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Serum γ-Glutamyltransferase Level is Associated with Periodontal Disease Independent of Drinking Habits in Japanese Adults

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Background: Non-alcoholic fatty liver disease is considered a hepatic manifestation of metabolic syndrome. Periodontal disease is a mild chronic inflammatory disease with systemic effects, and many studies have indicated an association between metabolic syndrome and periodontitis. In the present study, we investigated the relationship between periodontitis and liver biochemical parameters according to alcohol drinking habits through a cross-sectional study based on data from Japanese people in occupational settings.

Material/Methods: The subjects were 1510 employees (1218 males, 292 females, mean age 50.4 years) who underwent dental and medical checkups in 2012. Associations between the presence of periodontal pockets and serum levels of liver biochemical parameters were assessed.

Results: Alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) levels were higher in subjects with than without periodontal pockets. Multiple logistic regression analysis (adjusting for age, gender, cigarette smoking, and alcohol drinking habits, and components of metabolic syndrome) with GGT or ALT as the dependent variable revealed that there was a significant association between periodontal pockets and GGT (odds ratio, OR=1.48), but not ALT. Similar associations were observed when an analysis was performed according to the presence or absence of alcohol drinking habits; the OR was higher in subjects without (OR=1.84) than with drinking habits (OR=1.41).

Conclusions: The presence of periodontal pockets was associated with serum levels of GGT, a liver biochemical parameter, in Japanese adults with no drinking habit, suggesting that periodontal disease is associated with liver function, independent of alcohol ingestion.

MeSH Keywords: Cross-Sectional Studies • gamma-Glutamyltransferase • Liver Function Tests • Periodontal Diseases

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Background

According to a recent National Health and Nutrition Survey performed by the Ministry of Health, Labor, and Welfare, about 50% of Japanese males and about 20% of Japanese females aged 40 years or older have metabolic syndrome or are in the borderline group [1]. Metabolic syndrome indicates conditions of concomitant hypertension, hyperglycemia, and dyslipidemia, with underlying visceral fat-type obesity; the accumulation of these abnormalities increases the incidence of arteriosclerotic disease synergistically [2,3]. Non-alcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of metabolic syndrome, and its frequency as a complication in metabolic syndrome patients has been reported to be high [4–8]. It is considered that adipocyte hypertrophy induces the production of cytokines, such as tumor necrosis factor (TNF)-α and resistin in visceral fat, and that these cytokines then induce insulin resistance and inflammation, leading to NAFLD [9].

Periodontitis is a chronic inflammatory disease in which periodontal tissues are destroyed by infection with Gram-negative anaerobic bacteria. Elevated blood levels of inflammatory markers, such as C-reactive protein (CRP), TNF-α and interleukin (IL)-6, have been reported in periodontal disease patients [10,11], suggesting that periodontal disease is a mild chronic inflammatory disease with systemic effects [12,13]. Many studies have indicated an association between periodontal disease and metabolic syndrome, based on analyses of Japanese community residents and industrial workers, adults in Northern Jordan and China [14–17], and the United States National Health and Nutrition Examination Survey III [18]. A systematic review and meta-analysis also presented clear evidence for an association between periodontitis and metabolic syndrome, with case-control and cross-sectional studies [19]. Moreover, we recently showed in a prospective cohort study that the risk of metabolic syndrome was high in periodontal disease patients [20].

In NAFLD, serum levels of the liver biochemical parameters, alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) are elevated [21]. In addition to these abnormal parameters, the risk of end-stage liver disease, such as hepatic cirrhosis and hepatocellular carcinoma, is increased in NAFLD. Yoneda et al. [22] recently reported that NAFLD progression in a mouse model of high-fat diet-induced NAFLD was promoted by infection with *Porphyromonas gingivalis*, which plays an important role in the onset and progression of adult periodontitis. They also reported that 3 months of non-surgical periodontal treatment decreased serum AST and ALT levels in NAFLD patients with periodontitis [22]. In an epidemiological study involving female Japanese community residents, Saito et al. [23] reported that serum ALT and AST levels were increased significantly in patients with periodontitis (with periodontal pockets ≥4 mm) versus subjects without periodontitis. Furuta et al. [24] also reported that the level of serum ALT was significantly associated with periodontitis in male university students.

Because serum levels of liver biochemical parameters increase according to alcohol drinking habits, it is important to investigate liver biochemical parameters in subjects with no alcohol drinking habits to examine any association between periodontal disease and NAFLD. However, few reports have assessed the association between periodontal disease and liver biochemical parameters in epidemiological studies of adults without alcohol drinking habits.

The aim of the present study was to evaluate the association between serum liver biochemical parameters and periodontal disease according to the presence of alcohol drinking habits in Japanese adult employees in a cross-sectional study.

Material and Methods

Subjects

This study was approved by the Nihon University School of Dentistry Ethics Committee. The subjects were office employees of a household products company in Tokyo, Japan, who underwent periodic health and dental checkups, performed independently by a health insurance association, in 2012. Nearly all (99.9%) employees underwent systemic medical checkups, and 84.2% also had dental examinations. In total, 1527 employees received both checkups and gave consent to be included in the study. Of them, 1510 employees (1218 males, 292 females, aged 39–64 years, mean age 50.4 years) had no missing data for the checkups or lifestyle survey.

Examinations for periodontal disease

The presence of periodontal disease was assessed according to the World Health Organization (WHO) Community Periodontal Index (CPI) criteria [25]. To determine the CPI measurements, dental hygienists examined 10 representative teeth in 6 sextants under the supervision of dentists. The subjects were divided into 2 groups: individuals with a CPI score of <2 (with no periodontal pocket), and individuals with at least 1 sextant with a CPI score of ≥3 (periodontal pockets 4 mm or deeper).

Systemic checkup

Blood samples were collected from an arm vein in the morning after fasting from 9:00 pm on the previous day. GGT, AST, ALT, triglyceride, high-density lipoprotein (HDL) cholesterol, and fasting blood glucose levels were measured from these samples. Body mass index (BMI) was calculated from the height

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and body weight of each participant. Elevated levels of serum GGT were defined as >40 U/L for men and >30 U/L for women [26]. Elevated levels of serum AST and ALT were defined as >35 and >30 U/L, respectively [26]. The test values for hypertension, lipid abnormalities, and hyperglycemia were based on the definitions and diagnostic criteria for metabolic syndrome in Japan [27,28] as in our previous studies [15,20]: a ≥130 mmHg systolic or ≥85 mmHg diastolic blood pressure was deemed to indicate hypertension, ≥150 mg/dL triglycerides or <40 mg/dL HDL cholesterol was considered an abnormal lipid profile, and ≥110 mg/dL fasting blood glucose was deemed to indicate hyperglycemia. Blood pressure was measured with an automatic hemomanometer while the patients were in a sitting position. A BMI ≥25 kg/m^2 was regarded as positive for a metabolic disorder.

Lifestyle survey

Regarding lifestyle, cigarette smoking and alcohol drinking habits were surveyed at the time of the periodic health checkup using a self-administered questionnaire. Responses for cigarette smoking habits were divided into 2 categories: 'I do not smoke,' and 'I currently smoke.' Responses for alcohol drinking habits were divided into 4 categories: 'I do not drink alcohol at all,' 'I drink 2 or 3 days a week,' 'I drink 4 or 5 days a week,' and 'I drink every day.'

Statistical analyses

Differences in mean blood test values and the distributions of subject characteristics (age, gender, cigarette smoking, alcohol drinking habits, components of metabolic syndrome, and liver biochemical parameters) according to periodontal pocket depth were evaluated using *t*-tests and Pearson's χ^2 tests. Additionally, with GGT, ALT, and AST as the response variables, associations with the presence of periodontal pockets were analyzed by multiple logistic regression (adjusted for age, gender, cigarette smoking and alcohol drinking habits, and components of metabolic syndrome). For the analysis of significance, odds ratios (ORs) and 95% confidence intervals (CIs) were determined. JMP software (ver. 9.03; SAS Institute, Tokyo, Japan) was used, and the significance level was set at <5%.

Results

Presence of periodontal pockets, liver biochemical parameters, components of metabolic syndrome, and subject characteristics

The subjects were divided into 2 groups based on the depth of their periodontal pockets. In total, 998 (66.1%) subjects had no periodontal pockets, and 512 (33.9%) did. For each group, the mean values of liver biochemical parameters, components of metabolic syndrome, and age, as well as subject characteristics, such as gender, cigarette smoking, and alcohol drinking habits, are shown in Table 1. Significant differences between the groups were found in GGT, ALT, BMI, systolic and diastolic blood pressure, triglycerides, HDL cholesterol, fasting blood glucose levels, HbA1c, age, gender, cigarette smoking, and alcohol drinking habits.

Association between presence of periodontal pockets and liver biochemical parameters

Multiple logistic regression analysis (adjusting for age, gender, cigarette smoking, and alcohol drinking habits, and components of metabolic syndrome) was performed with GGT or ALT or AST as the dependent variable, respectively. The OR for GGT with the presence of periodontal pockets was 1.48, indicating a significant association (Table 2). However, ALT and AST were not significantly associated with the presence of periodontal pockets (data not shown).

Because alcohol drinking is known to be strongly associated with GGT and the OR was highest among the adjustment factors considered in the present study (Table 2), a further analysis was performed according to the presence or absence of an alcohol drinking habit (Table 3). After adjusting for age, gender, cigarette smoking, and the components of metabolic syndrome, a significant association between GGT and the presence of periodontal pockets was detected with and without an alcohol drinking habit, but the OR was higher in the absence of an alcohol drinking habit.

Discussion

In the present study, associations between the presence of periodontal pockets and liver biochemical parameters were evaluated in Japanese adults aged 39-64 years. In a multiple logistic regression analysis, adjusting for age, gender, cigarette smoking, and alcohol drinking habits, and components of metabolic syndrome, GGT levels were significantly associated with the presence of periodontal pockets (Table 2), but no association was found with AST or ALT.

GGT in serum is considered a 'leaking' enzyme because it enters the circulation when cells of the liver and bile duct are destroyed. Thus, elevated serum GGT activity is found in abnormalities of the liver, biliary system, and pancreas. Fatty liver is an abnormality that is observed frequently in general health checkups [4–8]. Moreover, there is a strong association between alcohol consumption and elevated GGT levels in fatty liver patients [29]. The present study also showed that the OR for the association of GGT with alcohol drinking habits was higher than

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Table 1. Subject characteristics and mean values of serum hepatic markers and components of metabolic syndrome in subjects with and without periodontal pockets.

Variables	Value (mean ±SD)		p-value
	Without pockets (n=998)	With pockets (n=512)	
GGT (IU/L)	46.0±47.3	56.5±58.5	<0.001
ALT (IU/L)	24.9±14.9	26.6±16.7	0.041
AST (IU/L)	24.6±9.2	25.3±11.2	0.221
BMI	23.1±3.1	24.0±3.2	<0.001
Systolic blood pressure (mmHg)	123.1±15.6	127.2±15.2	<0.001
Diastolic blood pressure (mmHg)	78.4±11.6	81.2±10.9	<0.001
Triglycerides (mg/dL)	108.0±87.3	127.3±94.7	<0.001
HDL cholesterol (mg/dL)	63.1±15.6	59.2±14.3	<0.001
Fasting blood glucose (mg/dL)	95.0±15.6	99.8±19.3	<0.001
HbA1c (%)	5.03±0.53	5.13±0.57	0.001
Age (years)	49.6±6.5	51.9±6.8	<0.001
Gender (n,%)			
Male	762 (76.4)	456 (89.1)	<0.001
Female	236 (23.6)	56 (10.9)	
Smoking habit (n,%)			
Never	805 (80.7)	352 (68.8)	<0.001
Current	193 (19.3)	160 (31.2)	
Drinking habit (n,%)			
Never	324 (32.5)	148 (28.9)	0.028
2 or 3 days a week	245 (24.5)	104 (20.3)	
4 or 5 days a week	190 (19.0)	123 (24.0)	
Every day	239 (24.0)	137 (26.8)	

those for the other adjustment factors (age, gender, cigarette smoking, and components of metabolic syndrome; Table 2). Thus, a further analysis was performed according to the presence or absence of an alcohol drinking habit, adjusting for age, gender, cigarette smoking, and components of metabolic syndrome. The results showed a significant association between GGT and the presence of periodontal pockets in the presence and absence of an alcohol drinking habit and the OR was higher in the absence of an alcohol drinking habit (Table 3). Serum levels of GGT and ALT were reported to be elevated in NAFLD previously [21]. These results suggest that periodontal disease is associated with liver function, independent of drinking habits.

Saito et al. [23] investigated the association between periodontitis and hepatic condition in Japanese female community residents using blood test values. They reported that serum levels of AST, ALT, and GGT were significantly associated with periodontitis when the influence of known risk factors for periodontitis (age, smoking history, and oral hygiene) was eliminated in their multivariate linear regression analysis. Moreover, they performed logistic regression analysis of periodontitis with these liver function markers after multivariate adjustment for the known risk factors for periodontitis described above. Their analysis revealed that the incidence of periodontitis was significantly increased when serum levels of AST and ALT were elevated. Thus, there are inconsistencies between that study and the present results for AST, ALT, and GGT. The subjects in the study by Saito et al. were female community residents, whereas the subjects in our study were adults in occupational settings, with males accounting for 80.7% of subjects. This suggests that differences in gender and living environment between the community residents and adults in occupational settings may have influenced the results.

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Table 2. Association between GGT and the presence of periodontal pockets and other variables.

Variables	Number of subjects (%)				Adjusted OR (95%CI)
	Negative* (n=899)		Positive (n=611)		
Pocket depth (mm)					
<4	647	(64.8)	351	(35.2)	1
≥4	252	(49.2)	260	(50.8)	1.48 (1.16–1.90)***
BMI (kg/m^2)					
<25	724	(65.2)	386	(34.8)	1
≥25	175	(43.7)	225	(56.3)	1.87 (1.43–2.44)***
Blood pressure					
<130 and <85	639	(67.5)	308	(32.5)	1
≥130 or ≥85	260	(46.2)	303	(53.8)	1.46 (1.14–1.86)***
Triglycerides HDL cholesterol					
<150 and ≥40	780	(65.9)	404	(34.1)	1
≥150 or <40	119	(36.5)	207	(63.5)	2.40 (1.80–3.20)***
Fasting blood glucose					
<110	828	(61.8)	511	(38.2)	1
≥110	71	(41.5)	100	(58.5)	1.55 (1.07–2.25)**
Smoking habit					
Never	733	(63.3)	424	(36.7)	1
Current	166	(47.0)	187	(53.0)	1.42 (1.08–1.86)**
Drinking habit					
Never	378	(80.1)	94	(19.9)	1
2 or 3 days a week	210	(60.2)	139	(39.8)	2.20 (1.57–3.09)***
4 or 5 days a week	147	(47.0)	166	(53.0)	3.72 (2.64–5.26)***
Every day	164	(43.6)	212	(56.4)	4.62 (3.32–6.49)***
Age (years)					
39–49	495	(63.9)	280	(36.1)	1
50–64	404	(55.0)	331	(45.0)	1.00 (0.78–1.27)
Gender					
Male	658	(54.0)	560	(46.0)	1
Female	241	(82.5)	51	(17.5)	0.58 (0.40–0.83)***

* Cut-off points for GGT: negative, male ≤40 and female ≤30; positive, male >40 and female >30; ** p<0.05; *** p<0.01.

In the present study, GGT, but not ALT, was associated with the presence of periodontal pockets. Differences in reactivity between GGT and ALT regarding the severity of NAFLD are unclear. GGT levels were found to be significantly higher in alcoholic fatty liver than in NAFLD; by contrast, there was no significant difference in ALT levels between these 2 types of fatty liver [30]. GGT is strongly influenced by the consumption of only a small volume of alcohol [29], and GGT is more sensitive to liver diseases than ALT [31]. Based on these findings, we suggest that the impact of periodontal disease on

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Table 3. Association between GGT and the presence of periodontal pockets in subjects with and without drinking habits.

Variables	Number of subjects (%)				Adjusted OR (95%CI)**
	Negative*		Positive		
Subjects without a drinking habit					
Pocket depth (mm)					
<4	272	(84.0)	52	(16.0)	1
≥4	106	(71.6)	42	(28.4)	1.84 (1.12–3.02)***
Subjects with drinking habit					
Pocket depth (mm)					
<4	375	(55.6)	299	(44.4)	1
≥4	146	(40.1)	218	(59.9)	1.41 (1.06–1.87)***

* Cut-off points for GGT: negative, male ≤40 and female ≤30; positive, male ≥40 and female ≥30; ** Adjusted for age, gender, smoking habits, and components of metabolic syndrome; *** p<0.05.

hepatic condition may be similar to that of very modest alcohol consumption, which can still induce elevated GGT levels. Furthermore, we consider that NAFLD severity may have been mild if it was present in the subjects in the present study, resulting in the finding that only GGT was associated with periodontal disease.

Periodontitis is a chronic inflammatory disease in which periodontal tissues are destroyed by infection with Gram-negative anaerobic bacteria. Yoneda et al. [22] reported that NAFLD progression in a mouse model of high-fat diet conditions was promoted by infection with *Porphyromonas gingivalis* via the jugular vein. Upon pathological evaluation of the liver, marked accumulation of lipids was observed in mice infected with *P. gingivalis.* Marked increases in ALT levels and liver triglyceride levels were also observed. Other studies have also revealed that lipopolysaccharide (LPS), derived from Gram-negative anaerobic bacteria, and cytokines produced in inflammation induce rapid increases in hepatic *de novo* fatty acid synthesis [32–34]. These findings and the present results suggest that Gram-negative anaerobe-induced periodontal disease has some influence on liver lipid metabolism independently of alcohol ingestion.

The association between periodontal disease and GGT may indicate another phenomenon – promotion of periodontal disease progression by GGT. GGT induces osteoclast differentiation by increasing production of the osteoclast differentiation factor "receptor activator of NF-κB ligand" (RANKL), which is a member of the TNF family of cytokines and plays a key role in bone resorption [35] in osteoblasts and bone marrow cells [36,37]. Hiramatsu et al. [38] reported that bone mass was significantly reduced in GGT-overexpressing transgenic mice compared with wild-type mice. These findings indicated that GGT in the circulation could influence bone resorption. Recently, a number of studies have indicated that many systemic disorders can be associated with periodontal health. Diabetes mellitus induces changes in the microcirculation [39,40], immune function, and the oxidative stress response [41–43]; these can all cause damage in periodontal tissue. Age-related physiological changes, such as menopause, may induce periodontal bone resorption via osteoporosis [44–47]. Moreover, genetic disorders, including connective tissue metabolism disorders, metabolic disorders generally, skin disorders, leukocyte defects, and chromosome abnormalities, can act as risk factors for the progression of periodontal disease [48]. Thus, there is a need to further investigate associations between these systemic disorders and the progression of periodontitis.

The present study had several limitations. Because it was performed as a cross-sectional analysis, no causal relationship between serum GGT levels and periodontal disease could be determined. We considered cigarette smoking and alcohol drinking habits and components of metabolic syndrome to be factors that could influence periodontal disease and steatohepatitis. Thus, these factors were included as adjustment factors to remove confounding. However, lifestyle habits that we did *not* investigate in this study may *also* influence periodontal disease and liver function. We were unable to include information concerning eating and exercise habits, which are considered to influence NAFLD. Thus, further studies involving these factors are needed. Periodontal disease was evaluated based on the depth of periodontal pockets in representative teeth. It is possible that the proportion of subjects with periodontal pockets was underestimated using only representative teeth, and that this underestimation influenced the association between the presence of periodontal pockets and GGT. Assessment of periodontal tissue in all teeth would be necessary to overcome this problem.

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Conclusions

The presence of periodontal pockets was associated with serum levels of GGT, a liver biochemical parameter, in Japanese adults without drinking habits, suggesting that periodontal disease is associated with liver function, independent of alcohol ingestion.

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