Association between the number of natural teeth and diabetic retinopathy among type 2 diabetes mellitus

The Korea national health and nutrition examination survey

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Abstract
The aim of this study was to investigate the relationship between the number of teeth and diabetic retinopathy among Korean population.

This was a retrospective analysis using data of total 45,811 individuals who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) 2008 to 2012. Among these, 2593 (5.7%) participants were identified as having type 2 diabetes mellitus. After excluding participants without ophthalmic evaluation or other variables, 2078 (80%) participants were included. Demographic factors including dental status were analyzed and compared between participants with and without diabetic retinopathy.

Among the 2078 type 2 diabetes, 358 (17.2%) had diabetic retinopathy. Type 2 diabetes with fewer teeth were more likely to have diabetic retinopathy (P < .001). Multivariate analysis showed that type 2 diabetes with < 20 teeth had an 8.7-fold risk of having vision-threatening diabetic retinopathy when compared with type 2 diabetes with ≥ 28 teeth (95% confidence interval: 2.69–28.3) after adjusting for age, sex, body mass index, smoking, drinking, exercise, hypertension, diabetes mellitus duration, and glycated hemoglobin level.

The number of teeth was found to be an independent risk factor for diabetic retinopathy. Thus, a comprehensive approach of dentists and ophthalmologists is needed to minimize the complications of diabetes mellitus. Whether the teeth number reflects microvascular changes of the retina among type 2 diabetes warrants further investigation.

Abbreviations: BMI = body mass index, CI = confidence interval, CSME = clinically significant macular edema, CWS = cotton-wool spots, ETDRS = Early Treatment for Diabetic Retinopathy Study, HbA1c = glycated hemoglobin, HE = hard exudates, IRMA = intraretinal microvascular abnormalities, KNHANES = Korean National Health and Nutrition Examination Survey, MA = microaneurysm, VTD = vision-threatening diabetic retinopathy.

Keywords: dentition, diabetic retinopathy, health surveys, oral health, periodontitis, teeth, tooth loss

1. Introduction
Diabetes mellitus and periodontal disease are known to be closely related and affecting each other.[1–5] Diabetes mellitus is a risk factor for periodontal disease prevalence and severity, and, in turn, periodontal disease may affect the metabolic control in persons with diabetes.[1–5]

Many studies have shown that periodontitis is associated with an increased risk of cardiovascular and cerebrovascular morbidity among persons with diabetes.[1–3] Moreover, in addition to cardiovascular or cerebrovascular diseases, studies regarding periodontal status as a risk factor for diabetic nephropathy have demonstrated that the incidences of macroalbuminuria and end-stage renal disease are higher in persons with diabetes.[1–3] and periodontitis has been reported to predict the development of overt nephropathy and end-stage renal disease in individuals with type 2 diabetes.[1–7] However, when considering studies regarding the relationship between diabetic retinopathy and periodontal disease, the information remains limited. Most of these studies included small numbers of subjects and did not consider possible confounders.[8,9] One study performed among 100 patients with type 2 diabetes found that the oral hygiene score, probing pocket depth, and clinical attachment loss were significantly different between patients with and without diabetic retinopathy; however, after adjusting for confounders, these results
failed to show significant effects. As diabetic retinopathy is the most common cause of blindness among the working population worldwide, evaluating the relationship between diabetic retinopathy and periodontal disease will provide important clinical information for persons with diabetes, and this information may help improve the socioeconomic burden caused by diabetes-related complications in the future.

In addition to periodontitis, tooth loss or missing teeth have been used as a marker of periodontal status. Changes in oral health status because of caries and periodontitis may lead to a reduced number of teeth, and the number of natural teeth is a rapid and easy index for both clinicians and patients. Hence, in this study, we aimed to analyze the relationship between the number of teeth and diabetic retinopathy among patients with type 2 diabetes, using data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2008 to 2012.

2. Methods

2.1. Survey of participants

This survey was reviewed and approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention, and all participants provided written informed consent. This study is a secondary analysis of data collected during the KNHANES from 2008 to 2012. The Institutional Review Board at the Catholic University of Korea approved this study. All study procedures were in accordance with the Declaration of Helsinki.

Among the 45,811 individuals who participated in the KNHANES 2008 to 2012, 2593 (5.6%) participants were identified as having type 2 diabetes. After excluding participants without ophthalmic evaluation or other variables, 2078 (80%) type 2 diabetes participants were included in this analysis.

2.2. Demographic variables

All participants were asked about their smoking status, alcohol consumption, physical activity, educational level, and monthly household income. On the basis of their answers to the self-reported questionnaire, the participants were classified as nonsmokers or ever-smokers. Ever-smokers were defined as participants who had smoked at least 5 packs of cigarettes during their life. Participants were categorized as nondrinkers, light to moderate drinkers (1–30 g/day), or heavy drinkers (>30 g/day) on the basis of their average daily alcohol intake in the month before the interview. Depending on the International Physical Activity Questionnaire short form modified for Korea, participants were considered regular physical exercisers if they exercised moderately more than 5 times per week for ≥30 minutes per session or exercised vigorously more than 3 times per week for ≥20 minutes per session. Educational level was categorized into 2 groups according to the number of years of schooling: ≥12 years (high school graduate) or less. The monthly household income level was divided into the lower 25th percentile of the total participants or higher.

2.3. Anthropometric measurements

Trained staff members performed the measurements of the participants. Waist circumference was measured at the narrowest point between the lower border of the rib cage and the iliac crest. Body mass index (BMI) was calculated by the following formula: weight (kg)/height (m)^2. Systolic blood pressure and diastolic blood pressure were measured on the right arm using a standard mercury sphygmomanometer (Baumanometer; W.A. Baum Co., Inc., Copiague, NY). Systolic and diastolic blood pressure measurements were performed 2 times at a 5-minute interval, and the average of the 2 measurements was used for the analysis.

2.4. Ophthalmic examination

Nonmydriatic fundus photography (TRC-NW6S; Topcon, Tokyo, Japan) was performed in all KNHANES participants. In participants with a history of diabetes mellitus or a random blood glucose level of ≥200 mg/dL and/or suspicion of diabetic retinopathy on nonmydriatic photography, 7 standard field photographs were obtained from each eye after pharmacological pupil dilation as per the Early Treatment for Diabetic Retinopathy Study (ETDRS) protocol. Diabetic retinopathy was identified as defined by the ETDRS severity scale according to the presence of microaneurysms (MAs), hemorrhages, hard exudates (HEs), cotton wool spots, intraretinal microvascular abnormalities, venous beading, and retinal new vessels. A diabetic retinopathy severity score was assigned to each eye according to the modification of the Airlie House Classification system, as follows: level 1, no retinopathy present; level 2, any combination of definite HEs, cotton-wool spots (CWS), intraretinal microvascular abnormalities (IRMAs), or venous loops in the absence of definite MA; level 15, hemorrhage present without any definite MA; level 20, MA only with no other diabetic lesion present; level 31, MA and one or more of the following: hemorrhage or MA < standard photograph 2A, HE, venous loops, questionable CWS, IRMA, or venous beading; level 41, MA and one or more of the following: venous beading, hemorrhage or MA > 2A, IRMA > 8A; level 60, fibrous proliferation with no other proliferative lesion; levels 61 to 64, laser scatter photocoagulation scars with retinopathy levels 31 to 51; level 63, proliferative diabetic retinopathy without high-risk characteristics, as defined in the Diabetic Retinopathy Study; level 70, proliferative diabetic retinopathy with several high-risk characteristics; and level 80, total vitreous hemorrhage. The level of retinopathy was graded based on the worse eye. The eyes were graded according to the following criteria: no diabetic retinopathy (levels 10–13), nonproliferative diabetic retinopathy (levels 14–51), and proliferative diabetic retinopathy (level >60).

Clinically significant macular edema (CSME) was defined according to the ETDRS criteria as follows: retinal thickening at or within 500 μm of the center of the macula of the retina; HEs at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina (but not HEs remaining after disappearance of retinal thickening); and one or more zones of retinal thickening and at least 1 large-size disk area large, any part of which is within 1 disc diameter of the center of the macula.

Vision-threatening diabetic retinopathy (VTDR) was defined as the presence of severe nonproliferative diabetic retinopathy, proliferative retinopathy, or CSME.

2.5. Diabetes mellitus

Diabetes mellitus was diagnosed if the fasting blood sugar level was > 126 mg/dL or the individual was currently using antidiabetic medications. Metabolic syndrome was defined if 3 or more of the following were fulfilled: waist circumference ≥90 cm in men and ≥80 cm in women; fasting triglycerides ≥150 mg/dL or use of lipid-lowering medication; high-density lipoprotein cholesterol ≤40 mg/dL, total cholesterol ≥200 mg/dL, or triglycerides ≥150 mg/dL. All participants were asked to report antidiabetic medication use. Metabolic syndrome was defined as the presence of 3 or more of the following: waist circumference ≥90 cm in men and ≥80 cm in women; fasting triglycerides ≥150 mg/dL; total cholesterol ≥200 mg/dL; high-density lipoprotein cholesterol ≤40 mg/dL; and antidiabetic medication use.
lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women or use of lipid-lowering medication; blood pressure ≥130/85 mm Hg or the use of antihypertensive medication; and fasting blood glucose ≥100 mg/dL or current use of antidiabetic medication. Hypertension was defined as a systolic blood pressure of >160 mm Hg, a diastolic blood pressure of >90 mm Hg, or the current use of systemic antihypertensive drugs. The estimated glomerular filtration rate was calculated using the following equation: estimated glomerular filtration rate (mL/min/1.73 m²) = 186.3 × (serum creatinine\(^{-0.203}\)) × (age\(^{-0.023}\)); the result was then multiplied by the constant 0.742 if the patient was female. The equation was developed from the modified diet in renal disease formula.\\(^{20}\)\\n
### 2.6. Oral health

The KNHANES oral health data recorded the status for each of the 28 teeth. In this study, the total number and pairs of natural teeth were counted after excluding the third molars. On the basis of this information, we categorized the subjects into 3 groups according to the total number of natural teeth: full dentition (≥28 teeth), 20 to 27 teeth, and <20 teeth.

For further analysis, the numbers of teeth were categorized as follows: 0 to 4, 5 to 9, 10 to 14, 15 to 19, 20 to 24, and ≥25 teeth. In addition to the frequency of tooth brushing per day, the use of secondary oral products was also recorded as oral health behaviors. Secondary oral products included dental floss, mouthwash, interdental brushes, and electric toothbrushes.

### 2.7. Statistical analyses

All data are presented as the mean± standard error or as % (standard error). The Chi-square test for categorical variables or the independent t test for continuous variables was performed to assess the differences in characteristics according to the number of teeth. Multiple logistic regression analyses were performed to assess the associations between the number of teeth and diabetic retinopathy. For multivariate analysis, the participants were divided into 3 groups based on the numbers of remaining teeth: <20, 20 to 27, and ≥28. Model 1 was age- and sex-adjusted, whereas Model 2 was adjusted for the variables in Model 1 and BMI, smoking, drinking, exercise, and hypertension. Model 3 was adjusted for the variables in Model 2 and glycated hemoglobin (HbA1c) level, duration of diabetes mellitus, frequency of brushing, and frequency of using extra dental care. The survey procedure of SAS version 9.2 for Windows (SAS Institute, Cary, NC) was used for statistical analyses to account for the complex sampling design. Two-sided P values of <.05 were considered statistically significant.

### 3. Results

Among the 2078 type 2 diabetes, 358 (17.2%) type 2 diabetes had diabetic retinopathy. Table 1 summarizes the baseline demographic features of the study type 2 diabetes based on their number of teeth. Type 2 diabetes with fewer teeth tended to be older, have longer duration of diabetes mellitus, lower BMI, lower education status, lower frequency of brushing, to be less likely to use secondary oral products, have lower education or income, and to be more likely to have diabetic retinopathy (Table 1). A significant difference in the prevalence of diabetic retinopathy was noted among the type 2 diabetes according to the number of remaining teeth (Fig. 1). When compared with type 2 diabetes with ≥25 teeth, type 2 diabetes with ≤4 teeth were more than twice as likely to have diabetic retinopathy (12.3% vs 28.6%). Also, when we consider blood HbA1c level addition to
number of teeth, there was statistically significant difference between prevalence of diabetic retinopathy (Fig. 2) Even among type 2 diabetes with proper blood glucose control (defined as HbA1c < 6.5%), type 2 diabetes with teeth < 20 had more than twice of prevalence of diabetic retinopathy when compared with those of teeth ≥ 20 (5.2% vs 13.0%, \( P = .02 \), Fig. 2). Moreover, among type 2 diabetes with improper blood glucose control (defined as HbA1c > 6.5%), patients with teeth < 20 had almost twice of prevalence of diabetic retinopathy when compared with those of teeth ≥ 20 (17.0% vs 30.0%, \( P < .001 \), Fig. 2).

Subgroup analysis based on the diabetic retinopathy severity showed that the number of teeth and severity of diabetic retinopathy correlated well, even after adjusting for possible confounders (Table 2). It was also shown that age, sex, smoking, and drinking did not show the statistical significance after adjusting for possible confounders.

Multivariate analysis showed that type 2 diabetes with < 20 teeth had a 2.3-fold higher risk of having non-VTDR than type 2 diabetes with ≥ 28 teeth [95% confidence interval (CI): 1.36–3.95]. Moreover, after adjusting for age, sex, BMI, smoking, drinking, exercise, hypertension, diabetes duration, and HbA1c, type 2 diabetes with diabetes with < 20 teeth had an 8.7-fold risk of having VTDR when compared with those with ≥ 28 teeth (95% CI: 2.69–28.3).

4. Discussion

Our study showed that the number of natural teeth was an independent risk factor for diabetic retinopathy after adjusting for a number of possible confounders. Moreover, this result was found to be amplified as the severity of diabetic retinopathy increased. Type 2 diabetes with fewer (< 20) teeth had an 8.7-fold risk of VTDR, as compared with type 2 diabetes with more (≥ 28) teeth, after adjusting for possible confounders. This result is in concordance with previous studies showing that there is an association between periodontal disease and diabetic retinopathy, supporting the hypothesis that diabetes mellitus not only acts as a risk factor for periodontal disease, but also that the periodontal health state is conversely a risk factor for diabetes mellitus related complications.\[1–6]\n
For more than a decade, dentists have been aware of diabetes mellitus as an important risk factor for periodontitis,\[1–6]\ with inflammation acting as a common pathologic mechanism for both disease entities.\[1–6]\ Accordingly, both periodontitis and diabetic retinopathy are associated with increased levels of inflammatory markers, and chronic inflammation associated with periodontitis may lead to systemic endothelial dysfunction, which may compromise the retina vessel endothelium and subsequently result in development of diabetic retinopathy.\[1–6]\n
The prevalence of periodontitis in the general Korean population is known to be as high as 30%, making periodontal disease a major disease entity for Koreans seeking medical care.\[22]\ The recent exponential increase in persons with diabetes among the Korean population has led to a rapid increase in the socioeconomic burden due to diabetes-related complication treatments. Together with diabetic nephropathy, diabetic retinopathy is the most common microvascular complication.\[23]\ Hence, clarifying the association of periodontitis with diabetic retinopathy is expected to have a huge impact on patients with diabetes, as well as on the general population.

In the present study, contrary to our expectations, low BMI was associated with an increased risk of diabetic retinopathy after adjusting for age sex, hypertension, diabetes mellitus duration, smoking, exercise, and HbA1c (Table 1). The mechanisms for this association can partially be explained by the obesity paradox.\[23–26]\ Adults who are of normal weight at the time of incident diabetes mellitus have been reported to have higher mortality than adults who were overweight or obese.\[23–26]\ Previous reports have shown that high BMI may indicate more muscle mass and more optimal physical and nutritional state against catabolic conditions.\[26–28]\ Moreover, obesity may produce a protective effect through differences in the immune response and more metabolic reserves.\[26–28]\ However, as this was a cross-sectional study, we cannot determine the temporal relationship between BMI and diabetic retinopathy.

In addition to the number of teeth, the blood HbA1c level and diabetes duration were found to be independent risk factors for diabetic retinopathy in the present study (Table 1). Numerous studies have reported glycemic control as the most important risk factor for diabetic retinopathy.\[29–32]\ Our results supports the fact that glycemic control is the most important systemic factor for both vision and oral health, and not only diabetologists but also dentists should be fully aware and monitor the patients’ glycemic control status accordingly.

Our study has several limitations that need to be addressed. First, our study was cross-sectional; hence, we could not determine the cause–effect relationship between the number of teeth and diabetic retinopathy. Further prospective studies with long follow-up periods are needed to confirm the cause–effect relationship. Second, instead of the periodontitis grade, we used the number of natural teeth as a parameter for the periodontal health state. However, compared with the periodontitis grade,
the number of natural teeth may be a more objective, easy, and quick screening method to assess the periodontal health. Further, many studies using the number of teeth as a parameter for periodontal health status have been published to date, thus supporting our methodology. Moreover, using the number of teeth can have additional advantages over using the periodontitis grade, as it reflects both periodontal health status and dental function. In conclusion, our study evaluated the relationship between the number of teeth and diabetic retinopathy by using Korean national representative data. The risk of diabetic retinopathy increased with having fewer teeth among patients with type 2 diabetes, and this effect was more pronounced for severe diabetic retinopathy. This indicates that comprehensive efforts of both diabetologists and dentists are important to reduce the socioeconomic burden associated with diabetic retinopathy. Furthermore, dentists should acknowledge the risk of diabetic retinopathy when examining patients with diabetes with missing teeth and, if indicated, refer them to an ophthalmologist for fundus examination.

On the basis of our study results, number of teeth was found to be an independent risk factor for diabetic retinopathy. And this risk was more pronounced as severity of diabetic retinopathy increases. These 2 remote structures may have close association among diabetes.

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