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Relationship between periodontitis and hepatic abnormalities in young adults

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Abstract

Objective. Obesity has been implicated as a risk factor for periodontitis and non-alcoholic fatty liver disease (NAFLD). In NAFLD, elevated alanine aminotransferase (ALT) is associated with obesity. Although a possible interrelationship between liver function and periodontitis has been reported among the middle-aged population, the correlation in young adults is little known. This study was designed to investigate the relationship between ALT and the presence of periodontitis in university students in Japan. ***Material and methods***. Medical and oral health data were collected in a cross-sectional examination conducted by the Health Service Center of Okayama University. Systemically healthy, non-smoking students aged 18 and 19 years old ($n = 2225$) were included. The protocol of the United States National Health and Nutrition Examination Survey was applied. Subjects with probing pocket depth ≥ 4 mm were defined as having periodontitis. Logistic regression analysis was used to estimate the association between ALT, body mass index and periodontitis. ***Results***. The number of subjects with periodontitis was 104 (4.7%). In males, having periodontitis was significantly associated with an increased level of ALT (≥ 41 IU/l) in logistic regression analysis (adjusted odds ratio 2.3; 95% confidence interval 1.0–5.2; $p < 0.05$). However, there was no significant association between periodontitis and ALT in female students. ***Conclusions***. Elevated ALT could be a potential risk indicator for periodontitis among young males. Monitoring hepatic abnormalities to prevent periodontitis must be better understood, even in the young adult population.

Key Words: *Alanine aminotransferase, obesity, periodontitis, risk indicator, young adults*

Introduction

Epidemiological studies have shown that obesity is significantly associated with periodontitis [1]. Obesity contributes to progression of periodontitis in experimental animals [2]. These findings suggest that periodontitis may be exacerbated by conditions associated with obesity and that obesity is a risk factor for periodontitis [3].

The proportion of obese individuals has been gradually increasing. This has now become a well-recognized public health concern worldwide [4]. Data from the National Nutrition Surveys of Japan have shown evidence of increasing numbers of overweight or obese adult males [5]. Regarding Japanese young females, the number of those who are obese/overweight is decreasing and the number of lean women has increased in the last 20 years [5]. Obesity is considered as a major risk factor for chronic conditions, including type 2 diabetes [6], cholelithiasis [6], hyperlipidaemia [7], cardiovascular disease [6,7], hypertension [7], certain forms of cancer [8] and non-alcoholic fatty liver disease (NAFLD) [9], as well as periodontitis.

NAFLD is an obesity-associated chronic liver disease, now recognized to occur even in children as well as adults [10]. The diagnosis of NAFLD is often established after identification of elevated serum

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alanine aminotransferase (ALT), which is most commonly used for screening of liver diseases in obese and asymptomatic patients [11]. In NAFLD, serum ALT levels range from mildly increased to five times that of normal [12]. Elevated ALT is associated with evidence of being overweight or obese [13], including greater body mass index (BMI) and waist circumference [11].

The incidence of periodontitis [deepest probing pocket depth (PPD) ≥ 4 mm] in Japanese females (20–59 years old) is significantly increased with elevated serum levels of ALT [14]. However, to our knowledge, few studies have investigated liver abnormalities as a risk factor for periodontitis in young populations. The severity of periodontitis increases with age [15]. In younger populations, it is important to prevent periodontitis by controlling risk factors at an early stage. Thus, we hypothesized that liver abnormalities may be a risk indicator for periodontitis in the young population. The purpose of the present study was to investigate whether or not there is an association between liver abnormalities, as determined by ALT measurement and periodontal disease, in healthy Japanese university students.

Material and methods

Subjects

First year students (n = 2459; mean ± SD 18.6 ± 2.1 years) at Okayama University, who had undergone general and oral examinations in April 2008, were included. Since the health examination was mandatory, no sampling procedure was performed.

General examination

BMI was assessed as an indicator of overall adiposity. Venous blood samples were collected and serum concentrations of ALT and total cholesterol were determined using an automated blood analyzer (model 7600; Hitachi Co., Tokyo, Japan). The serum level of hemoglobin was measured by using a hematology automated analyzer (model XE-2100; Sysmex Co., Kobe, Japan). Urinalysis was performed by urine test strip (Bayer HealthCare Co., Tokyo, Japan). In addition, blood pressure was measured.

ALT is most commonly used for screening of liver diseases [11]. The other biological factors related to obesity and/or hepatic abnormalities (e.g. levels of plasma glucose, hemoglobin A1c, triglyceride, aspartate aminotransferase, etc.) were not measured. Because our study was combined with routine health screening, the number of measurable biochemical parameters was limited.

Oral examination

The periodontal examination was done by five trained dentists. Following the Third National Health and Nutrition Examination Survey (NHANES III) protocol, a periodontal examination was performed on randomly selected quadrants, one maxillary and one mandibular [16]. The PPD was measured at mesiobuccal and mid-buccal sites for all of the teeth in the two quadrants. The numbers of teeth present and decayed and the percentage of sites of bleeding on probing in each participant were also examined. For PPD, agreement to within 1 mm was 100% on preliminary calibration.

Self-reported questionnaire

A questionnaire was used to assess a number of oral health-related variables [17]. The questions included "Are you a current or past smoker?", "Do you use dental floss or an interdental brush?" and "Do you visit a dental clinic on a regular basis?"

Ethical considerations

Health screening is mandatory for first year students and has been routinely conducted by the Health Service Center of Okayama University. Ethical considerations include anonymity, privacy and ensuring informed consent is obtained. The Health Service Center were informed in advance that the results of the examination would be published without identifying individuals. After verbal consent was obtained from all the participants during the examination period, a questionnaire and oral examination were completed by the dentists, and a general examination was performed by physicians and pubic health nurses.

Statistical analysis

Of 2459 students, data from non-smoking subjects (n = 2225; 1264 males, 961 females) aged 18–19 years were analyzed in this study. Liver diseases which affect the ALT level, such as chronic viral hepatitis, autoimmune liver disease and drug hepatotoxicity, were not reported. Periodontitis was defined as the presence of one or more teeth with PPD ≥ 4.0 mm [18]. Two BMI categories were defined using WHO criteria: normal weight (BMI < 25 kg/m^2); and overweight and obese (BMI ≥ 25 kg/m^2) [19]. Since the reference range and cut-off values for ALT are controversial [20], three criteria for serum ALT were defined as follows: ≤ 20 U/l (normal); 21–40 U/l (subclinical); and ≥ 41 U/l (abnormal). The normal range of total cholesterol was defined as < 220 mg/dl [21]. The study subjects were grouped by the use of

dental floss or an interdental brush, or no use. The subjects were also classified according to the self-reported frequency of dental visits. Individuals who visited a dentist on a regular basis for dental health care were classified as having regular dental visits.

Because the data were skewed, the Mann–Whitney U-test and the χ^2 test were used to determine if there were any significant differences ($p < 0.05$) between groups. Any possible associations of BMI and ALT with periodontitis were examined in a series of logistic regression models, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. The logistic regression models were reviewed for goodness of fit and validated using the Hosmer–Lemeshow statistic [22]. The Statistical Package for the Social Sciences (11.0J for Windows; SPSS Japan, Tokyo, Japan) was used for the statistical analyses.

Results

There were significant differences between males and females in the number of teeth present, the number of decayed teeth, the percentage of bleeding on probing, PPD, BMI, levels of serum ALT and serum total cholesterol, serum hemoglobin, systolic blood pressure, diastolic blood pressure and pulse rate (Table I).

The presence of periodontitis (PPD ≥ 4.0 mm) was 5.8% in males and 3.2% in females. BMI and level of serum ALT were significantly associated with periodontitis in males ($p < 0.001$) (Table II). In females, BMI was significantly associated with periodontitis ($p < 0.001$) (Table II). Hemoglobin level, systolic blood pressure, diastolic blood pressure, pulse rate and data from the urine test were not significantly associated with periodontitis (data not shown).

In logistic regression analyses, males with a high level of serum ALT (≥ 41 IU/l) were significantly more likely to have periodontitis than those with a low level of serum ALT (OR = 2.3; 95% CI 1.0–5.2) (Table III). The analysis showed no significant associations between BMI categories and periodontitis among males. However, overweight and obese females were significantly more likely to have periodontitis than normal females (OR = 4.5; 95% CI 1.8–10.7).

Discussion

In this study of male Japanese university students aged 18–19 years, a higher ALT level was associated with increased risk of periodontitis (PPD ≥ 4mm). Elevated ALT is associated with liver diseases such as chronic viral hepatitis, autoimmune liver disease, drug hepatotoxicity and NAFLD [12]. The possible relationship between liver function and periodontitis has been discussed with regard to lipid metabolism [3]. A significant association between the incidence of periodontitis and elevated serum levels of ALT in the Japanese middle-aged population (20–59 years old) has been reported [14]. In this study, the range of ALT in males and females were 4–217 and 3–279 IU/l, respectively. The percentages of males and females with an abnormal level of serum ALT (≥ 41 IU/l) were 7.5% and 1.4%, respectively (data not shown). It is possible that increased ALT could be a potential risk indicator for periodontitis, even among the young male population.

Conversely, periodontitis could contribute to hepatic abnormalities. Studies suggested that intestinal lipopolysaccharide (LPS) is involved in the development of NAFLD [23]. In an animal study, chronic administration of LPS and proteases to the gingival sulcus induces not only periodontal inflammation but also NAFLD by increasing the level of serum LPS [24]. LPS triggers the production of various cytokines that affect lipid metabolism, leading to dyslipidaemia [23]. LPS that enters the bloodstream as a result of periodontal pathogens can affect the liver, leading to hepatic dyslipidaemia [25,26]. It is also conceivable that periodontitis can induce liver injury.

In the present study, an association between a higher ALT level and an increased risk of periodontitis was not significant in female university students. This finding is not consistent with the previous report [14] that the incidence of periodontitis in females aged 20–59 years was significantly increased with elevated serum levels of ALT. This discrepancy in study findings may be due to differences in the age of the subjects or in the sample size. In this study, the number of female students with both elevated ALT level (≥ 21 UI/l) and periodontitis was only three, whereas the corresponding number was 12 (≥ 32 UI/l) in the previous study [14].

On the other hand, females showed a positive relationship between BMI and the occurrence of periodontitis. This result was consistent with another study employing females aged 30–65 years [27]. The association between BMI and tumor necrosis factor-α (TNF-α) in gingival crevicular fluid [28] suggests that TNF-α in this fluid is derived from adipose tissue in obese subjects [3]. TNF-α plays an important role in the progression of periodontitis [29]. This suggests that TNF-α related to obesity may deteriorate periodontal tissue [3]. BMI increases with age [30], and a proportion of children aged 7–15 years with normal BMI become overweight or obese adults (BMI > 25 kg/m^2) [31]. Therefore, evaluation of BMI might be required even for young women for prevention of periodontitis. In Japan, health examination is implemented on a regular basis according to a school health law. As preventing periodontitis at an early stage is important to control risk factors in younger populations, monitoring of ALT and BMI by means of regular health examinations may be useful.

Table I. Characteristics of subjects.

	Males (n = 1264)				Females (n = 961)				Total (n = 2225)			
Variable	Mean (SD)		Median (25%, 75%)		Mean (SD)		Median (25%, 75%)		Mean (SD)		Median (25%, 75%)	
Number of teeth present[a]	28.5	(1.4)	28.0	(28.0, 29.0)	28.2	(1.3)	28.0	(28.0, 28.0)	28.4	(1.4)	28.0	(27.0, 28.0)
Number of decayed teeth[b]	0.23	(0.70)	0	(0, 0)	0.17	(0.56)	0	(0, 0)	0.21	(0.64)	0	(0, 0)
Bleeding on probing (%)[a]	6.4	(9.7)	3.6	(0, 10.7)	4.3	(7.5)	0	(0, 7.1)	5.5	(8.9)	0	(0, 7.1)
PPD (mm)[a]	1.73	(0.3)	1.70	(1.5, 1.9)	1.67	(0.24)	1.60	(1.5, 1.8)	1.70	(0.28)	1.70	(1.5, 1.9)
BMI (kg/m^2)[a]	21.2	(3.1)	20.6	(19.1, 22.8)	20.7	(2.8)	20.3	(18.8, 22.0)	21.0	(3.0)	20.5	(19.0, 22.4)
ALT (IU/l)[a]	20.8	(18.4)	16.0	(12.0, 23.0)	13.7	(12.4)	12.0	(9.0, 15.0)	17.7	(16.4)	14.0	(10.5, 19.0)
Total cholesterol (mg/dl)[a]	168.8	(27.5)	167.0	(149.0, 184.0)	180.1	(29.6)	177.0	(166.0, 197.0)	173.7	(29.0)	171.0	(154.0, 190.0)
Haemoglobin (g/dl)[a]	15.7	(0.8)	15.7	(15.1, 16.2)	13.4	(0.9)	13.4	(12.9, 14.0)	14.7	(1.4)	14.8	(13.6, 15.8)
Systolic blood pressure (mmHg)[a]	128.3	(13.3)	128.0	(119.0, 137.0)	115.0	(12.9)	114.0	(106.0, 123.0)	122.6	(14.7)	122.0	(112.0, 132.0)
Diastolic blood pressure (mmHg)[a]	74.4	(8.7)	74.0	(68.0, 80.0)	68.9	(8.4)	69.0	(63.0, 74.0)	72.0	(9.0)	72.0	(66.0, 78.0)
Pulse rate (beats per min)[c]	83.0	(13.7)	81.0	(73.0, 92.0)	84.4	(13.0)	83.0	(75.0, 93.0)	83.6	(13.4)	82.0	(74.0, 92.0)

[a]$p < 0.001$, gender difference according to the Mann–Whitney U-test.
[b]$p < 0.05$, gender difference according to the Mann–Whitney U-test.
[c]$p < 0.01$, gender difference according to the Mann–Whitney U-test.

Table II. Distribution of subjects according to BMI, the serum biochemical tests and behavioral characteristics by periodontitis category.

	Males				Females			
	Normal (n = 1191)		Periodontitis (n = 73)		Normal (n = 930)		Periodontitis (n = 31)	
Variable	n	%	n	%	n	%	n	%
BMI (kg/m^2)								
Normal (< 25.0)	1084	95.0	57[a]	5.0	865	97.4	23[a]	2.6
Overweight/obese (≥ 25.0)	107	87.0	16	13.0	65	89.0	8	11.0
ALT (IU/l)								
Normal (< 20)	881	95.8	39[a]	4.2	854	96.8	28	3.2
Subclinical (21–40)	227	91.2	22	8.8	63	96.9	2	3.1
Abnormal (≥ 41)	83	87.4	12	12.6	13	92.9	1	7.1
Total cholesterol (mg/dl)								
Normal (< 220)	1136	94.0	72	6.0	838	96.8	28	3.2
Abnormal (≥ 220)	55	98.2	1	1.8	92	96.8	3	3.2
Dental visit								
Regular	120	98.4	2	1.6	169	98.8	2	1.2
Irregular	1071	93.8	71	6.2	761	96.3	29	3.7
Dental floss or interdental brush use								
Use	108	97.3	3	2.7	117	98.3	2	1.7
No use	1083	93.9	70	6.1	813	96.6	29	3.4

[a]$p < 0.001$ compared to the normal group, according to the χ^2 test or Fisher's exact test.

A variety of potential mechanisms could explain an association between obesity and periodontitis. Although increasing evidence has shown that obesity is significantly associated with periodontitis, all of those studies were cross-sectional or case-control studies. Although the underlying biological mechanisms underpinning the association between obesity and periodontitis are not well understood, adipose tissue-derived cytokines and hormones may play a role [32]. One of the possible mechanisms that explains an association between obesity and periodontitis may include hepatic disorders, as shown in this study and previous reports [3,14]. In the future, prospective cohort studies and laboratory studies are required to clarify whether liver function is one of the key factors that can explain the association between obesity and periodontal disease.

Our study showed that the frequency of use of interdental oral hygiene devices and regular visits to dental clinics were not associated with the prevalence of periodontitis in the multivariate analysis. However, past population studies suggest that a high level of oral hygiene is correlated with a low risk of periodontal disease [33]. Our results may be explained by the low prevalence of periodontitis (4.7%). On the other hand, plaque-induced gingivitis is highly prevalent among young adults [34]. If we assess gingivitis, the effects of interdental cleaning and regular dental visits on gingival health may be revealed.

This study had some limitations. Since the design of the study limited interpretability about temporal relationships, prospective cohort studies may provide information beyond what we have presented here. The role of local and behavioral factors (e.g. dental plaque, calculus, nutrition, coping stress levels, alcohol consumption, etc.), which have been shown to affect the prevalence of periodontitis, were not considered in our study. The total amounts of alcohol consumption of the young students aged < 20 years in this study may have been small; therefore, the effect of alcohol consumption may not be a factor affecting the periodontal conditions in this study, compared to middle-aged and elderly people. A report that alcohol consumption is not associated with ALT in males [11] also supports our assumption. Periodontitis was evaluated using the NHANES III method. Since this method does not examine lingual and palatal sites, it is possible that the prevalence of periodontitis was underestimated. In fact, the prevalence of periodontitis was only 5% in the present study, while that for the WHO Global Oral Health Data Bank for 15–19-year-old children based on the Community Periodontal Index is around 10% [35].

In conclusion, elevated ALT is a potential risk indicator for periodontitis among healthy young males. Monitoring hepatic abnormalities to prevent periodontitis must be better understood, even in the young adult population.

Table III. ORs and 95% CIs of BMI, ALT, dental care and oral hygiene in the student population.

	Males (n = 1264)				Females (n = 961)			
Independent variable	Crude OR (95% CI)	p	Adjusted OR[a] (95% CI)	p	Crude OR (95% CI)	p	Adjusted OR (95%CI)	p
BMI (kg/m^2)								
Normal (< 25.0)	1.0		1.0		1.0		1.0	
Overweight/obese (≥ 25.0)	2.8 (1.6–5.1)	0.001	1.8 (0.9–3.6)	0.114	4.6 (2.0–10.8)	< 0.001	4.5 (1.8–10.7)	0.001
ALT (IU/L)								
Normal (≤ 20)	1.0		1.0		1.0		1.0	
Subclinical (21–40)	2.2 (1.3–3.8)	0.005	1.9 (1.1–3.5)	0.028	1.0 (0.2–4.2)	0.965	0.7 (0.1–3.2)	0.660
Abnormal (≥ 41)	3.3 (1.6–6.5)	0.001	2.3 (1.0–5.2)	0.048	2.3 (0.3–18.6)	0.419	1.0 (0.1–9.3)	0.965
Dental care								
Regular	1.0		1.0		1.0		1.0	
Irregular	4.0 (0.9–16.4)	0.056	3.7 (0.9–15.6)	0.061	3.2 (0.18–13.6)	0.112	2.8 (0.6–12.0)	0.171
Dental floss or interdental brush use								
Use	1.0		1.0		1.0		1.0	
No use	2.3 (0.7–7.5)	0.158	2.1 (0.7–7.0)	0.210	2.1 (0.5–8.9)	0.319	1.6 (0.4–7.0)	0.523

[a]Adjusted for BMI, ALT, dental care and oral hygiene.
Logistic regression analysis with periodontitis (≥ 1 site; PPD ≥ 4 mm) as a dependent variable.

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