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RESEARCH ARTICLE

A low ratio of high molecular weight adiponectin to total adiponectin associates with periodontal status in middle-aged men

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Abstract

Background: Periodontitis has been reported to relate closely to systemic diseases. However, a biomarker for periodontal status has not been established.

Methods: A cross-sectional study was conducted using oral and systemic health checkup data of 151 middle-aged men. The serum levels of adiponectin and its subfractions were also analysed.

Results: The ratio of high molecular weight adiponectin to total adiponectin was significantly lower in subjects with periodontal pockets. Moreover, this ratio independently associated with periodontal condition.

Conclusions: The ratio of HMW adiponectin to total adiponectin could be a novel biomarker for evaluation of periodontal health in middle-aged men.

Key words: *Biomarkers; periodontitis; inflammation; atherosclerosis; diabetes*

Introduction

Periodontitis is a chronic infectious disease of the oral cavity (Pihlstrom et al., 2005). In addition to inflammation of the gingiva, this bacterial disease causes destruction of connective tissue around teeth, which is followed by the formation of periodontal pockets. In the advanced stage, patients often lose a number of teeth due to the resorption of alveolar bone, and their quality of life is impaired.

Recently, periodontitis has attracted increasing attention because of its relevance to systemic disorders. The risk of periodontitis is high in patients with some common systemic diseases, such as diabetes mellitus (Taylor et al., 2008), obesity (Saito et al., 1998) and metabolic syndrome (Bullon et al., 2009). Moreover, periodontitis is regarded as one of the major complications of diabetes mellitus (Loe, 1993). It is also considered as a risk factor of coronary heart disease (Dietrich et al., 2008). Therefore, early detection and treatment of periodontitis is important for both oral and systemic health.

Aging and smoking have been pointed out as risk factors for periodontitis (Page et al., 1997). However, the blood markers that specifically correlate with the periodontal status have not been investigated extensively. In the present study, we searched for systemic markers that are useful for the evaluation of periodontal status in an apparently healthy population.

Adiponectin is an adipocytokine with several biological functions, such as anti-atherogenic, anti-inflammatory or insulin resistance-improving activities (Nishida et al., 2007). The serum concentrations of adiponectin are inversely associated with body weight, especially with the accumulation of abdominal visceral fat (Ryo et al., 2004). Similar to periodontitis, both atherosclerosis and obesity exhibit aspects of chronic inflammatory

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diseases (Hansson, 2005, Xu et al., 2003). Based on these observations, we investigated the relevance of serum adiponectin levels and periodontal status. We also measured the high molecular weight (HMW) form of adiponectin, which is regarded as an active form of this cytokine (Pajvani et al., 2004). Considering that there is a gender difference in the serum concentration of total and HMW adiponectin (Fujimatsu et al., 2009, Ebinuma et al., 2006), and that the prevalence of periodontitis increase in middle age (Page et al., 1997), in the present study, we focused on male subjects between 40 and 67 years old. Here, we report that, in middle-aged men, the ratio of HMW adiponectin to total adiponectin is significantly lower in subjects with periodontal pockets.

Methods

Subjects

We asked male employees of a university over 40 years old (up to 67 years old) to enroll in this research. Yearly health checkup data of all subjects who agreed to participate in this project (151 men) were used for analysis. Because all subjects were at work without any apparent health problems on the day of the checkup, nobody was excluded from the subjects. The research was approved by the Osaka Dental University Medical Ethics Committee (Approval No. 070504), and written informed consent was obtained from all participants.

Measurements

Body mass index (BMI) was calculated by dividing a subject's weight by the square of their height. Blood was drawn from antecubital vein after overnight fasting. Serum was separated by centrifugation (2500 rpm x 10 min), and aliquots were frozen in a deep freezer for ELISA. Urine sample was collected before breakfast of the health checkup day. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, uric acid and glucose were measured by enzymatic methods. Glycated hemoglobin A1C (HbA1C) and insulin were determined by chemiluminescent luminoassay, C-reactive protein (CRP) and urine albumin were assayed by an immunoturbidimetric method, and total and HMW adiponectin were estimated using a human adiponectin ELISA kit for total and multimers (Ebinuma et al., 2006) (Daiichi Pure Chemicals, Tokyo, Japan) following the manufacturer's instructions.

Smoking Habit

A subject is identified as a smoker if he meets both of the following criteria; (1) a person who has ever smoked more than 100 cigarettes, or who has ever smoked for more than 1 month, and (2) a person who has been smoking during the past month (Husten, 2009, Bondy et al., 2009). The criteria have been used to identify smoking habit in physical checkups for metabolic syndrome in Japan.

Periodontal Examination

For the assessment of periodontal condition, we used the World Health Organization (WHO) community periodontal index (CPI) and the CPI probe (*Oral health surveys: basic methods*, 1997). The examination was conducted by experienced dentists who fully understand the methods to determine CPI. The mouth of each subject was divided into six sections (sextants), which consist of four left back teeth, six front teeth, and four right back teeth of upper and lower jaws. The depth of the gingival sulcus was evaluated by probing, and the teeth were examined for supragingival or subgingival calculus. Any bleeding after gentle probing was also noted. The index teeth used for each sextant were two molars for back sections, and upper right and lower left central incisors for front sections. CPI code was determined based on the following rules; 0: normal, 1: gingival bleeding after gentle probing, 2: supragingival or subgingival calculus, 3: pathologic pockets 4 - 5 mm deep, 4: pathologic pockets ≥ 6 mm deep. The worst finding was recorded as CPI code of each sextant. Periodontal status of each subject was judged by the maximum CPI code (max CPI) of all sextants. Subjects with a max CPI of 3 or 4 were categorized as the Pocket (+) group (n = 62), and subjects with a max CPI of 0 to 2 were categorized as the Pocket (-) group (n = 89).

Statistical Analysis

We used Student's *t*-test for continuous, and the chi-square test for categorical variables. To detect independent predictive valuables, multiple logistic regression analysis was performed using SPSS Ver. 17 (SPSS Japan, Tokyo, Japan). A significance level of 0.05 (two-tailed) was used for all statistical tests.

Results

The distribution of max CPI by age is shown in Table 1. Out of the 151 men enrolled in the present study, 62 subjects (41.1%) were classified as the Pocket (+) group. The periodontal status of subjects over 50 years of age was obviously worse than those in their 40s. The mean age of subjects was 52.8 years. The number of subjects with

Table 1. Max CPI of subjects.

	Max CPI	0	1	2	3	4		Pocket depth ≥ 4mm
Age (years)	Findings	Healthy	Bleeding	Calculus	Pocket 4-5mm	Pocket ≥ 6mm	Total	(Max CPI = 3 or 4)
40 - 49	Number	18	6	17	11	1	53	12
	%	34.0	11.3	32.1	20.8	1.9	100.0	22.6
over 50	Number	9	9	30	35	15	98	50
	%	9.2	9.2	30.6	35.7	15.3	100.0	51.0
Total	Number	27	15	47	46	16	151	62
	%	17.9	9.9	31.1	30.5	10.6	100.0	41.1

Max CPI, maximum CPI code; CPI, community periodontal index.

diabetes (HbA1C ≥ 6.5%) was 9 (6.0%), and with obesity (BMI ≥ 25), 57 (37.7%).

The systemic data of the participants with or without periodontal pocket are shown in Table 2. Subjects of the Pocket (+) group were significantly older than those of the Pocket (-) group ($p < 0.001$). There was no statistically significant difference between the two groups in blood pressure (BP), BMI or results of standard blood tests including parameters for diabetes mellitus (glucose, HbA1C and insulin), although trends of lower HDL cholesterol ($p = 0.059$) and higher CRP ($p = 0.067$) were observed in the Pocket (+) group. Also, tendency of lower HMW adiponectin concentration ($p = 0.095$) was seen in the Pocket (+) group, whereas total adiponectin level was not different ($p = 0.75$) between the two groups. When the ratio of HMW adiponectin to total adiponectin was compared, it was significantly lower in the Pocket (+) group ($p = 0.039$).

As shown in Table 3, there was a significant correlation between smoking and periodontitis in subjects over 50 years old ($p = 0.04$). However, the correlation was not observed when all the subjects were analysed ($p = 0.12$).

Finally, we conducted multiple logistic regression analysis using the following parameters; smoking habit, age, systolic BP, GGT, HDL cholesterol, triglycerides, uric acid, CRP, urine albumin, and the ratio of HMW adiponectin to total adiponectin. We selected these parameters based on p values shown in Table 2. The results reveal that aging, smoking, and the low ratio of HMW adiponectin to total adiponectin are associated with periodontal condition after backward variable selection (Table 4).

Discussion

Periodontitis has been recognized as a new risk factor for atherosclerosis (Friedewald et al., 2009). According to the report by the WHO, the ratio of people between 35- and 44-year-old with a max CPI of 3 or 4 was as high as 40 - 60%, depending on their ethnicity (Petersen et al., 2005). Therefore, if a factor that correlates with periodontal status is identified and can be screened on certain occasions such as a systemic health checkup, it would be very useful for improvement of both oral and systemic health.

In the present study, we analysed the relevance of oral and systemic health in apparently healthy men between 40 and 67 years old. Periodontal pockets are formed because of the destruction of periodontal tissue, and we categorized the subjects whether they have significant periodontal pockets or not. Aging and smoking are well-established risk factors for periodontitis (Page et al., 1997), and this was confirmed in the present study as shown in Tables 1, 2 and 3.

When systemic markers were compared between the Pocket (+) group and the Pocket (-) group, the ratio of HMW adiponectin to total adiponectin was significantly lower in the Pocket (+) group (Table 2). Trends of lower HDL cholesterol, higher CRP and lower HMW adiponectin were also observed in the Pocket (+) group. The inflammatory reactions caused by periodontal pathogens were reported to be involved in atherogenesis (Beck et al., 2005), and both adiponectin and HDL have aspects of anti-inflammatory and anti-atherogenic molecules (Ouchi et al., 2007, Barter et al., 2004). As HMW form of adiponectin has been reported to play a primary role in the physiological function of this adipocytokine (Pajvani et al., 2004), the lower ratio of HMW adiponectin to total adiponectin in the Pocket (+) group may suggest the deterioration of adiponectin activity in subjects with poor periodontal condition. It was also reported that the anti-atherogenic action of HDL deteriorated in periodontitis patients (Pussinen et al., 2004). Taken together, the results of the present study are considered to reflect the inflammatory and atherogenic characteristics of periodontitis.

To identify the factors that independently associate with periodontitis, we carried out multiple logistic regression analysis and excluded the influence of confounders. The results reveal that, in addition to smoking and aging, a low ratio of HMW adiponectin to total adiponectin correlates independently with poor periodontal condition (Table 4). There was no correlation between the age and the ratio of HMW adiponectin to total adiponectin ($r = 0.003$). We also confirmed that this ratio was not significantly different between smokers and non-smokers ($p = 0.39$).

Table 2. Systemic data of subjects with or without periodontal pocket.

	Pocket (+) (n = 62)		Pocket (-) (n = 89)		
	Mean	SD	Mean	SD	*p*
Age (years)	55.7	5.97	50.7	7.15	< 0.001
Systolic BP (mmHg)	134	16.9	132	14.6	0.368
Diastolic BP (mmHg)	83.7	10.4	84.2	11.5	0.803
Body mass index (kg/m^2)	24.4	3.58	24.2	3.19	0.808
AST (IU/L)	25.9	19.6	24.9	15	0.726
ALT (IU/L)	26	21.6	28.7	18.4	0.407
GGT (IU/L)	77.8	137.5	51.5	49.7	0.154
Total cholesterol (mg/dL)	218	39.1	216	33	0.704
LDL cholesterol (mg/dL)	138	30.6	135	30.4	0.524
HDL cholesterol (mg/dL)	57.1	14.1	62	16.6	0.059
Triglycerides (mg/dL)	158	154	129	69.7	0.13
Uric acid (mg/dL)	6.42	1.43	6.11	1.21	0.144
Glucose (mg/dL)	96.6	11	99.9	27.4	0.368
HbA1C (%)	5.45	0.4	5.53	0.96	0.522
Insulin (μU/mL)	6.47	3.57	7.3	6.72	0.374
CRP (mg/dL)	0.098	0.109	0.069	0.084	0.067
Urine albumin (mg/g Cre)	41.8	107.6	25.5	45.8	0.226
Total adiponectin (ng/mL)	3.52	1.9	3.63	2.19	0.75
HMW adiponectin (ng/mL)	1.32	0.87	1.62	1.32	0.095
HMW/Total adiponectin ratio	0.365	0.145	0.413	0.136	0.039

SD, standard deviation; BP, blood pressure; AST, aspartate aminopeptidase; ALT, alanine aminopeptidase; GGT, γ-glutamyltransferase; LDL, low density lipoprotein; HDL, high density lipoprotein; HbA1C, glycated hemoglobin A1C; CRP, C-reactive protein; HMW, high molecular weight

Table 3. Smoking habit and periodontal status (analyzed by the chi-square test).

	Pocket (+)	Pocket (-)	Total	*p*
All subjects (40 to 67years old)				0.12
Smoking habit (+)	22	15	37	
Smoking habit (-)	40	74	114	
Total	62	89	151	
Subjects over 50 years old				0.04
Smoking habit (+)	18	8	26	
Smoking habit (-)	32	40	72	
Total	50	48	98	

Table 4. Factors related to periodontal status.

	OR	95% CI	*p*
Age	1.124	1.062 - 1.190	< 0.001
Smoking	2.484	1.090 - 5.660	0.03
HMW/Total adiponectin ratio	0.062	0.004 - 0.891	0.041

OD, odds ratio; CI, confidence interval; HMW, high molecular weight.

Multiple logistic regression analysis was conducted using parameters shown below. After backward variable selection using SPSS, three factors showed significant correlations with periodontal status. Smoking habit was categorized numerically (Non smokers = 0, Smokers = 1).

Variables analyzed: Smoking habit, Age, Systolic blood pressure, γ–glutamyltranspeptidase (GGT), High density lipoprotein (HDL) cholesterol, Triglycerides, Uric acid, C-reactive protein (CRP), Urine albumin, High molecular weight (HMW) adiponectin/Total adiponectin ratio.

There are some reports that show the relevance of HMW adiponectin and systemic diseases. HMW adiponectin has been suggested as a predictor of metabolic syndrome (Seino et al., 2009). It has been reported as a useful marker for the prediction of type 2 diabetes mellitus (Satoh et al., 2010) or coronary artery disease (Komura et al., 2008, von Eynatten et al., 2008). A low ratio of HMW adiponectin to total adiponectin has also been shown to associate with coronary atherosclerosis (Liang et al., 2009).

We did not find any correlation between parameters for diabetes and periodontal status. This contradictory observation might be explained by the small number of subjects with elevated HbA1C values, as we used the yearly health checkup data of apparently healthy men. Some of the results, such as GGT, triglycerides, insulin and urine albumin showed relatively high SD values. These data are influenced by the conditions related to obesity, i.e., fatty liver, hyperlipidemia, diabetes or hypertension. Considering that 37.7% of the subjects showed BMI ≥ 25 in the present study, it is possible that the high SD values of these tests are caused by the obese subjects. The number of smokers in the Pocket (+) group was significantly greater in subjects over 50 years old. But when all the subjects were analysed, the difference was not significant (Table 3). This suggests that the accumulation of years of smoking may influence the onset of periodontitis.

We used CPI to classify the subjects into two groups. CPI, originally called as CPI for treatment needs (CPITN), is an easily determinable index established by the WHO (Ainamo et al., 1982), and is included in the standard method for oral examination (*Oral health surveys: basic*

methods, 1997). It has been used to report the periodontal condition of people all over the world (Petersen et al., 2005). Moreover, CPI has been used in a number of clinical or epidemiological studies (Angeli et al., 2003, Katz et al., 2002, Saito et al., 1998). Because the data are obtained from a routine health checkup, and the research has an epidemiological aspect, we think it is suitable to use CPI in this cross-sectional study. However, there have been some criticisms of CPI. Almas et al. pointed out the discrepancies between CPI and the results of other periodontal indices, whereas they state that there was a tendency for CPITN to relate to periodontal pocket depth, which is an index we used in the present study (Almas et al., 1991).

As an index to estimate periodontal status, the importance of clinical attachment loss has been also pointed out. Baelum et al. reported the age-dependent discrepancy between CPITN and the periodontal attachment loss, in a Kenyan population (Baelum et al., 1995). Furugen et al. investigated 76 year-old subjects (Furugen et al., 2008) and showed that, by simple correlation analysis of adiponectin and mean probing depth, mean attachment loss, and percentage of bleeding on probing, adiponectin levels were negatively correlated with mean attachment loss, but not with mean probing depth or percentage of bleeding on probing. Our result that the ratio of HMW adiponectin to total adiponectin was significantly different between the Pocket (+) and the Pocket (-) group may not be the same if different method is used for examination of periodontal state.

Furugen et al. also showed in their paper that, when their subjects were categorized into periodontitis group and control group by probing depth, no significant difference was demonstrated in serum concentration of total adiponectin between the two groups (Furugen et al., 2008). Saito et al. classified the periodontal condition of middle-aged women by probing depth, and reported that adiponectin concentration was not significantly different between periodontitis and control groups (Saito et al., 2008). These results are similar to our result of total adiponectin levels between the Pocket (+) group and the Pocket (-) group, although the subjects investigated are different from ours in age or gender, and the criteria to judge subjects into two groups are not identical to ours.

Recently, Tonetti *et al.* showed that flow-mediated dilatation of vessels significantly improved after treatment of periodontitis (Tonetti et al., 2007). They also showed the improvement of some blood markers for inflammation after the treatment. Buhlin *et al.* reported that periodontal treatment improved risk factors for atherosclerosis (Buhlin et al., 2009). As our present study is a cross-sectional one, further investigations are required to assess whether HMW adiponectin to total adiponectin ratio increases when the inflammation is controlled by periodontal treatment.

Conclusions

We reported the association between periodontal pocket formation and a decreased ratio of HMW adiponectin to total adiponectin in middle-aged men. This ratio would be a useful systemic marker that can be measured for the evaluation of periodontal status, and is expected to prevent periodontal diseases.

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Declaration of interest

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