. All statistical analyses were performed by the Department of Health Insurance Research, Ilsan Hospital, NHIS using the Statistical Analysis System (version 9.2, SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics and incidence of periodontal disease

Figure 1 shows a flow chart of the inclusion and exclusion process for participants in this study. Among the 514,866 South Korean subjects originally included, 354,850 (68.9%) were recruited: 199,886 men (56.3%) and 154,964 women (43.7%). Those aged 40 to 59 years (n = 178,670) accounted for 50.4% of the surveyed subjects, while 127,465 (35.9%) were in the fifth quintile of household income, 233,385 (65.8%) were in the NHIS (employees), 218,276 (61.5%) did not live in metropolitan areas, and 353,251 (99.5%) had a healthy status. Among the 354,850 subjects, 200,026 (56.4%) patients with PD were recruited, consisting of 121,236 men (60.6%) and 78,790 women (39.4%). Those aged 40 to 59 years (n = 106,148) accounted for 53.1% of the surveyed subjects, while 75,232 (37.6%) were in the fifth quintile of household income, 138,273 (69.1%) were in the NHIS (employees), 120,092 (60.0%) did not live in metropolitan areas, and 199,292 (99.6%) had a healthy status (Table 1).

3.2. Results of the health checkup examinations

The numbers of the subjects identified as smokers, nonsmokers, and not providing responses in health checkup examinations were 81,454 (23.1%), 256,105 (72.2%), and 16,900 (4.7%), respectively. The mean levels of BMI, DBP, TC, hemoglobin, AST, ALT, and r-GTP were higher in the PD population than in those with a healthy oral status, while SBP and FBG were lower in the PD population. Smoking status, BMI, SBP, FBG, TC, hemoglobin, ALT, and r-GTP differed significantly between the healthy oral and PD populations (Table 2).

3.3. Associations of non-communicable diseases with periodontal disease

As indicated in Table 3, the univariate logistic regression analysis showed that PD was significantly positively related to diabetes mellitus (OR = 1.02, 95% CI = 1.01–1.04, P < .001), and significantly negatively related to hypertension (OR = 0.95, 95% CI = 0.93–0.96, P < .001), osteoporosis (OR = 0.77, 95% CI = 0.76–0.78, P < .001), and cerebral infraction (OR = 0.84, 95% CI = 0.83–0.86, P < .001).

In the multivariate logistic regression analysis with adjustment for sex, age, household income, insurance status, residence area,
health status, and smoking status, PD was significantly positively related to hypertension (OR = 1.04, 95% CI = 1.01–1.07, P < .014), diabetes mellitus (OR = 1.16, 95% CI = 1.12–1.20, P < .001), osteoporosis (OR = 1.22, 95% CI = 1.18–1.27, P < .001), angina pectoris (OR = 1.22, 95% CI = 1.17–1.27, P < .001), cerebral infarction (OR = 1.20, 95% CI = 1.15–1.25, P < .001), and myocardial infarction (OR = 1.18, 95% CI = 1.13–1.23, P < .001).

### Table 1: Baseline characteristics of participants in the National Health Insurance Service–Health Examinee Cohort Study (NHIS–HEC).

| Characteristic                  | Healthy oral population | PD population | P*  |
|--------------------------------|-------------------------|---------------|-----|
| Total                          | 154,824                 | 200,026       |     |
| Sex                            |                         |               |     |
| Male                           | 78,650                  | 121,236       | .001|
| Female                         | 76,174                  | 78,790        |     |
| Age group, y                   |                         |               |     |
| 40–49                          | 72,522                  | 106,148       | .001|
| 50–59                          | 42,712                  | 59,676        |     |
| 60–69                          | 30,271                  | 20,005        |     |
| 70–79                          | 9,319                   | 5,107         | 2.6 |
| Household income†              |                         |               |     |
| First quintile                 | 25,089                  | 28,159        | .001|
| Second quintile                | 22,032                  | 25,517        |     |
| Third quintile                 | 23,965                  | 29,757        |     |
| Fourth quintile                | 31,505                  | 41,361        |     |
| Fifth quintile                 | 52,233                  | 75,232        |     |
| Insurance status               |                         |               |     |
| NHIS (self-employed)           | 59,712                  | 61,753        | .001|
| NHIS (employees)               | 95,112                  | 138,273       |     |
| Residence area‡                |                         |               |     |
| Metropolitan                   | 56,640                  | 79,934        | .001|
| Others                         | 98,184                  | 120,092       |     |
| Health status                  |                         |               |     |
| Healthy                        | 153,959                 | 199,292       | .001|
| Major condition                | 339                     | 251           |     |
| Minor condition                | 526                     | 483           | 0.2 |

### Table 2: Results of health checkup examinations.

| Parameter                     | Healthy oral population | PD population | P*  |
|-------------------------------|-------------------------|---------------|-----|
| Self-reported questionnaire   |                         |               |     |
| Smoking                       |                         |               |     |
| Yes                           | 30,391                  | 51,454        | .001|
| No                            | 117,578                 | 138,527       |     |
| No answer                     | 6855                    | 10,045        |     |
| Anthropometric measurements   |                         |               |     |
| Body mass index, kg/m²‡       | 23.6±3.1                | 24.1±2.9      | .001|
| Systolic blood pressure, mm/Hg| 127.5±18.8              | 126.0±17.4    | .001|
| Diastolic blood pressure, mm/Hg| 79.4±11.8              | 79.5±11.5     | .334|
| Blood laboratory measurements |                         |               |     |
| Fasting blood glucose, mg/dL  | 98.0±36.8               | 97.4±33.0     | .017|
| Total cholesterol, mg/dL      | 199.0±38.8              | 200.3±38.1    | .001|
| Hemoglobin, g/dL              | 13.7±1.5                | 14.1±1.5      | .001|
| AST, I/UL                     | 26.7±16.9               | 26.8±17.4     | .558|
| ALT, I/UL                     | 24.3±19.1               | 26.7±22.0     | .001|
| r-GTP, I/UL                   | 94.0±50.2               | 38.7±52.0     | .001|

Data are n or mean±SD values.  
AST = aspartate aminotransferase, ALT = alanine aminotransaminase, r-GTP = r-glutamyltranspeptidase.

### Table 3: Association of non-communicable diseases with periodontal disease in univariate analyses.

| Parameter                   | Healthy oral population | PD population | OR  | 95% CI | P*  |
|-----------------------------|-------------------------|---------------|-----|--------|-----|
| Hypertension                | 78,254                  | 98,373        | 0.95| 0.93–0.96|     |
| No                          | 76,570                  | 101,653       |     |        |     |
| Diabetes mellitus           |                         |               |     |        |     |
| Yes                         | 47,630                  | 62,376        | 1.02| 1.01–1.04| .007|
| No                          | 107,194                 | 137,650       |     |        |     |
| Osteoporosis                |                         |               |     |        |     |
| Yes                         | 44,560                  | 47,396        | 0.77| 0.76–0.78| .001|
| No                          | 110,264                 | 152,630       |     |        |     |
| Cerebral infarction         |                         |               |     |        |     |
| Yes                         | 17,896                  | 19,874        | 0.84| 0.83–0.86| .001|
| No                          | 136,928                 | 180,152       |     |        |     |
| Angina pectoris             |                         |               |     |        |     |
| Yes                         | 26,259                  | 33,932        | 1.00| 0.98–1.02| 1.00|
| No                          | 128,565                 | 166,094       |     |        |     |
| Myocardial infarction       |                         |               |     |        |     |
| Yes                         | 3656                    | 4,508         | 0.95| 0.91–1.00| .033|
| No                          | 151,168                 | 195,518       |     |        |     |
| Obesity                     |                         |               |     |        |     |
| Yes                         | 679                      | 925           | 1.05| 1.00–1.17| .294|
| No                          | 154,145                 | 199,101       |     |        |     |

CI = confidence interval, OR = odds ratio.

P values for the t test; boldface denotes statistical significance (P < .05).
normal ranges and medically insignificant. Changes in dietary habits, decreased physical activity, and increased stress are related to metabolic disorders such as severe obesity, hypertension, diabetes mellitus, and hyperlipidemia, and have been reported to be relevant to the increasing prevalence of PD. The common biological mechanisms underlying both PD and metabolic disorders have yet to be clarified, but the involvement of PD (a chronic inflammatory disease) in various immune reactions of the host and the resulting effects on glucose and lipid metabolism have been established in several studies. The present multivariate logistic regression analyses only showed a significant positive association of PD with angina pectoris (OR = 1.22, 95% CI = 1.17–1.27, \( P < .001 \)) in major cardiovascular disease; the negative association with both cerebral infarction (OR = 0.98, 95% CI = 0.94–1.03, \( P = .418 \)) and myocardial infarction (OR = 0.88, 95% CI = 0.81–0.97, \( P = .007 \)) could be attributed to the use of the NHIS–HEC database, wherein voluntary health examiners were included by simple sampling. Since cerebral and myocardial infarctions are associated with high mortality rates and serious sequelae in the middle-age and elderly population, patients suffering these diseases might have been excluded from the NHIS–HEC database. It was suspected that the patients with PD with these 2 diseases were unlikely to visit dental clinics to be diagnosed with PD, resulting in the lower ORs in this study. Several research studies have suggested a connection between cardiovascular disease and PD, they share certain physiological and sociodemographic risk factors, such as sex, smoking, obesity, stress, lower income, and senility. The presence of PD may lead to transient or intermittent cardiac bacteremia by periodontal pathogens such as Porphyromonas gingivalis (P. gingivalis), Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum. In particular, the introduction of P. gingivalis into the bloodstream can represent a source of infection and it underlies systemic inflammation, endothelial dysfunction, and isoproterenol-induced cardiac hypertrophy.

Diabetes mellitus and hypertension are reportedly important risk factors for PD; therefore, controlling these 2 factors is likely to be critical in the prevention and treatment of adult PD. In this study, the OR for the association of PD with diabetes mellitus in the multivariate analysis was 1.16 (CI = 1.12–1.20, \( P = .001 \)), while that for hypertension was 1.04 (CI = 1.01–1.07, \( P = .014 \)). The association between diabetes mellitus and PD can be explained as a manifestation of systemic inflammation and the corresponding mechanisms of insulin sensitivity and glucose dynamics. The increased severity or chronicity of PD increases the insulin resistance and aggravates glycemic control. Many studies have yielded evidence for a link between diabetes mellitus and essential hypertension via hyperinsulinemia. Therefore, the interrelatedness of diabetes mellitus, hypertension, and PD may affect the manifestation of the disease.

The association of PD with obesity exhibited the highest OR (1.30, CI = 1.04–1.63, \( P = .022 \)) in the multivariate analysis. Obesity is associated with a higher fat level, and it has recently been recognized as a both major risk factor for NCDs and a pathological disease that affects individuals irrespective of age. Obesity causes increased oxidative stress which leads not only to local and systemic endothelial dysfunction, but also to an early connection between PD and obesity. A recent systematic review found a fixed-effects summary OR of 1.35 (CI = 1.23–1.47, \( P < .005 \)), which is similar to that obtained in the present study. In particular, a significantly higher association among younger adults, women, and nonsmokers was found. Conversely,
another 5-year cohort study examining the association between PD and obesity found a higher prevalence in men. Moreover, another study found greater periodontal destruction including clinical attachment loss in patients with a higher BMI, while yet another found no significant association between PD and a BMI of >30 kg/m². While any definitive relationships between the clinical periodontal parameters associated with PD and obesity remain to be clarified, several reports on the potential effects of increased leptin and interleukin (IL)-6 levels on PD and obesity must be taken into consideration.

Many previous studies have found no association between PD and osteoporosis due to either an inadequate number of subjects or the included subjects being limited by old age or being postmenopausal women. A recent nationwide population cohort study that controlled for sociodemographic and economic factors found a significant association between PD and osteoporosis (OR = 1.96, 95% CI = 1.17–3.26), and the present study conducted with adult man and woman subjects older than 40 years also found a significant association in the multivariate analysis (OR = 1.22, 95% CI = 1.18–1.27, P < .001). Osteoporosis is a disease shared with risk factors such as age, smoking, alcohol consumption, diabetes mellitus, obesity, and common clinical features of bone loss and destruction. Patients with osteoporosis show increased activity of inflammatory cytokines such as IL-1 and IL-6, tumor necrosis factor-α, and increased activity of osteoclasts in alveolar bone. Most longitudinal and cross-sectional studies demonstrated the relationship between PD and osteoporosis based on radiographic measurements and clinical parameters. The underlying mechanisms suspected include the disruption of both homeostatic bone metabolism and inflammation resolution. Osteoporosis, therefore, needs to be considered a possible risk factor for the progression and aggravation of PD.

This study was subject to some important limitations. First, as mentioned above, since only the diagnostic and corresponding prescription codes that are registered in the NHIS were used in the present analyses, databases of voluntary non-reimbursable treatments or of the MAP that are not registered in the NHIS were neglected. Moreover, the personal health checkup examination database was also excluded. The MAP is planned to be included in the NHIS-HEC in the future, which is expected to decrease selection bias. Second, since the NHIS-HEC was prepared by diverse medical and dental specialties under NHIS supervision, there is a possibility of inconsistency between cases with identical diagnoses. In particular, since PD can be diagnosed either with or without panoramic/periapical radiographic images, this could increase the likelihood of inconsistency in such diagnoses. Nevertheless, difficulties due to such problems were avoided in the present study by employing the NHIS-HEC data on national oral checkup examinations, which allowed patients with PD to be accurately distinguished.

The study demonstrated that the presence of PD is associated with a significantly elevated risk of NCDs in the Korean adult population, especially obesity, osteoporosis, and angina pectoris. Additional studies are required to confirm this association and to establish in detail the role of the inflammatory pathway in the pathogenesis of periodontitis as a triggering and mediating mechanism.

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References

[1] Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366:1809–20.
[2] Lee JH, Lee JS, Choi JK, et al. National dental policies and socio-demographic factors affecting changes in the incidence of periodontal treatments in Korea: A nationwide population-based retrospective cohort study from 2002–2013. BMC Oral Health 2016;16:118.
[3] Seymour GJ, Ford PJ, Cullinan MP, et al. Relationship between periodontal infections and systemic disease. Clin Microbiol Infect 2007;13(Suppl):3–10.
[4] Badran Z, Steuroll X, Vernet C, et al. Periodontitis as a risk factor for systemic disease: Are microparticles the missing link? Med Hypotheses 2015;84:555–6.
[5] Buset SL, Walter C, Friedmann A, et al. Are periodontal diseases really silent? A systematic review of their effect on quality of life. J Clin Periodontol 2014;43:333–44.
[6] Mendis S, Davis S, Norrving B. Organizational update: the world health organization global status report on noncommunicable diseases 2014: one more landmark step in the combat against stroke and vascular disease. Stroke 2015;46:e121–2.
[7] Schmidt MI, Duncan BB, Azevedo e Silva G, et al. Chronic non-communicable diseases in Brazil: burden and current challenges. Lancet 2011;377:1949–61.
[8] Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380:219–29.
[9] Watt RG, Sheehan A. Integrating the common risk factor approach into a social determinants framework. Community Dent Oral Epidemiol 2012;40:289–96.
[10] Beck JD, Offenbacher S. Systemic effects of periodontitis: epidemiology of periodontal disease and cardiovascular disease. J Periodontol 2005;76:2089–100.
[11] Tonetti MS, Van Dyke TE. working group 1 of the joint EFP/AAP. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2015;84:524–9.
[12] Lee JH, Lee JS, Park JY, et al. Association of lifestyle-related comorbidities with periodontitis: A nationwide Cohort study in Korea. Medicine (Baltimore) 2015;94:e1567.
[13] Lee JH, Choi JK, Kim SH, et al. Association between periodontal flap surgery for periodontitis and vasculogenic erectile dysfunction in Koreans. J Periodontal Implant Sci 2017;47:96–105.
[14] Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1–6.
[15] Thompson KS, Yonke ML, Rapley JW, et al. Relationship between a self-reported health questionnaire and laboratory tests at initial office visits. J Periodontol 1999;70:1133–7.
[16] Saito T, Shimazaki Y. Metabolic disorders related to obesity and periodontal diseases. Periodontol 2000 2007;43:254–66.
[17] Pschon N, Heng N, Bernimoulin JP, et al. Obesity, inflammation, and periodontal disease. J Dent Res 2007;86:400–9.
[18] D’Anto F, Subbah W, Neturel G, et al. Association of the metabolic syndrome with severe periodontitis in a large U.S. population-based survey. J Clin Endocrinol Metab 2008;93:3989–94.
[19] Freisinger E, Malvar NM, Reinecke H. Peripheral artery disease is associated with high in-hospital mortality particularly in males with acute myocardial infarction in a nationwide real-world setting. VASA 2016;45:169–74.
[20] Dhadse P, Gattani D, Mishra R. The link between periodontal disease and cardiovascular disease: How far we have come in last two decades? J Indian Soc Periodontol 2010;14:148–54.
[21] Van Dyke TE, Starr JR. Unraveling the link between periodontitis and cardiovascular disease. J Am Heart Assoc 2013;2:e000657.
[22] Offenbacher S, Beck JD, Moss K, et al. Results from the Periodontitis and vascular events (PAVE) study: a pilot multicentred, randomised controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. J Periodontol 2009;80:190–201.
[23] Zhang B, Khalaf H, Sirsjo A, et al. 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;83:4256–65.
[24] Sato H, Suzuki JI, Aoyama N, et al. A Periodontal pathogen Porphyromonas gingivalis deteriorates lipoprotein-induced myocardial remodeling in mice. Hypertens Res 2017;40:33–40.
[25] Holmlund A, Holm G, Lind L. Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. J Periodontol 2006;77:1173–8.

[26] Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci 2015;6:63–72.

[27] Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. Periodontol 2000 2007;44:127–53.

[28] Serné EH, IJzerman RG, Gans RO, et al. Direct evidence for insulin-induced capillary recruitment in skin of healthy subjects during physiological hyperinsulinemia. Am Diabetes Assoc 2002;51:1515–22.

[29] DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173–94.

[30] Dursun E, Akalin FA, Genc T, et al. Oxidative stress and periodontal disease in obesity. Medicine (Baltimore) 2016;95:e3136.

[31] Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289:76–9.

[32] Chaffee BW, Weston SJ. Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. J Periodontol 2010;81:1708–24.

[33] Morita I, Okamoto Y, Yoshii S, et al. Five-year incidence of periodontal disease is related to body mass index. J Dent Res 2011;90:199–202.

[34] Buduneli N, Biyikoglu B, Ilgenli T, et al. Is obesity a possible modifier of periodontal disease as a chronic inflammatory process? A case-control study. J Periodontal Res 2014;49:463–71.

[35] Karthikeyan BV, Pradeep AR. Gingival crevicular fluid and serum leptin: their relationship to periodontal health and disease. J Clin Periodontol 2007;34:467–72.

[36] Bullon P, Gobena B, Guerrero JM, et al. Serum, saliva, and gingival crevicular fluid osteocalcin: their relation to periodontal status and bone mineral density in postmenopausal women. J Periodontol 2003;74:513–9.

[37] Hattatoglu-Sonmez E, Ozccakar I, Gokce-Katsal Y, et al. No alteration in bone mineral density in patients with periodontitis. J Dent Res 2008;87:79–83.

[38] Lin TH, Lung CC, Su HP, et al. Association between periodontal disease and osteoporosis by gender a nationwide population-based Cohort study. Medicine (Baltimore) 2015;94:e553.

[39] Kim JW, Kong KA, Kim HY, et al. The association between bone mineral density and periodontitis in Korean adults (KNHANES 2008–2010). Oral Dis 2014;20:609–15.

[40] Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000 2013;62:59–94.

[41] Tezal M, Wactawski-Wende J, Grossi SG, et al. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol 2010;81:1492–8.

[42] Wang CJ, McCauley LK. Osteoporosis and periodontitis. Curr Osteoporos Rep 2016;14:284–91.

[43] Juluri R, Prashanth E, Gopalakrishnan D, et al. Association of postmenopausal osteoporosis and periodontal disease: A double-blind case-control study. J Int Oral Health 2015;7:119–23.

[44] Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. Ann Periodontol 2001;6:197–208.