Journal of Oral Science, Vol. 57, No. 4, 335-343, 2015

Original

Association of periodontal status with liver abnormalities and metabolic syndrome

Aisyah Ahmad[1)], Michiko Furuta[1)], Takashi Shinagawa[2)], Kenji Takeuchi[1)], Toru Takeshita[1)], Yoshihiro Shimazaki[1,3)], and Yoshihisa Yamashita[1)]

[1)]Section of Preventive and Public Health Dentistry, Division of Oral Health, Growth and Development, Kyushu University Faculty of Dental Science, Fukuoka, Japan
[2)]Heisei Yokohama Hospital, Yokohama, Japan
[3)]Department of Preventive Dentistry and Dental Public Health, School of Dentistry, Aichi Gakuin University, Nagoya, Japan

(Received July 2, 2015; Accepted August 22, 2015)

Abstract: Although an association between periodontal status and liver abnormalities has been reported, it has not been described in relation to metabolic syndrome (MetS), which often coexists with non-alcoholic fatty liver disease. We examined the association of a combination of liver abnormality and MetS with periodontal condition in Japanese adults, based on the level of alcohol consumption. In 2008, 4,207 males aged 45.4 ± 8.9 years and 1,270 females aged 45.9 ± 9.7 years had annual workplace health check-ups at a company in Japan. Periodontal status was represented as periodontal pocket depth at the mesio-buccal and mid-buccal sites for all teeth. Alanine aminotransferase (ALT), and metabolic components were examined. Multiple linear regression analysis showed a significant association between deep pocket depth and the coexistence of elevated ALT and MetS in males with low alcohol consumption. Females showed no such relationship. In conclusion, the association between periodontal condition and the combination of elevated ALT and MetS was confirmed in males. That is, a clear association between liver abnormalities and periodontal condition was seen in male subjects with no or low alcohol consumption and MetS, providing new insights into the connection between liver function and periodontal health.
(J Oral Sci 57, 335-343, 2015)

Keywords: periodontal disease; liver abnormalities; metabolic syndrome.

Correspondence to Dr. Yoshihisa Yamashita, Section of Preventive and Public Health Dentistry, Division of Oral Health, Growth and Development, Kyushu University Faculty of Dental Science, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
E-mail: yoshi@dent.kyushu-u.ac.jp

doi.org/10.2334/josnusd.57.335
DN/JST.JSTAGE/josnusd/57.335

Introduction

Periodontal disease has multiple risk factors, including various microbial, environmental, behavioral, and systemic factors (1). As a systemic factor, hepatic conditions have suggested a positive association with periodontal disease (2). A study in Japan reported that individuals with periodontal disease had elevated levels of liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (3). Liver abnormalities are associated with some systemic changes, including obesity, dyslipidemia, and glucose intolerance, which are features of metabolic syndrome (MetS) (4). These diseases may be linked via a common pathophysiological pathway; however, most studies on the associations between periodontal disease and liver conditions have not considered MetS.

In examining the association between periodontal and liver condition, it is important to consider the effects of alcohol consumption on these conditions. Alcohol may have adverse effects on periodontal condition through impaired host defenses (5) and/or elevated levels of acetaldehyde, which is harmful to tissue (6). Chronic alcohol consumers also often have ‘negative’ lifestyle

Table 1 Baseline characteristics of employees, classified into two groups: those who received medical examination; and those who received both medical and dental examination

	Employees receiving medical examination (n = 11,144)†	Employees receiving both medical and dental examination (n = 5,683)†	P value
Age (years)*	50.4 ± 10.5	45.7 ± 9.1	<0.001
Gender			0.989
Males	8,582 (77.0)	4,377 (77.0)	
Females	2,562 (23.0)	1,306 (23.0)	
ALT (IU/L)*	26.6 ± 18.4	26.9 ± 10.2	0.368
Normal	9,649 (86.6)	4,875 (85.8)	0.152
Elevated (≥40)	1,495 (13.4)	808 (14.2)	
HDL (mg/dL)*	60.1 ± 15.5	61.3 ± 15.4	<0.001
Normal	10,304 (92.5)	5,359 (94.3)	<0.001
Reduced (males <40, females <50)	840 (7.5)	324 (5.7)	
Triglycerides (mg/dL)*	125.4 ± 92.4	114.8 ± 84.4	<0.001
Normal	7,677 (68.9)	4,322 (76.1)	<0.001
Elevated (≥150)	3,467 (31.1)	1,361 (23.9)	
Systolic blood pressure (mmHg)*	122.6 ± 16.8	117.8 ± 15.2	<0.001
Diastolic blood pressure (mmHg)*	76.8 ± 11.3	73.7 ± 10.4	<0.001
Normal	6,660 (59.8)	4,162 (73.2)	<0.001
Elevated (≥130 / ≥85)	4,484 (40.2)	1,521 (26.8)	
Waist circumference (cm)*	82.4 ± 8.8	81.2 ± 8.9	<0.001
Normal	8,232 (73.9)	4,394 (77.3)	<0.001
Elevated (males ≥90, females ≥80)	2,912 (26.1)	1,289 (22.7)	
Fasting glucose (mg/dL)*	102.7 ± 19.4	99.1 ± 13.9	<0.001
Normal	5,907 (53.0)	3,488 (61.4)	<0.001
Elevated (≥100)	5,237 (47.0)	2,195 (38.6)	
MetS			<0.001
Without	8,726 (78.3)	4,846 (85.3)	
With (MetS component ≥3)	2,418 (21.7)	837 (14.7)	
Smoking status			<0.001
No	5,981 (53.7)	3,486 (61.3)	
Yes	5,163 (46.3)	2,197 (38.7)	
Alcohol consumption			<0.001
Low	8,125 (72.9)	4,309 (75.8)	
High	3,019 (27.1)	1,374 (24.2)	

n (%), *mean ± SD

†Excluding individual with missing value (174 individuals receiving medical examinations and 40 receiving both medical and dental examinations)

t-test for continuous variable and χ^2 test for categorical variable

ALT, alanine aminotransferase; HDL, high-density lipoprotein; MetS, metabolic syndrome.

factors, such as smoking and poor oral hygiene, which are also related to periodontal disease (5,7). Furthermore, excess alcohol consumption is considered to be a cause of hepatic steatosis and liver injury (8). To clearly understand the association between periodontal and liver condition, it is advisable to consider this association in separating minor and major alcohol consumption.

A recent study showed that the presence of periodontal pockets was associated with elevated levels of γ-glutamyltransferase, independent of alcohol consumption, and with components of MetS in Japanese adults (9). However, the association of combined liver abnormalities and MetS with periodontal disease remains unclear. Liver abnormalities are closely related to MetS, and it is possible that MetS and liver abnormalities have an additive effect on periodontal disease. We hypothesize that the presence of both liver abnormalities and MetS is associated with poor periodontal health.

Furthermore, liver abnormalities and MetS are more prevalent in men than in women (10,11), and men generally have worse periodontal condition than do women (12). Based on these observations, we aimed to determine whether periodontal status is associated with combined liver abnormality and MetS in each gender, and how this is affected by level of alcohol consumption.

Materials and Methods

Study population

At a health examination center in Yokohama, Japan, 17,041 employees (age, 22-83 years) of a manufacturing company received a general workplace health examination between April 2008 and March 2009. A dental examination was conducted for employees who wished to receive it as an optional part of the general health examination. In this cross-sectional study, 5,723 employees (33.6%) received both medical and dental examinations, and these subjects were enrolled in the study. Differences in health conditions were observed between employees who had received medical examinations and those who had received both medical and dental examinations (Table 1). For this study, 187 participants with histories of viral hepatitis, hepatic cirrhosis, liver cancer, cholelithiasis, and cholecystitis were excluded. We also excluded two participants who had fewer than 10 teeth due to difficulties in properly assessing their current periodontal health status, as well as 57 for whom some data were missing. Finally, 5,477 participants (4,207 males with a mean age of 45.4 ± 8.9 years and 1,270 females with a mean age of 45.9 ± 9.7 years) were analyzed.

Written informed consent was obtained from all participants. The ethics committee of the Kyushu University Faculty of Dental Sciences, Fukuoka, Japan, approved the study design, data collection methods, and procedure for obtaining informed consent (19B-5).

Oral examination

Periodontal examinations were carried out by 12 dentists trained to perform clinical examinations of oral health status. Periodontal status was assessed in terms of pocket depth (PD) and clinical attachment loss (CAL) at the mesio-buccal and mid-buccal sites for all teeth, based on the Third National Health and Nutrition Examination Survey (NHANES III) method, except for the third molars because these teeth, when partially impacted, frequently have pseudo-pockets. Inter-examiner agreement with the 'gold standard' examiner (Y Shimazaki) for PD measurements within ±1.0 mm was high (κ values ranged from 0.775 to 1.000). Mean values for PD and CAL were used to evaluate periodontal status, and were calculated by the sum of values of maximum PD or CAL per tooth divided by the number of present teeth for each individual. Oral hygiene status, such as the level of debris and calculus, was assessed using the oral hygiene index-simplified (13).

General examination

Blood samples were collected from the antecubital vein, and serum cholesterol, triglycerides, fasting glucose levels and ALT were determined. Blood pressure and waist circumferences at the level of the umbilicus were measured. ALT is the liver enzyme most commonly used as an indicator of hepatocellular damage in acute and chronic hepatitis (14,15) and we defined liver abnormality as ALT levels greater than or equal to 40 IU/L (16). MetS was defined based on the Joint Interim Societies criteria (17). For this determination, waist circumference was assessed based on the International Obesity Task Force central obesity criteria for Asians, according to the International Diabetes Federation's suggestion that ethnic-specific cutoff values of waist circumference are appropriate for diagnosing MetS (18). The criteria for MetS were as follows: elevated waist circumference (≥90 cm in males, and ≥80 cm in females), elevated triglycerides (≥150 mg/dL or drug treatment for elevated triglycerides), reduced HDL (<40 mg/dL in males and <50 mg/dL in females), elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or antihypertensive drug treatment), and elevated fasting glucose (≥100 mg/dL or drug treatment for elevated glucose). Individuals with positive results for three or more components were deemed to have MetS.

Questionnaire

Information on smoking habits, alcohol intake, regular dental check-ups, and tooth brushing frequency was obtained using a self-administered questionnaire. Smokers were categorized as either current or non-smokers. Alcohol intake was assessed based on information about frequency of alcohol intake and the amount of alcoholic beverages in terms of the number of '*go*', a traditional Japanese unit of volume for *sake* (1 *go* = 0.18 L and contains 23 g of ethanol). The daily amount of drinking (grams per day) was estimated by multiplying the weekly frequency of consuming alcoholic beverages by the weight of ethanol and dividing the sum by seven. Alcohol consumption was divided into two groups: low versus high consumption (cutoff, ≥30 g/day for males and ≥20 g/day for females) (16). To investigate the behavioral aspects of oral health, the regularity of dental check-ups and the frequency of tooth brushing was assessed by direct questioning ("do you go to the dentist regularly for dental check-ups?" and "how often do you brush your teeth?"). The frequency of tooth brushing was categorized as once per a day or less, twice a day, or three times per a day or more.

Statistical analysis

The χ^2 test for categorical data and the *t*-test for contin-

Table 2 Characteristics of participants

Variable	Low alcohol consumption		*P* value	High alcohol consumption		*P* value
	Males (*n* = 2,991)	Females (*n* = 1,166)		Males (*n* = 1,216)	Females (*n* = 104)	
Age (years)*	44.8 ± 8.8	46.1 ± 9.8	<0.001	46.9 ± 8.8	43.5 ± 8.0	<0.001
Mean PD (mm)*	2.11 ± 0.36	1.97 ± 0.34	<0.001	2.16 ± 0.42	2.00 ± 0.36	<0.001
Mean CAL (mm)*	2.18 ± 0.41	2.02 ± 0.38	<0.001	2.24 ± 0.46	2.09 ± 0.39	0.001
ALT (IU/L)*	28.9 ± 19.5	18.6 ± 12.6	<0.001	29.4 ± 19.2	16.1 ± 6.7	<0.001
Normal	2,480 (82.9)	1131 (97.0)	<0.001	1,007 (82.8)	101 (97.1)	<0.001
Elevated (≥40)	511 (17.1)	35 (3.0)		209 (17.2)	3 (2.9)	
HDL (mg/dL)*	56.6 ± 12.9	71.8 ± 14.7	<0.001	61.9 ± 15.5	76.2 ± 15.1	<0.001
Normal	2,790 (93.3)	1,108 (95.0)	0.036	1,174 (96.5)	100 (96.2)	0.834
Reduced (males <40, females <50)	201 (6.7)	58 (5.0)		42 (3.5)	4 (3.8)	
Triglycerides (mg/dL)*	119.1 ± 80.6	78.5 ± 39.6	<0.001	141.1 ± 109.8	77.3 ± 34.7	<0.001
Normal	2,217 (74.1)	1,059 (90.8)	<0.001	800 (65.8)	97 (93.3)	<0.001
Elevated (≥150)	774 (25.9)	107 (9.2)		416 (34.2)	7 (6.7)	
Systolic blood pressure (mmHg)*	118.1 ± 14.2	111.6 ± 16.1	<0.001	122.8 ± 14.6	112.9 ± 13.6	<0.001
Diastolic blood pressure (mmHg)*	73.9 ± 9.9	69.2 ± 10.4	<0.001	77.5 ± 10.1	70.2 ± 9.0	<0.001
Normal	2,202 (73.6)	976 (83.7)	<0.001	763 (62.7)	91 (87.5)	<0.001
Elevated (≥130 / ≥85)	789 (26.4)	190 (16.3)		453 (37.3)	13 (12.5)	
Waist circumference (cm)*	81.6 ± 8.7	77.5 ± 8.6	<0.001	83.6 ± 8.0	79.2 ± 9.3	<0.001
Normal	2,505 (83.8)	729 (62.5)	<0.001	955 (78.5)	60 (57.7)	<0.001
Elevated (males ≥90, females ≥80)	486 (16.2)	437 (37.5)		261 (21.5)	44 (42.3)	
Fasting glucose (mg/dL)*	99.6 ± 13.3	94.1 ± 10.2	<0.001	102.3 ± 15.3	95.6 ± 10.9	<0.001
Normal	1,763 (58.9)	933 (80.0)	<0.001	605 (49.8)	74 (71.2)	<0.001
Elevated (≥100)	1,228 (41.1)	233 (20.0)		611 (50.2)	30 (28.8)	
MetS						
Without	2,567 (85.8)	1,062 (91.1)	<0.001	967 (79.5)	97 (93.3)	<0.001
With (MetS component ≥3)	424 (14.2)	104 (8.9)		249 (20.5)	7 (6.7)	
Combinations of ALT and MetS			<0.001			<0.001
Elevated ALT (-), MetS (-)	2,242 (75.0)	1,039 (89.1)		849 (69.8)	97 (93.3)	
Elevated ALT (-), MetS (+)	238 (8.0)	92 (7.9)		158 (13.0)	4 (3.8)	
Elevated ALT (+), MetS (-)	325 (10.9)	23 (2.0)		118 (9.7)	0 (0)	
Elevated ALT (+), MetS (+)	186 (6.2)	12 (1.0)		91 (7.5)	3 (2.9)	
Toothbrushing frequency						
1 time and less/day	849 (28.4)	67 (5.7)	<0.001	406 (33.4)	11 (10.6)	<0.001
2 times/day	1,656 (55.4)	585 (50.2)		636 (52.3)	55 (52.9)	
3 times and more/day	486 (16.2)	514 (44.1)		174 (14.3)	38 (36.5)	
Smoking status						
No	1,759 (58.8)	1,072 (91.9)	<0.001	466 (38.3)	65 (62.5)	<0.001
Yes	1,232 (41.2)	94 (8.1)		750 (61.7)	39 (37.5)	
Dental check-up						
Regular	2,104 (70.3)	681 (58.4)	<0.001	850 (69.9)	75 (72.1)	0.636
Irregular	887 (29.7)	485 (41.6)		366 (30.1)	29 (27.9)	
Number of teeth*	28.2 ± 2.2	27.6 ± 2.4	<0.001	28.1 ± 2.3	27.8 ± 2.3	0.223
Dental plaque (Debris Index-Simplified)*	0.56 ± 0.38	0.42 ± 0.32	<0.001	0.57 ± 0.37	0.45 ± 0.32	<0.001
Calculus (Calculus Index-Simplified)*	0.36 ± 0.36	0.21 ± 0.25	<0.001	0.38 ± 0.38	0.22 ± 0.25	<0.001

n (%), *Mean ± SD

t-test for continuous variable and χ^2 test for categorical variable

PD, pocket depth; CAL, clinical attachment level; ALT, alanine aminotransferase; HDL, high-density lipoprotein; MetS, metabolic syndrome.

uous data were used to determine significant differences ($P < 0.05$, two sided) between males and females. Associations between the mean PD and CAL as dependent variables, and ALT and MetS as independent variables were examined using a multiple linear regression model. We previously showed that different mean PD cutoff values may give different results in an analysis of associations between periodontal health and MetS (19). It is possible that the results lack consistency due to different definitions of periodontal disease; therefore, we used the continuous values of mean PD and CAL. Linear regression assumes that the predictor variables are linearly related to the dependent variable. The continuous value of ALT was not linearly related to mean PD and CAL. Categorical values (i.e., normal/elevated, ≥40 IU/L) of ALT represent scientifically meaningful constructs,

in addition to MetS. For these reasons, we used the categorical values of both ALT and MetS. To explore the additive effects of liver abnormalities and MetS on periodontal condition, participants were classified into the following four groups: normal ALT without MetS; normal ALT with MetS; elevated ALT without MetS; and elevated ALT with MetS. Multiple linear regression models were tested: 1) model including ALT and MetS; and 2) model including the combination of ALT and MetS. To determine whether this association differed according to alcohol consumption, participants were divided into low and high alcohol consumption groups. As potential confounders, age, smoking, regular dental check-ups, oral hygiene status, number of teeth and toothbrushing frequency were included in the multiple linear regression model. SPSS software (ver. 20.0 for Windows; IBM SPSS, Tokyo, Japan) was used for data analyses.

Results

Mean PD and CAL was 2.12 ± 0.38 (mean ± SD) and 2.20 ± 0.42 for males and 1.97 ± 0.34 and 2.03 ± 0.38 for females, respectively. Oral and systemic health status is shown in Table 2. The percentage of subjects with elevated ALT and low alcohol consumption was 17.1% in males and 3.0% in females. There were 673 (16.0%) males with three or more of the five MetS components, and 111 (8.7%) females. Males had significantly higher mean values for PD, ALT, and number of MetS components when compared with females in both the low and high alcohol consumption groups.

The multiple linear regression models included periodontal condition, such as mean PD or CAL, as a dependent variable and ALT and MetS as independent variables in both alcohol consumption groups (Tables 3-6). Adjusted for age, smoking, regular dental check-ups, oral hygiene status, number of teeth and tooth brushing frequency, MetS was significantly associated with high mean PD (B = 0.035, $P = 0.042$) in males with low alcohol consumption (Table 3). When we examined the combined effects of ALT and MetS, compared with those who had normal ALT without MetS, elevated ALT with MetS was significantly associated with high mean PD (B = 0.049, $P = 0.002$) in males with low alcohol consumption (Table 5), whereas no significant association was found in males with high alcohol consumption or in females with low or high alcohol consumption.

Discussion

In this study, a combination of elevated ALT and MetS was positively associated with mean PD in males with low alcohol consumption. Our results were similar to a previous study that demonstrated an association between hepatic abnormalities, defined by ALT ≥ 41 IU/L, and periodontal disease in young Japanese males (aged 18-19 years) who did not seem to consume alcohol due to Japanese law prohibiting alcohol consumption by those under 20 years of age (20). The present study extends the findings of the previous study by indicating an association between liver abnormalities and periodontal conditions in middle-aged males with both low alcohol consumption and MetS.

Studies to date (3,20) have not examined the association of MetS and hepatic abnormalities with periodontal disease. Recently, Morita et al. (9) found that hepatic abnormalities were associated with periodontal disease regardless of alcohol consumption after adjusting for the components of MetS; we found no statistically significant association between elevated ALT and high PD values in males with high alcohol consumption. Participants in the study by Morita et al. were assessed for liver abnormalities in terms of γ-glutamyltransferase and for periodontal disease by the World Health Organization (WHO) Community Periodontal Index (CPI) criteria. These differences in definitions may explain the discrepancy between their report and ours. Although caution is needed with regard to the difference, one reason for the lack of an association between hepatic and periodontal condition in the high alcohol consumption group in our study might be the weaker association of hepatic condition than of alcohol with periodontal condition. Alcohol has adverse effects on host defenses, clotting mechanisms, bone metabolism and healing, and it has direct toxic effects on periodontal tissues (21). In our study, high alcohol consumption was significantly associated with high PD and CAL values after adjusting for confounding factors (data not shown). Alcohol may therefore have more direct effects than hepatic condition has on periodontal condition in those with high alcohol consumption.

An association of a combination of elevated ALT and MetS with periodontal condition was found in males with low alcohol consumption. This association may reflect a chain reaction of inflammation. Not only obesity and insulin resistance as major features of MetS, but also liver abnormalities with low alcohol consumption are closely associated with chronic inflammation, which is characterized by abnormal cytokine production (22,23). On the other hand, periodontal disease is a local inflammatory condition and is linked to systemic inflammation via host responses. Several cross-sectional studies have reported that systemic inflammation is higher in patients with periodontal disease than in healthy individuals (24,25). Systemic inflammation has been suggested

Table 3 Association of ALT and MetS with periodontal condition according to level of alcohol consumption in males

Variable		PD			CAL		
	n	Mean ± SD	B	*P* value	Mean ± SD	B	*P* value
Low alcohol consumption group	2,991						
ALT							
Normal*	2,480	2.10 ± 0.36			2.17 ± 0.41		
Elevated (≥40)	511	2.16 ± 0.36	0.027	0.106	2.21 ± 0.39	0.033	0.063
MetS							
Without*	2,567	2.10 ± 0.36			2.16 ± 0.40		
With (MetS component ≥3)	424	2.20 ± 0.39	0.035	0.042	2.26 ± 0.45	0.014	0.443
R^2				0.247			0.182
High alcohol consumption group	1,216						
ALT							
Normal*	1,007	2.15 ± 0.40			2.24 ± 0.44		
Elevated (≥40)	209	2.21 ± 0.47	0.002	0.942	2.26 ± 0.52	-0.007	0.809
MetS							
Without*	967	2.14 ± 0.41			2.22 ± 0.44		
With (MetS component ≥3)	249	2.23 ± 0.44	0.056	0.032	2.32 ± 0.51	0.050	0.070
R^2				0.256			0.176

n = 4,207

Multiple linear regression model included mean PD or CAL as dependent variable and ALT category, MetS, age, smoking, regular dental check-ups, oral hygiene status, number of teeth, and toothbrushing frequency as independent variables.

*Reference category in multiple linear regression model

MetS, metabolic syndrome; PD, pocket depth; CAL, clinical attachment level; B, standardized coefficient

Table 4 Association of ALT and MetS with periodontal condition according to level of alcohol consumption in females

Variable		PD			CAL		
	n	Mean ± SD	B	*P* value	Mean ± SD	B	*P* value
Low alcohol consumption group	1,166						
ALT							
Normal*	1,131	1.97 ± 0.34			2.02 ± 0.38		
Elevated (≥40)	35	2.01 ± 0.35	0.010	0.702	2.04 ± 0.37	0.014	0.612
MetS							
Without*	1,062	1.96 ± 0.33			2.02 ± 0.37		
With (MetS component ≥3)	104	2.05 ± 0.40	0.014	0.626	2.08 ± 0.42	-0.025	0.398
R^2				0.165			0.129
High alcohol consumption group	104						
ALT							
Normal*	101	2.00 ± 0.35			2.09 ± 0.39		
Elevated (≥40)	3	2.02 ± 0.66	0.065	0.604	2.10 ± 0.56	-0.028	0.823
MetS							
Without*	97	2.01 ± 0.35			2.08 ± 0.39		
With (MetS component ≥3)	7	1.91 ± 0.48	-0.214	0.098	2.16 ± 0.45	-0.029	0.823
R^2				0.238			0.233

n = 1,270

Multiple linear regression model included mean PD or CAL as dependent variable and ALT category, MetS, age, smoking, regular dental check-ups, oral hygiene status, number of teeth, and toothbrushing frequency as independent variables.

*Reference category in multiple linear regression model

MetS, metabolic syndrome; PD, pocket depth; CAL, clinical attachment level; B, standardized coefficient

to be an underlying risk factor in periodontal disease as a localized inflammatory disease. It is likely that periodontal disease, MetS, and liver abnormalities with low alcohol consumption are linked through a common pathophysiological pathway. In addition, in our study, when the combined association of elevated ALT and MetS with CRP was examined in participants with low alcohol consumption, the percentage of participants with elevated CRP (>0.3 mg/dL) (26) was 4.6% of those who had normal ALT without MetS, 8.6% of those with normal ALT with MetS, 8.8% of those with elevated ALT without MetS, and 16.1% of participants with elevated ALT and MetS in males with low alcohol consumption. This indicates that having both liver abnormalities and MetS in individuals with low alcohol consumption might be more likely to cause systemic inflammation than

Table 5 Association of combination of ALT and MetS with periodontal condition according to level of alcohol consumption in males

Variable			PD			CAL	
	n	Mean ± SD	B	*P* value	Mean ± SD	B	*P* value
Low alcohol consumption group	2,991						
Combinations of ALT and MetS							
Elevated ALT (-), MetS (-)*	2,242	2.09 ± 0.36			2.16 ± 0.40		
Elevated ALT (+), MetS (-)	325	2.12 ± 0.35	0.015	0.345	2.19 ± 0.38	0.026	0.122
Elevated ALT (-), MetS (+)	238	2.18 ± 0.41	0.018	0.264	2.26 ± 0.49	0.010	0.578
Elevated ALT (+), MetS (+)	186	2.21 ± 0.36	0.049	0.002	2.25 ± 0.40	0.031	0.063
R^2			0.247			0.182	
High alcohol consumption group	1,216						
Combinations of ALT and MetS							
Elevated ALT (-), MetS (-)*	849	2.14 ± 0.40			2.23 ± 0.44		
Elevated ALT (+), MetS (-)	118	2.14 ± 0.47	-0.009	0.724	2.19 ± 0.47	-0.016	0.562
Elevated ALT (-), MetS (+)	158	2.19 ± 0.42	0.037	0.147	2.29 ± 0.48	0.032	0.231
Elevated ALT (+), MetS (+)	91	2.31 ± 0.47	0.047	0.062	2.36 ± 0.56	0.037	0.164
R^2			0.256			0.176	

n = 4,207

Multiple linear regression model included mean PD or CAL as dependent variable and the combination of ALT and MetS, age, smoking, regular dental check-ups, oral hygiene status, number of teeth, and toothbrushing frequency as independent variables.

*Reference category in multiple linear regression model

MetS, metabolic syndrome; PD, pocket depth; CAL, clinical attachment level; B, standardized coefficient

Table 6 Association of combination of ALT and MetS with periodontal condition according to level of alcohol consumption in females

Variable			PD			CAL	
	n	Mean ± SD	B	*P* value	Mean ± SD	B	*P* value
Low alcohol consumption group	1,166						
Combinations of ALT and MetS							
Elevated ALT (-), MetS (-)*	1,039	1.96 ± 0.33			2.02 ± 0.37		
Elevated ALT (+), MetS (-)	92	1.97 ± 0.32	0.010	0.344	2.00 ± 0.31	-0.033	0.259
Elevated ALT (-), MetS (+)	23	2.05 ± 0.40	0.002	0.082	2.07 ± 0.42	-0.005	0.846
Elevated ALT (+), MetS (+)	12	2.08 ± 0.40	0.020	0.726	2.11± 0.48	0.023	0.416
R^2			0.165			0.129	
High alcohol consumption group	104						
Combinations of ALT and MetS							
Elevated ALT (-), MetS (-)*	97	2.01 ± 0.35			2.08 ± 0.39		
Elevated ALT (+), MetS (-)	4	1.83 ± 0.39	-0.164	0.098	2.21 ± 0.43	-0.022	0.823
Elevated ALT (-), MetS (+)	0	-	-	-	-	-	-
Elevated ALT (+), MetS (+)	3	2.02 ± 0.66	0.012	0.899	2.10 ± 0.56	-0.047	0.616
R^2			0.238			0.233	

n = 1,270

Multiple linear regression model included mean PD or CAL as dependent variable and the combination of ALT and MetS, age, smoking, regular dental check-ups, oral hygiene status, number of teeth, and toothbrushing frequency as independent variables.

*Reference category in multiple linear regression model

MetS, metabolic syndrome; PD, pocket depth; CAL, clinical attachment level; B, standardized coefficient

having only one, perhaps leading to a higher incidence of periodontal disease. Following the suggestion from our finding that liver abnormalities in combination with MetS could make individuals more susceptible to periodontal disease in individuals with low alcohol consumption, coexisting liver abnormalities and MetS should receive attention as potential risk factors for periodontal disease.

In the present study, PD, but not CAL, was significantly associated with liver abnormalities and MetS in males with low alcohol consumption. High PD values are associated with increased inflammatory mediators and cytokines and thus a higher inflammatory burden compared with low values (i.e. shallow pockets) (27,28). CAL is an estimate of a historical amount of periodontal destruction and might be less responsive to inflammation. Because it is possible that periodontal disease, MetS, and liver abnormalities with low alcohol consumption are linked by systemic inflammation, PD is more likely to be

related to liver abnormalities and Mets than CAL would be.

Our study showed no significant association between elevated ALT and poor periodontal condition among females. This finding may be explained by a protective effect of female hormones. Because estrogen has been shown to prevent inflammatory reactions (29), it seems unlikely that hepatic condition is associated with periodontal condition. However, our findings are inconsistent with the finding of Saito et al. (3) that periodontal disease in females aged 20–59 years was significantly increased with elevated ALT. This difference in study findings may be due to differences in the periodontal assessment and study setting. In the Saito et al. and present studies, respectively, periodontal status was evaluated by the WHO CPI criteria and the NHANES III method, and participants were community residents and adults in an occupational setting. In addition, the lack of a significant association between liver abnormalities and periodontal health condition was probably due to the small number of females with elevated ALT levels. There were 35 females with elevated ALT levels in the low alcohol consumption group and 3 in the high-consumption group. Such a small number of participants was not sufficient to perform a multivariate statistical analysis.

This study has some limitations. First, the design of the study limited the possible interpretation of results in terms of temporal relationships. Longitudinal studies are needed to gain a clearer understanding of the association between liver abnormalities and poor periodontal condition. Second, a liver biopsy is the gold standard to establish a diagnosis of liver abnormalities. However, liver biopsy is impossible in population-based surveys due to its invasive nature. Elevated ALT can be used as a first step to diagnose liver abnormalities in large-sample surveys like our study. Third, this study used a partial-mouth assessment of periodontal condition. The NHANES III method did not include examinations of lingual or palatal sites, which are susceptible to periodontal disease. Therefore, it is possible that periodontal condition was underestimated. Fourth, we did not investigate alcohol-related genes, alcohol activity, or inflammatory parameters such as tumor necrosis factor-α, which may be associated with ALT levels, MetS, and periodontal health. Future studies are desirable to assess the significance of these factors. Finally, we recruited participants who wished to receive dental examinations. Although the ALT levels did not differ significantly between individuals who received medical examination and those who received both medical and dental examinations, differences in the MetS components were found (see Table 1); therefore, there may have been sampling bias. Furthermore, a small number of females had elevated ALT levels. Our sample may limit the ability to extrapolate these findings to all middle-aged Japanese, and caution is warranted in generalizing our findings to the rest of the Japanese population.

In conclusion, we identified an association of liver abnormalities and MetS with periodontal condition in males with low alcohol consumption. Periodontal disease may be further aggravated by the coexistence of liver abnormalities and MetS in Japanese middle-aged males with low alcohol consumption.

Acknowledgments

This study was supported by Grants-in-Aid for Scientific Research (22390401, 25293428, and 26861832) from the Ministry of Education, Science, Sports, and Culture of Japan, Tokyo, Japan. The authors have no conflicts of interest to declare.

References

1. Genco RJ (1996) Current view of risk factors for periodontal diseases. J Periodontol 67, 1041-1049.
2. Saito T, Shimazaki Y (2007) Metabolic disorders related to obesity and periodontal disease. Periodontol 2000 43, 254-266.
3. Saito T, Shimazaki Y, Koga T, Tsuzuki M, Ohshima A (2006) Relationship between periodontitis and hepatic condition in Japanese women. J Int Acad Periodontol 8, 89-95.
4. D'Aiuto F, Sabbah W, Netuveli G, Donos N, Hingorani AD, Deanfield J et al. (2008) Association of the metabolic syndrome with severe periodontitis in a large U.S. population-based survey. J Clin Endocrinol Metab 93, 3989-3994.
5. Tezal M, Grossi SG, Ho AW, Genco RJ (2001) The effect of alcohol consumption on periodontal disease. J Periodontol 72, 183-189.
6. Nishida N, Tanaka M, Sekine S, Takeshita T, Nakayama K, Morimoto K et al. (2010) Association of ALDH2 genotypes with periodontitis progression. J Dent Res 89, 138-142.
7. Mizutani S, Ekuni D, Furuta M, Tomofuji T, Irie K, Azuma T et al. (2012) Effects of self-efficacy on oral health behaviours and gingival health in university students aged 18- or 19-years-old. J Clin Periodontol 39, 844-849.
8. Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N et al. (2009) Light and moderate alcohol consumption significantly reduces the prevalence of fatty liver in the Japanese male population. Am J Gastroenterol 104, 2189-2195.
9. Morita T, Yamazaki Y, Fujiharu C, Ishii T, Seto M, Nishinoue N et al. (2014) Serum γ-glutamyltransferase level is associated with periodontal disease independent of drinking habits in Japanese adults. Med Sci Monit 20, 2109-2116.
10. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO (2006) Gender differences in the metabolic syndrome and their role for cardiovascular disease. Clin Res Cardiol 95, 136-147.

11. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S et al. (2007) Prevalence of non-alcoholic fatty liver disease: population based study. Ann Hepatol 6, 161-163.
12. Borrell LN, Papapanou PN (2005) Analytical epidemiology of periodontitis. J Clin Periodontol 32, Suppl 6, 132-158.
13. Greene JC, Vermillion JR (1964) The simplified Oral Hygiene Index. J Am Dent Assoc 68, 7-13.
14. Katkov WN, Friedman LS, Cody H, Evans A, Kuo G, Choo QL et al. (1991) Elevated serum alanine aminotransferase levels in blood donors: the contribution of hepatitis C virus. Ann Intern Med 115, 882-884.
15. Chang CJ, Ko YC, Liu HW (2000) Serum alanine aminotransferase levels in relation to hepatitis B and C virus infections among drug abusers in an area hyperendemic for hepatitis B. Dig Dis Sci 45, 1949-1952.
16. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R (2006) Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver Int 26, 856-863.
17. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA et al. (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120, 1640-1645.
18. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA et al. (2005) Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112, 2735-2752.
19. Furuta M, Shimazaki Y, Takeshita T, Shibata Y, Akifusa S, Eshima N et al. (2013) Gender differences in the association between metabolic syndrome and periodontal disease: the Hisayama Study. J Clin Periodontol 40, 743-752.
20. Furuta M, Ekuni D, Yamamoto T, Irie K, Koyama R, Sanbe T et al. (2010) Relationship between periodontitis and hepatic abnormalities in young adults. Acta Odontol Scand 68, 27-33.
21. Tezal M, Grossi SG, Ho AW, Genco RJ (2004) Alcohol consumption and periodontal disease. The Third National Health and Nutrition Examination Survey. J Clin Periodontol 31, 484-488.
22. Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature 444, 860-867.
23. Haukeland JW, Damås JK, Konopski Z, Løberg EM, Haaland T, Goverud I et al. (2006) Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. J Hepatol 44, 1167-1174.
24. Fredriksson MI, Figueredo CM, Gustafsson A, Bergström KG, Asman BE (1999) Effect of periodontitis and smoking on blood leukocytes and acute-phase proteins. J Periodontol 70, 1355-1360.
25. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E (2001) Periodontal infections contribute to elevated systemic C-reactive protein level. J Periodontol 72, 1221-1227.
26. Kobayashi S, Inoue N, Ohashi Y, Terashima M, Matsui K, Mori T et al. (2003) Interaction of oxidative stress and inflammatory response in coronary plaque instability: important role of C-reactive protein. Arterioscler Thromb Vasc Biol 23, 1398-1404.
27. Lindy O, Suomalainen K, Mäkelä M, Lindy S (2008) Statin use is associated with fewer periodontal lesions: a retrospective study. BMC Oral Health 8, 16.
28. Demmer RT, Kocher T, Schwahn C, Völzke H, Jacobs DR Jr, Desvarieux M (2008) Refining exposure definitions for studies of periodontal disease and systemic disease associations. Community Dent Oral Epidemiol 36, 493-502.
29. Ghisletti S, Meda C, Maggi A, Vegeto E (2005) 17β-estradiol inhibits inflammatory gene expression by controlling NF-κB intracellular localization. Mol Cell Biol 25, 2957-2968.