Associations of Periodontal Damage and Tooth Loss with Atherogenic Factors among Patients with Type 2 Diabetes Mellitus

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Abstract

Objective To clarify the associations of periodontal damage and tooth loss with atherogenic factors among diabetic patients.

Methods We examined the correlations of age, sex, smoking, oral hygiene score, blood pressure, body mass index, and blood chemical data with the mean depth of periodontal pockets or the number of remaining teeth.

Patients One hundred outpatients with type 2 diabetes aged 29 to 77 years.

Results The mean depth of periodontal pockets was significantly associated with smoking, oral hygiene score, and HbA1c; the Spearman correlation coefficients (r) were 0.220, 0.417, and 0.260, respectively. Age, oral hygiene score, and HbA1c were inversely correlated with the number of remaining teeth ($r=-0.306$, -0.287 , and -0.275 , respectively). Serum total cholesterol was significantly correlated with the mean depth of pockets after adjustment for smoking, oral hygiene score, and HbA1c ($r=0.211$; $P=0.044$), while serum HDL cholesterol tended to be negatively associated with depth ($r=-0.202$; $P=0.055$). Serum HDL cholesterol was also associated with an increased number of teeth, which remained significant after adjustment for age, oral hygiene score, and HbA1c ($r=0.202$; $P=0.048$). The estimated glomerular filtration rate was significantly and positively correlated with the number of teeth in the univariate analysis, although consideration of the potential confounding factors somewhat weakened the association ($r=0.186$; $P=0.069$).

Conclusions We may expect better management of oral health in diabetic patients with control of dyslipidemia in addition to blood glucose.

Key words: diabetic patients, periodontal disease, hyperlipidemia, dyslipidemia, atherosclerosis

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Introduction

Periodontitis has been referred to as the sixth complication of diabetes after microangiopathy including retinopathy, nephropathy, neuropathy, macrovascular disease, and delayed wound healing (1, 2). Many studies have long recognized that the disease is common among diabetic patients

and becomes worse with the progression of diabetes. Type 2 diabetic patients are more likely to have deep periodontal pockets and to lose teeth than non-diabetic controls (3). Deterioration of periodontal condition and subsequent tooth loss result in impaired chewing ability and unhealthier diets such as decreased intake of fruits and vegetables (4). In addition, chewing ability may be an independent predictor of physical fitness measurements in the elderly (5). Thus, pre-

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ventive dental care aimed to maintain chewing ability may enhance activities of daily living (ADL) and quality of life in diabetic patients.

Although the pathogenic role of a microbial plaque and hyperglycemia is beyond doubt, several other factors could influence the initiation and progression of periodontal damage in diabetics. Dyslipidemia combined with hyperglycemia may be responsible for deregulation of cytokine production by immune cells and increased inflammatory destruction of periodontal tissue (2). This is supported by recent investigations, which found associations between impaired lipid metabolism and periodontal disease (6-10). Furthermore, atherosclerotic diseases such as cardiovascular diseases have recently been associated with periodontal disease (11, 12). Atherogenic factors other than hyperglycemia including hypertension, dyslipidemia, and obesity may induce atherosclerosis and subsequent ischemia also in periodontal tissue. Chronic kidney disease has also attracted attention in relation to periodontal disease (13).

Whether atherogenic factors other than hyperglycemia are linked with periodontal damage, however, is still being debated, and previous studies have reported inconsistent results (6-10, 13-21). Further, only a few studies examined such associations among patients with diabetes (14). The associations may differ between diabetics and non-diabetics. Thus, we investigated the associations of blood pressure, body mass index (BMI), and blood chemical data relating atherosclerosis with oral health in patients with diabetes, using the mean depth of periodontal pockets and the number of remaining teeth as indices.

Patients and Methods

Patients

The subjects of the present study were 100 outpatients with type 2 diabetes mellitus at the Aichi Medical University Hospital (from March to October 2001) and the Fushimi Clinic (Nagoya, Japan; from November 2002 to January 2003). They were enrolled from diabetic outpatient clinics when one of the authors (TF: a dentist) was available. They included 72 men and 28 women aged 29 to 77 years. Mean ages ($\pm$ standard deviation) of the patients were 59 ± 7 years for men and 60 ± 11 years for women. The diagnosis of diabetes was made according to the criteria of the Japan Diabetes Society (22). The Ethical Board of the Research Center of Health, Physical Fitness and Sports, Nagoya University approved the protocol of this investigation, and all participants verbally provided informed consent.

General health examination

The patients underwent a routine check-up including anthropometric and manometric measurements and blood chemical analysis. Blood pressure was measured using a mercury sphygmomanometer, with patients in a sitting position. Because blood was not necessarily drawn when the pa-

tients were fasting, we did not adopt data on serum triglyceride. The blood samples were analyzed for HbA1c and serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and creatinine. Serum creatinine was determined using the enzymatic method. The method and period of treatment were abstracted from the clinical charts. Diabetic retinopathy was examined at least annually by expert ophthalmologists using ophthalmoscopy. Urinalysis was performed to check albuminuria and/or proteinuria. Nephropathy was diagnosed in patients with urine microalbumin levels of greater than 30 mg/dl and/or with positive dip stick (23).

Information on smoking habits was obtained using a self-administered questionnaire, which elicited the number of cigarettes smoked per day in six categories: 0, 1-9, 10-19, 20-29, 30-39, or ≥ 40 cigarettes/day.

Dental examination

Subjects underwent a series of dental examinations including the number of decayed, missing, and filled teeth. Twenty-eight was the highest number of remaining teeth because we excluded third molars. In addition, to assess periodontal condition, we probed all existing teeth to determine depth of periodontal pockets with a specially-designed periodontal probe. The pocket depth was averaged over all teeth of each subject. The depth was not available for those without remaining teeth. The oral hygiene status was scored as follows: 0: almost no plaque; 1: plaque covers less than one third of tooth surface; and 2: plaque covers more than one third of tooth surface. One of the authors (TF) conducted all dental examinations.

Statistical analysis

The associations between potential demographic (age and sex) or conventional [smoking (number of cigarettes smoked per day), oral hygiene score, HbA1c, and duration of therapy for diabetes] risk factors for periodontal disease (24) and the mean depth of periodontal pockets or number of remaining teeth were examined by calculating Spearman correlation coefficients. These coefficients were also computed for medical factors including blood pressure, serum total cholesterol, BMI, and estimated glomerular filtration rate (GFR). GFR was estimated using the MDRD (Modification of Diet in Renal Disease Study Group) 4-variable formula (25): Estimated GFR ($\text{ml}/\text{min}/1.73 \text{ m}^2$) = $175 \times (\text{serum creatinine} [\text{mg}/\text{dl}])^{-1.154} \times (\text{age} [\text{years}])^{-0.203} \times 0.742$ (if woman). We further adjusted the correlation coefficients of medical variables for the demographic or conventional risk factors significantly correlated with the mean depth of periodontal pockets or number of teeth, by computing partial correlation coefficients. The factors were smoking, oral hygiene score, and HbA1c for the mean depth of pockets, and age, oral hygiene score, and HbA1c for number of teeth. In addition, we repeated these analyses after excluding 33 current smokers or 34 individuals without 20 teeth. We also carried out a similar analysis for oral hygiene score. All P values were two-sided, and all the analyses were performed using the

Table 1. Characteristics of Study Subjects with Type 2 Diabetes Mellitus (n = 100)

Age (years)	59.1 ± 8.4
Female	28.0%
Duration of therapy for diabetes (years)	12.6 ± 7.2
HbA1c (%)	7.8 ± 1.3
Diabetic nephropathy (yes)	26.0%
Diabetic retinopathy (yes) ^{a)}	35.7%
Treatment ^{b)}	
Diet and exercise only	17.2%
With oral drugs	48.5%
With insulin injection	34.3%
Number of decayed teeth	0.5 ± 1.6
Number of filled teeth	8.2 ± 5.2
Systolic blood pressure (mmHg)	129.7 ± 12.0
Diastolic blood pressure (mmHg)	77.1 ± 7.7
Serum total cholesterol (mg/dl)	200.9 ± 30.1
Serum HDL cholesterol (mg/dl)	52.1 ± 12.9
Body mass index (kg/m ²) ^{a)}	23.8 ± 3.4
Serum creatinine (mg/dl)	0.83 ± 0.26
Estimated GFR (ml/min/1.73 m ²)	94.5 ± 24.4

Plus-minus values are means ± SD.

HDL: high-density lipoprotein; GFR: glomerular filtration rate.

a) Data were missing for two subjects.

b) Data were missing for one subject.

Statistical Analysis System, version 9.1 (SAS Institute Inc., Cary, NC, USA) (26).

Results

Table 1 shows the selected characteristics of the 100 eligible subjects. They have been treated for diabetes for a mean of more than 10 years and included a substantial number of patients with nephropathy (26.0%) and/or retinopathy (35.7%). About one-third (34.3%) of the patients were treated with insulin injection. The mean depth of periodontal pockets in more than 80% of subjects ranged from 2.0 to 4.4 mm with a peak of the distribution in 2.0-2.4 mm (Fig. 1). Twenty or more teeth were kept in two thirds (66.0%) of the patients, and so were 25 or more teeth in one-third (36.0%) (Fig. 2).

For age, sex, and conventional risk factors for periodontal disease, the mean depth of periodontal pockets was positively and significantly associated with smoking, oral hygiene score, and HbA1c; the Spearman correlation coefficients (*r*) were 0.220, 0.417, and 0.260, respectively (Table 2). On the other hand, age, oral hygiene score, and HbA1c were inversely correlated with the number of remaining teeth (*r*=-0.306, -0.287, and -0.275, respectively).

Serum total cholesterol was significantly correlated with the mean depth of pockets after adjustment for smoking, oral hygiene score, and HbA1c (*r*=0.211; *P*=0.044), while the serum HDL cholesterol tended to be negatively associated with the depth (*r*=-0.202; *P*=0.055) (Table 3). Serum HDL cholesterol was also associated with an increased number of teeth, which remained significant after adjustment for

Figure 1. Distribution of study subjects by mean depth of periodontal pockets (mm). **Figure 2.** Distribution of study subjects by number of remaining teeth.

age, oral hygiene score, and HbA1c (*r*=0.202; *P*=0.048). The estimated GFR was significantly and positively correlated with the number of teeth in the univariate analysis, although consideration of the potential confounding factors somewhat weakened the association (*r*=0.186; *P*=0.069). No clear association was observed between the mean depth of pockets or number of teeth and blood pressure or BMI.

The positive correlations between serum total cholesterol and the mean depth of periodontal pockets or serum HDL cholesterol and number of teeth and the negative correlation between serum HDL cholesterol and the mean pocket depth were still observed in the multivariate analyses limited to non-smokers or participants with 20 or more teeth (Table 4). Most of these associations, however, did not reach statistical significance probably due to the small sample size. In non-smokers, estimated GFR was positively associated with the number of teeth after adjustment for age, oral hygiene score, and HbA1c.

We also conducted a similar analysis for oral hygiene score as those for the mean pocket depth and number of remaining teeth. Of the conventional risk factors for periodontal disease listed in Table 2, smoking and HbA1c were positively correlated with oral hygiene score (*r*=0.258; *P*=0.010 for smoking and *r*=0.196; *P*=0.050 for HbA1c). Systolic and diastolic blood pressure, serum total and HDL cholesterol, BMI, and estimated GFR, however, were not associated with

Table 2. Spearman Correlation Coefficients (r) between Age, Sex, or Conventional Risk Factors for Periodontal Disease and Mean Depth of Periodontal Pockets or Number of Teeth

	Mean depth of periodontal pockets (n = 94)		Number of teeth (n = 100)	
	r	P	r	P
Age	0.098	0.35	-0.306	0.002
Female sex	-0.113	0.28	-0.019	0.85
Smoking	0.220	0.033	0.012	0.91
Oral hygiene score	0.417	< 0.001	-0.287	0.004
HbA1c	0.260	0.011	-0.275	0.006
Duration of therapy for diabetes	0.093	0.37	-0.020	0.85

Table 3. Spearman Correlation Coefficients (r) between Blood Pressure, Serum Cholesterol, Body Mass Index, or Estimated GFR and Mean Depth of Periodontal Pockets or Number of Teeth

	Mean depth of periodontal pockets (n = 94)				Number of teeth (n = 100)			
	Crude		Adjusted ^{a)}		Crude		Adjusted ^{b)}	
	r	P	r	P	r	P	r	P
Systolic blood pressure	-0.047	0.65	-0.028	0.79	-0.116	0.25	-0.116	0.26
Diastolic blood pressure	-0.082	0.43	-0.108	0.31	-0.055	0.58	-0.125	0.22
Serum total cholesterol	0.182	0.078	0.211	0.044	-0.029	0.78	-0.057	0.58
Serum HDL cholesterol	-0.191	0.065	-0.202	0.055	0.205	0.041	0.202	0.048
Body mass index	-0.042	0.69	-0.071	0.51	-0.069	0.50	-0.090	0.38
Estimated GFR	-0.140	0.18	-0.159	0.13	0.212	0.034	0.186	0.069

HDL: high-density lipoprotein; GFR: glomerular filtration rate.

a) Adjusted for smoking, oral hygiene score, and HbA1c.

b) Adjusted for age, oral hygiene score, and HbA1c.

Table 4. Spearman Correlation Coefficients (r) between Blood Pressure, Serum Cholesterol, Body Mass Index, or Estimated GFR and Mean Depth of Periodontal Pockets or Number of Teeth among Non-smokers or Those with ≥ 20 Teeth

	Non-smokers								Those with ≥ 20 teeth							
	Mean depth of periodontal pockets (n = 62)				Number of teeth (n = 67)				Mean depth of periodontal pockets (n = 65)				Number of teeth (n = 66)			
	Crude		Adjusted ^{a)}		Crude		Adjusted ^{b)}		Crude		Adjusted ^{c)}		Crude		Adjusted ^{b)}	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P
Systolic blood pressure	0.039	0.76	0.026	0.84	-0.192	0.12	-0.143	0.26	-0.079	0.53	-0.058	0.66	-0.139	0.27	-0.187	0.14
Diastolic blood pressure	-0.166	0.20	-0.158	0.23	0.031	0.80	-0.013	0.92	-0.105	0.40	-0.096	0.46	-0.037	0.77	-0.095	0.46
Serum total cholesterol	0.194	0.13	0.233	0.073	0.077	0.53	0.110	0.39	0.142	0.26	0.213	0.097	0.043	0.73	-0.005	0.97
Serum HDL cholesterol	-0.216	0.091	-0.203	0.12	0.191	0.12	0.179	0.16	-0.282	0.023	-0.250	0.050	0.364	0.003	0.336	0.007
Body mass index	-0.174	0.18	-0.184	0.17	-0.051	0.69	-0.091	0.48	0.084	0.51	0.037	0.78	-0.276	0.026	-0.250	0.050
Estimated GFR	-0.142	0.27	-0.135	0.30	0.329	0.007	0.309	0.013	-0.101	0.43	-0.083	0.52	0.102	0.41	0.071	0.58

HDL: high-density lipoprotein; GFR: glomerular filtration rate.

a) Adjusted for oral hygiene score and HbA1c.

b) Adjusted for age, oral hygiene score, and HbA1c.

c) Adjusted for smoking, oral hygiene score, and HbA1c.

oral hygiene score both in univariate analysis and in multivariate analysis with adjustment for smoking and HbA1c; all the absolute values of Spearman correlation coefficients were smaller than 0.1 with P values > 0.4 .

Discussion

The present study investigated possible associations of atherogenic factors and periodontal conditions or tooth loss

in patients with type 2 diabetes. Hypercholesteremia was found to be correlated with the depth of periodontal pockets independently of hyperglycemia. On the contrary, serum HDL cholesterol was inversely associated with tooth loss and tended to be so with the pocket depth even after considering confounders. Renal function assessed by the estimated GFR was correlated with the number of remaining teeth, but the adjustment for potential confounding factors somewhat attenuated the association.

Among atherogenic factors, the elevated serum total cholesterol was associated with periodontal damage assessed by the mean depth of periodontal pockets. Together with hyperglycemia, atherosclerosis will be accelerated by hypercholesterolemia (27, 28), which may develop ischemia in periodontal tissue as tissue ischemia from infarcts in coronary heart disease and stroke. Diabetic microangiopathy contributes to compromised delivery of nutrients to surrounding tissues and poor elimination of metabolic waste products (29). Periodontal tissue damage may thus be more expected in diabetics with hypercholesterolemia, as found in our study. Some (6, 9) but not all (7, 10, 14-16, 20) previous studies have associated hypercholesterolemia with periodontal disease.

On the other hand, a high level of serum HDL cholesterol suppresses atherosclerosis (27, 28), and therefore may be related to a reduced risk of periodontal disease and tooth loss, which was also suggested in the present study. Some reports associated a high level of HDL cholesterol with a lower risk of periodontal disease (7, 10) whereas others found no such association (8, 14-16, 20).

Periodontal disease and dyslipidemia may be more directly related (2). Elevated serum lipids including low-density lipoprotein cholesterol cause altered immune cell function resulting in impaired tissue response mainly due to increased production of proinflammatory cytokines such as TNF- α (tumor necrosis factor- α) and IL-1 β (interleukin-1 beta) by polymorphonuclear leukocytes and decreased production of essential polypeptide growth factors such as PDGF (platelet-derived growth factor), TGF- β 1 (transforming growth factor-beta 1), and bFGF (basic fibroblast growth factor) by tissue macrophages. Additionally, elevated serum lipids may cause a systemic monocytic hyperresponse trait leading to maintained elevations of serum TNF- α and IL-1 β . Compromised tissue response may predispose to periodontitis. On the other hand, periodontitis results in further elevation of serum lipid levels through systemic actions of proinflammatory cytokines (IL-1 β /TNF- α). Decreased serum HDL cholesterol levels were also reported in relation to infection to periodontal pathogens (30). Further studies that measure the inflammatory markers and evaluate the effect of treatment for hyperlipidemia on periodontal disease are warranted to support our findings.

Renal function evaluated using estimated GFR was correlated with number of teeth. Although the correlation was not statistically independent of age, oral hygiene score, and HbA1c, our study suggests that lowered filtration function of the kidneys due to diabetic nephropathy or other causes may have some deteriorating effect on teeth during long-term diabetes. Elevated serum creatinine has also been reported to be associated with advancing retinopathy and changes in vascular structure (31, 32). Similarly, decreased kidney function might indicate damage of periodontal tissue

by changing the structure of arteries that nourish the tissue. In fact, Kshirsagar et al (13) recently reported an association of periodontal damage or tooth loss with decreased renal function, although previous investigation does not support their findings (14).

Hypertension has been reported to be associated with periodontal disease as latent risks for ischemic heart disease in several studies (7, 15, 16, 20, 21), but in the present study no clear relation of the periodontal pockets or tooth loss was found with hypertension. It is possible, however, that the correlates of periodontal disease in patients with a long history of diabetes are different from those in the general population. Obesity has recently emerged as a possible risk indicator of periodontal disease (10, 17, 18), although we and other investigators (7, 15, 16, 19) found no support for it. Obesity is closely associated with type 2 diabetes (33), but weight loss is one of the symptoms of the disease (34). On the other hand, weight gain is often observed after the initiation of therapy with sulphonylurea or insulin, which suggests a "catch-up" weight re-gain (34). The role of obesity in periodontal disease, therefore, might be obscured in cross-sectional studies among patients with diabetes. The present study showed that duration of therapy was not significantly correlated with the depth of periodontal pockets or tooth loss. Diabetic control may be more important than the duration of treatment to maintain a good periodontal condition. Sandberg et al (35) also did not show any correlation between the prevalence or the severity of periodontal disease and the duration of diabetes.

Some methodological issues warrant consideration. First, because this is a cross-sectional study, it is difficult to make causal inferences based merely on its findings. Prospective and/or interventional studies are required to confirm the association of dyslipidemia with periodontal disease. Second, we could not obtain a detailed past smoking history for the participants, which may have led to overlooking an association of smoking with tooth loss. Finally, some teeth may have been lost due to dental caries. This, however, would have apparently attenuated the correlation between serum HDL cholesterol and the number of remaining teeth because previous caries seem not to be related to HDL cholesterol.

In summary, in addition to hyperglycemia, hypercholesterolemia was associated with deeper periodontal pockets, and so was the low level of serum HDL cholesterol with tooth loss. If our findings are further confirmed, we may expect better management of oral health in diabetic patients with improvements in not only plaque and blood glucose control but also in control of dyslipidemia.

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