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Association of Elevated C-reactive Protein Levels and Periodontal Status in Japanese Adults with and without Obesity

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Abstract

Aim: Obesity is a major public health issue, and may affect the relationship between elevation of the acute-phase inflammatory marker C-reactive Protein (CRP) level and periodontitis. The aim of this cross-sectional study was to investigate the relationship between elevated CRP levels and periodontal status in Japanese adults with and without obesity.

Materials and methods: We recruited 1328 participants who received oral health check-ups. Periodontal status was evaluated using the community periodontal index. Elevated CRP levels were defined as >3 mg/L. Obesity was defined as body mass index (BMI) ≥25.

Results: Multivariate logistic regression showed that the presence of elevated CRP levels in obese participants was significantly related to BMI (odds ratio [OR] = 1.186, 95% confidence interval [CI]=1.066-1.319) and presence of probing pocket depth (PPD) ≥6 mm (vs. PPD <6 mm, OR=2.716, 95% CI=1.107-6.660) after adjustment for confounding factors. Among non-obese participants, the presence of elevated CRP levels was significantly related to smoking habit (OR=2.805, 95% CI=1.391-5.665) and serum alanine aminotransferase levels (OR=1.028, 95% CI=1.005-1.051) after adjustment for confounding factors.

Conclusion: Having PPD ≥6 mm may be associated with elevated CRP levels in Japanese adults with obesity but not in non-obese individuals.

Introduction

Periodontitis is a chronic inflammatory disease of the tooth supportive tissues, and is initiated by bacterial pathogens in periodontal pockets. Previous studies have revealed that periodontitis could link to multiple systemic diseases, including diabetes mellitus [1-3], hypertension [4], ischemic stroke [5], liver diseases [6], chronic kidney diseases [7,8] and brain diseases [9,10]. The mechanisms by which periodontitis affect systemic diseases are not completely understood. However, it has been

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shown that periodontitis can be a chronic source of bacterial pathogens [11] and inflammatory cytokines [12] in the blood stream. Therefore, circulating mediators could potentially be involved in the initiation and progression of systemic diseases following periodontitis.

C-reactive Protein (CRP) is an acute-phase protein that is reflective of infection and chronic inflammatory diseases [13]. Clinical studies have investigated the relationship between CRP and periodontitis. A systematic review and meta-analysis of cross-sectional studies indicated that plasma CRP levels in periodontitis patients were higher than in periodontally healthy controls [14]. It is also reported that periodontal treatment significantly decreased the levels of CRP in patients with high baseline levels of CRP > 3 mg/L [15] and in patients undergoing haemodialysis and/or peritoneal dialysis [16]. These observations indicate that periodontitis is closely associated with circulating CRP levels. The role of CRP may not be limited to acute responses to illness, and is associated with cardiovascular risk, including coronary heart disease, myocardial infarction, and stroke [17]. Periodontitis may be associated with cardiovascular risk through modulating CRP level.

The relationship between systemic diseases and periodontitis may not be observed in all people. For instance, a report suggests that the relationship between diabetes mellitus and periodontitis could vary depending on Body Mass Index (BMI) and glycemic control conditions [18]. Like this, the relationship between CRP and periodontitis may also differ according to the population characteristics. It is important to identify and investigate the groups in which there is a strong association between CRP and periodontal disease.

Obesity is a major public health problem in Japan [19]. Increased BMI is associated with the risk of both elevation of CRP levels [20] and periodontitis [21]. Therefore, the relationship between CRP elevation and periodontitis might be affected by obesity. Some studies have investigated the effect of BMI on the relationship between CRP and periodontitis. For instance, a cross-sectional study showed that adjusting BMI attenuated the positive association between CRP and Probing Pocket Depth (PPD) in men by 15% [22]. On the other hand, it is also reported that BMI showed a positive association with periodontitis but not with CRP [23]. Similarly, the effect of BMI on the relationship between CRP and periodontitis is controversial. Furthermore, it remains unclear how the relationship between CRP and periodontitis differs according to the presence or absence of obesity.

The tested hypothesis was that the elevation of serum CRP levels would be associated with periodontal status, and this association might change according to the presence or absence of obesity. The purpose of this cross-sectional study was to investigate the relationship between elevation of CRP and periodontal status in Japanese adults with and without obesity.

Material and methods

Study population

Inclusion criteria were all Japanese adults ≥20 years old who underwent both dental and medical check-ups from Jan 2017 through Dec 2017 at our university hospital in Gifu, Japan. Since this study involves completing a survey, we did not perform sample size calculations. We excluded one participant with insufficient data. Accordingly, 1328 participants (827 men, 501 women; 20-88 years old) were eligible for our study. Some of the study participants had diabetes (n=40), hypertension (n=135), cancer (n=10), or rheumatoid arthritis (n=7). The study protocol was approved by the Ethics Committee of Asahi University (No. 27010). All participants provided written informed consent prior to study participation.

Measurement of serum parameters

After an overnight fasting of at least 8 hours, venous blood samples were collected in the fasting state. A simultaneous multi-item automatic analyzer (Dimension Vista 1500®, Siemens Healthineers Japan, Tokyo, Japan) was used to determine serum levels of CRP, triglyceride, High-Density Lipoprotein (HDL) cholesterol, and Low-Density Lipoprotein (LDL) cholesterol. This automatic analyzer combines four detection technologies, including photometry, nephelometry, V-LYTE® integrated multisensor technology, and LOCI® advanced chemilu minescence [24]. A diabetes automatic analyzer (DM-JACK, Kyowa Medex, Tokyo, Japan) was also used to measure serum hemoglobin A1c (HbA1c) level. Since normal CRP levels are typically below 3.0 mg/L, CRP > 3 mg/L was defined as the presence of elevated CRP [25,26].

Evaluation of periodontal status

Three dentists, who were blinded to the study design, independently evaluated periodontal status of the study participants using the Community Periodontal Index (CPI) [27]. Measurements of ten selected teeth, including two molars (16 and 17, 26 and 27, 36 and 37, and 46 and 47) in each posterior sextant, and the upper right and lower left central incisors, were made using a CPI probe (YDM, Tokyo, Japan) at six sites (mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual and mesio-lingual) per tooth. One or more teeth with ≥ 4 mm PPD and ≥ 6 mm PPD was defined as the presence of moderate periodontitis and severe periodontitis, respectively [28]. Good intra-and inter-examiner agreement was confirmed for repeated Probing Pocket Depth (PPD) measurements in the 10 teeth used for CPI (Kappa statistic, > 0.8). The presence or absence of teeth exhibiting Bleeding on Probing (BOP) was recorded. The number of teeth in the mouth was also counted.

Diagnosis of obesity

Height and body weight were measured using the automatic height scale with a body composition meter (TBF-110 / TBF-210 / DC-250, TANITA, Tokyo, Japan). Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters. BMI ≥ 25 was defined as the presence of obesity, according to the obesity classifications from the Japan Society for the Study of Obesity [29].

Different variables related to serum CRP levels

We collected information about sex, age, self-reported current medical history, regular exercise (presence/absence), smoking habit (presence/absence), and drinking habit (presence/absence). Systolic Blood Pressure (SBP) and diastolic blood pressure (DBP) were measured using an automatic blood pressure monitor (HBP-9021 / HBP-9020 / BP-230RV3, OMRON HEALTHCARE, Kyoto, Japan).

Statistical analysis

The Kolmogorov-Smirnov test was used to confirm the normality of our data. All continuous variables were not normally distributed, thus data are expressed as median (first and third quartiles). The Chi-square test and Mann Whitney U test were

used to assess significant differences in selected characteristics between study participants with and without CRP > 3 mg/L or obesity. Univariate and multivariate logistic regression analyses using a stepwise method (backward selection approach) were performed with the presence or absence of CRP > 3 mg/L dependent variables. Independent variables were selected when the p value was < 0.05 in the univariate model. In addition, we did not remove any variables to avoid multicollinearity, because there were no variables with |r| > 0.8 in the Spearman's correlation analysis [10].

Analyses were performed using the SPSS statistical package (IBM SPSS statistics version 25, IBM Japan, Tokyo, Japan). All reported p values were considered statistically significant if less than 0.05.

Results

Characteristics of the participants with and without CRP > 3 mg/L

The overall prevalence of CRP > 3 mg/L was 5.8%. Table 1 shows characteristics of study participants with different serum CRP concentration. There were significant differences between the participants with and without CRP > 3 mg/L in BMI (p < 0.001), self-reported current medical history (p < 0.05), serum AST level (p < 0.05), serum ALT level (p < 0.01), and serum HDL cholesterol level (p < 0.01). There were also significant differences between the participants with and without CRP > 3 mg/L in prevalence of PPD ≥ 6 mm (p < 0.05).

Characteristics of the participants with and without obesity

The number of participants with obesity was 309. The prevalence of CRP > 3 mg/L was 4.0% in non-obese participants and 11.7% in obese participants, and there was a significant difference in the prevalence of CRP > 3 mg/L between the participants with and without obesity (Table 2). There were significant differences between the participants with and without obesity in gender (p < 0.001), BMI (p < 0.001), self-reported current medical history (p < 0.001), regular exercise (p < 0.01), SBP (p < 0.001), DBP (p < 0.001), serum AST level (p < 0.001), serum ALT level (p < 0.001), serum HbA1c level (p < 0.001), serum triglyceride level (p < 0.001), serum HDL cholesterol level (p < 0.001), and serum HDL cholesterol level (p < 0.001). There were also significant differences between the participants with and without obesity in prevalence of BOP (p < 0.001) and PPD ≥ 4 mm (p < 0.001).

Logistic regression analysis with prevalence of CRP > 3 mg/L as the dependent variable

In univariate logistic regression analysis, the presence of CRP > 3 mg/L was related with BMI (odds ratio [OR]=1.184, 95% confidence interval [CI]=1.119–1.253), presence of self-reported current medical history (vs. absence, OR=1.770, 95% CI=1.098–2.852), serum AST level (OR=1.031, 95% CI=1.011–1.050), serum ALT level (OR=1.025, 95% CI=1.013–1.038), serum HbA1c level (OR=1.495, 95% CI=1.053–2.121), serum HDL cholesterol level (OR=0.978, 95% CI=0.965–0.992), and presence of PPD ≥ 6 mm (vs. absence, OR=2.075, 95% CI=1.129–3.814) (Table 3).

In multiple logistic regression analysis, the prevalence of presence of CRP > 3 mg/L was related with BMI (OR=1.184, 95% CI=1.119–1.253) and presence of PPD ≥ 6 mm (vs. absence, OR=2.003, 95% CI=1.078 - 3.723), after adjusting for BMI, self-reported current medical history, AST, ALT, HbA1c, HDL cholesterol, and PPD ≥ 6 mm (Table 4).

Logistic regression analysis with prevalence of CRP > 3 mg/L as the dependent variable among obese participants

In univariate logistic regression analysis, the presence of CRP > 3 mg/L was related with BMI (OR=1.175, 95% CI=1.057 – 1.305) and presence of PPD ≥ 6 mm (vs. absence, OR=2.404, 95% CI=1.002 – 5.767) (Table 5).

In multiple logistic regression analysis, the presence of CRP > 3 mg/L was related with BMI (OR=1.186, 95% CI=1.066–1.319) and presence of PPD ≥ 6 mm (vs. absence, OR= 2.716, 95% CI=1.107–6.660), after adjusting for BMI and PPD ≥ 6 mm (Table 6).

Logistic regression analysis with prevalence of CRP > 3 mg/L as the dependent variable among non-obese participants.

In univariate logistic regression analysis, the presence of CRP > 3 mg/L was related with smoking habit (OR=2.789, 95% CI=1.392–5.625), serum ALT level (OR=1.027, 95% CI=1.005–1.050), and serum HDL cholesterol level (OR=0.979, 95% CI=0.961–0.997) (Table 7).

In multiple logistic regression analysis, the presence of CRP > 3 mg/L was related with smoking habit (OR=2.805, 95% CI=1.391–5.665) and serum ALT level (OR=1.028, 95% CI=1.005–1.051), after adjusting for smoking habit, ALT, and HDL cholesterol (Table 8).

Table 1: Characteristics of study participants with different serum CRP concentration.

Variables	CRP ≤ 3 mg/L (n=1251)	CRP > 3 mg/L (n=77)	p value [1]
Gender (male, %)	775 (62.0)	52 (67.5)	0.397
Age, years	50 (41, 58)	51 (40, 58)	0.931
BMI	22.5 (20.2, 24.6)	24.3 (22.15, 27.45)	< 0.001
Self-reported current medical history (presence, %)	622 (49.7)	49 (63.6)	0.019
Regular exercise (presence, %)	270 (21.6)	13 (16.9)	0.391
Smoking habit (presence, %)	173 (13.8)	16 (20.8)	0.094
Drinking habit (presence, %)	211 (16.9)	7 (9.1)	0.081
SBP, mmHg	119 (108, 128)	121 (112, 131)	0.162
DBP, mmHg	73 (65, 81)	74 (67, 79)	0.981
Serum parameters			

AST, mg/dL	16 (12, 20)	18 (13, 23)	0.036
ALT, mg/dL	16 (11, 23)	21 (12.5, 34.5)	0.003
HbA1c, %	5.4 (5.2, 5.6)	5.4 (5.3, 5.8)	0.158
Triglyceride, mg/dL	66 (45, 102)	74 (45, 113)	0.103
HDL cholesterol, mg/dL	67 (55, 80)	59 (47, 77.5)	0.001
LDL cholesterol, mg/dL	112 (93, 130)	113 (91, 130.5)	0.838
Oral parameters			
Number of present teeth	28 (27, 29)	28 (27, 29.5)	0.926
BOP (presence, %)	883 (70.6)	55 (71.4)	1.000
PPD ≥ 4 mm (presence, %)	710 (56.8)	48 (62.3)	0.346
PPD ≥ 6 mm (presence, %)	121 (9.7)	14 (18.2)	0.030

Continuous variables were expressed as median (first quartile, third quartile).
[1]Chi-square test or Mann Whitney U test
Abbreviation: CRP: C-Reactive Protein; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AST: Aspartat Aminotransferase; ALT: Alanin Aminotransferase; Hba1c; Hemoglobin A1c; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; BOP: Bleeding On Probing; PPD: Periodontal Pocket Depth.

Table 2: Characteristics of study participants with and without obesity.

Variables	Non-obesity (n=1019)	Obesity (n=309)	p value [1]
Gender (male, %)	593 (58.1)	234 (75.7)	< 0.001
Age, years	50 (41, 58)	51 (43, 59)	0.129
BMI	21.6 (19.8, 23.2)	26.8 (25.8, 28.4)	< 0.001
Self-reported current medical history (presence, %)	479 (47.0)	192 (62.1)	< 0.001
Regular exercise (presence, %)	233 (22.9)	50 (16.2)	0.009
Smoking habit (presence, %)	138 (13.5)	51 (16.5)	0.194
Drinking habit (presence, %)	172 (16.9)	46 (14.9)	0.431
SBP, mmHg	117 (106, 126)	126 (118, 135)	< 0.001
DBP, mmHg	71 (64, 79)	78 (73, 85)	< 0.001
Serum parameters			
CRP > 3 mg/L (presence, %)	41 (4.0)	36 (11.7)	< 0.001
AST, mg/dL	15 (12, 19)	18 (14, 25)	< 0.001
ALT, mg/dL	14 (11, 20)	22 (16, 37)	< 0.001
HbA1c, %	5.4 (5.2, 5.6)	5.5 (5.3, 5.8)	< 0.001
Triglyceride, mg/dL	59 (41, 88)	95 (67, 113)	< 0.001
HDL cholesterol, mg/dL	69 (57, 84)	56 (47, 67)	< 0.001
LDL cholesterol, mg/dL	110 (91, 129)	118 (102, 135)	< 0.001
Oral parameters			
Number of present teeth	28 (27, 29)	28 (27, 29)	0.468
BOP (presence, %)	691 (67.8)	247 (79.9)	< 0.001
PPD ≥ 4 mm (presence, %)	555 (54.5)	203 (65.7)	< 0.001
PPD ≥ 6 mm (presence, %)	98 (9.6)	37 (12.0)	0.238

Continuous variables were expressed as median (first quartile, third quartile).
[1]Chi-square test or Mann Whitney U test
Abbreviation: BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CRP: C-Reactive Protein; AST: Aspartat Aminotransferase; ALT: Alanin Aminotransferase; Hba1c: Hemoglobin A1c; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; BOP: Bleeding On Probing; PPD: Probing Pocket Depth.

Table 3: Factors associated with CRP > 3 mg/L among all participants: univariate logistic regression analysis.

Variables	Crude odds ratio	95% Confidence interval	p value
Gender [1]	0.783	0.479-1.278	0.328
Age, years	1.002	0.982-1.023	0.813
BMI	1.184	1.119-1.253	< 0.001
Self-reported current medical history [2]	1.770	1.098-2.852	0.019
Regular exercise [2]	0.724	0.393-1.335	0.301
Smoking habit [2]	1.634	0.921-2.900	0.093
Drinking habit [2]	0.493	0.223-1.087	0.080
SBP, mmHg	1.011	0.995-1.026	0.170
DBP, mmHg	0.999	0.978-1.019	0.901
Serum parameters			
AST, mg/dL	1.031	1.011-1.050	0.002
ALT, mg/dL	1.025	1.013-1.038	< 0.001
HbA1c, %	1.495	1.053-2.121	0.024
Triglyceride, mg/dL	1.002	1.000-1.004	0.120
HDL cholesterol, mg/dL	0.978	0.965-0.992	0.002
LDL cholesterol, mg/dL	0.999	0.991-1.007	0.773
Oral parameters			
Number of present teeth	0.976	0.909-1.049	0.509
BOP [2]	1.042	0.626-1.734	0.874
PPD ≥ 4 mm [2]	1.261	0.785-2.027	0.338
PPD ≥ 6 mm [2]	2.075	1.129-3.814	0.019

[1]Female/male (reference was male), [2]Presence/absence (reference was absence)
Abbreviation: CRP: C-Reactive Protein; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AST: Aspartat Aminotransferase; ALT: Alanin Aminotransferase; Hba1c: Hemoglobin A1c; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; BOP: Bleeding On Probing; PPD: Probing Pocket Depth.

Table 4: Factors associated with CRP > 3 mg/L among all participants: multiple logistic regression analysis.

Variables	Adjusted odds ratio [1]	95% Confidence interval	p value
BMI	1.184	1.119-1.253	< 0.001
PPD ≥ 6 mm [2]	2.003	1.078-3.723	0.028

[1]Adjusted by BMI, self-reported current medical history, aspartat aminotransferase, alanin aminotransferase, hemoglobin A1c, high-density lipoprotein cholesterol, and PPD ≥ 6 mm
[2]Presence/absence (reference was absence)
Abbreviation: CRP: C-Reactive Protein; BMI: Body Mass Index; PPD: Probing Pocket Depth.

Table 5: Factors associated with CRP > 3 mg/L among obese participants: Univariate logistic regression analysis.

Variables	Crude odds ratio	95% Confidence interval	p value
Gender[1]	1.667	0.789-3.521	0.181
Age, years	0.989	0.957-1.022	0.989
BMI	1.175	1.057-1.305	0.003
Self-reported current medical history[2]	1.250	0.600-2.606	0.552
Regular exercise [2]	0.810	0.299-2.196	0.679

Smoking habit [2]	0.601	0.203-1.780	0.358
Drinking habit [2]	0.688	0.231-2.045	0.501
SBP, mmHg	1.000	0.974-1.027	0.988
DBP, mmHg	0.989	0.954-1.025	0.534
Serum parameters			
AST, mg/dL	1.028	1.000-1.058	0.052
ALT, mg/dL	1.010	0.993-1.028	0.232
HbA1c, %	1.367	0.863-2.168	0.183
Triglyceride, mg/dL	0.997	0.991-1.004	0.426
HDL cholesterol, mg/dL	1.000	0.976-1.025	0.970
LDL cholesterol, mg/dL	0.996	0.983-1.009	0.565
Oral parameters			
Number of present teeth	0.723	0.321-1.628	0.433
BOP [2]	1.042	0.626-1.734	0.874
PPD ≥ 4 mm [2]	1.213	0.572-2.572	0.615
PPD ≥ 6 mm [2]	2.404	1.002-5.767	0.049

[1]Female/male (reference was male), [2]Presence/absence (reference was absence)Abbreviation: CRP: C-Reactive Protein; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AST: Aspartat Aminotransferase; ALT: Alanin Aminotransferase; Hba1c: Hemoglobin A1c; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; BOP: Bleeding On Probing; PPD: Probing Pocket Depth.

Table 6: Factors associated with CRP > 3 mg/L among obese participants: multiple logistic regression analysis.

Variables	Adjusted odds ratio [1]	95% Confidence interval	p value
BMI	1.186	1.066-1.319	0.002
PPD ≥ 6 mm [2]	2.716	1.107-6.660	0.029

[1]Adjusted by BMI and PPD ≥ 6 mm.[2]Presence/absence (reference was absence)
Abbreviation: CRP: C-Reactive Protein; BMI: Body Mass Index; PPD: Probing Pocket Depth.

Table 7: Factors associated with CRP > 3 mg/L among non-obese participants: univariate logistic regression analysis.

Variables	Crude odds ratio	95% Confidence interval	p value
Gender [1]	0.635	0.325-1.241	0.184
Age, years	1.009	0.982-1.037	0.520
BMI	1.138	0.977-1.326	0.096
Self-reported current medical history [2]	1.803	0.951-3.420	0.071
Regular exercise [2]	0.794	0.362-1.774	0.566
Smoking habit [2]	2.798	1.392-5.625	0.004
Drinking habit [2]	0.378	0.115-1.239	0.108
SBP, mmHg	1.001	0.979-1.022	0.963
DBP, mmHg	0.978	0.949-1.007	0.132
Serum parameters			
AST, mg/dL	1.015	0.984-1.048	0.347
ALT, mg/dL	1.027	1.005-1.050	0.018
HbA1c, %	1.122	0.557-2.260	0.747
Triglyceride, mg/dL	1.004	1.000-1.009	0.051

HDL cholesterol, mg/dL	0.979	0.961-0.997	0.021
LDL cholesterol, mg/dL	0.995	0.984-1.006	0.387
Oral parameters			
Number of present teeth	0.987	0.883-1.103	0.820
BOP [2]	1.023	0.523-2.002	0.946
PPD ≥ 4 mm [2]	1.071	0.571-2.010	0.830
PPD ≥ 6 mm [2]	1.651	0.676-4.029	0.271

[1]Female/male (reference was male), [2]Presence/absence (reference was absence).

Abbreviation: CRP: C-Reactive Protein; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; AST: Aspartat Aminotransferase; ALT: Alanin Aminotransferase; Hba1c: Hemoglobin A1c; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; BOP: Bleeding On Probing; PPD: Probing Pocket Depth.

Table 8: Factors associated with CRP > 3 mg/L among non-obese participants: Multiple logistic regression analysis.

Variables	Adjusted odds ratio[1]	95% Confidence interval	p value
Smoking habit 2	2.805	1.391-5.665	0.004
ALT	1.028	1.005-1.051	0.018

[1]Adjusted by smoking habit, ALT, and high-density lipoprotein.

[2]Presence/absence (reference was absence).

Abbreviation: Crp: C-Reactive Protein; Alt: Alanin Aminotransferase.

Discussion

This study investigated the relationship between elevation of CRP levels and periodontal status in Japanese adults with and without obesity. In particular, we focused whether periodontal status could be an associated factor for systemic increase in CRP. Therefore, presence or absence of elevated serum CRP levels was selected as dependent variables in the logistic regression analysis. Among the total participants, the present analysis showed that the risk of having CRP > 3 mg/dL was higher in participants with PPD ≥ 6 mm than without PPD ≥ 6 mm (OR=2.003; 95% CI=1.078–3.723). In obese participants, the risk of having CRP > 3 mg/L was also higher in participants with PPD ≥ 6 mm than without PPD ≥ 6 mm (OR=2.003; 95% CI=1.078–3.723). However, in non-obese participants, the risk of having CRP > 3 mg/L was not correlated with presence of PPD ≥ 6 mm. The results show the elevation of CRP levels was significantly associated with severe periodontitis; however, this relationship was observed in only obese participants.

CRP is mainly produced by the liver and adipose tissues [30,31]. Therefore, it is conceivable that elevation of CRP levels following periodontitis varies according to the degree of the responses of the liver and adipose tissues against periodontal pathogens and inflammatory stimulus. Clinical studies have shown that elevation of CRP levels was positively associated with BMI [20,32,33]. These studies suggest that the production of CRP in the liver and adipose tissues increases according to BMI. In this study, periodontal status was associated with elevation of CRP levels in obese participants, but not in non-obese participants. Obese conditions chronically induce the over-production of CRP in the liver and adipose tissues; thus, responses against periodontal pathogens and inflammatory cytokines may be more easily elevated compared with non-obese conditions.

Several studies have reported on the relationship between CRP and periodontal status. A meta-analysis of cross-sectional studies showed that the weighted mean difference in CRP between subjects with and without periodontitis was 1.56 mg/L [14]. A cohort study also revealed that the OR for advanced periodontitis associated with high CRP was 2.49 after adjustment for confounders [34]. In addition, a meta-analysis of randomized controlled trials reported that periodontal treatment results in modest short-term reductions in circulating CRP [35]. Furthermore, a recent meta-analysis indicated that periodontal treatment significantly decreased CRP levels at less than or equal to baseline in dialysis patients [16]. The previous and present observations support the same concept: that periodontitis is positively associated with elevation of CRP levels.

On the other hand, our present observations show that the presence of PPD ≥ 4 mm was not associated with having CRP > 3 mg/L. This indicates that moderate periodontitis had little effect on the elevation of CRP. Thus, detectable increases in CRP levels following periodontitis would require periodontal pathogens and inflammatory stimulus to be above a certain level.

Elevation of CRP levels can contribute to the risk of coronary heart disease, myocardial infarction, and stroke [17]. This suggests that avoiding elevated CRP levels could provide clinical benefits in preventing cardiovascular diseases. Although our study did not demonstrate the direct effects of severe periodontitis on cardiovascular diseases, it is possible that improvement of severe periodontitis following periodontal treatment may suppress the risk of elevation of CRP levels, contributing to the prevention of cardiovascular diseases. However, because the evidence about the effects of periodontal treatment on the occurrence or recurrence of cardiovascular diseases is still very weak [36], further studies are needed to determine whether periodontal treatment can help prevent cardiovascular diseases. In addition, the present data clarified that the relationship between CRP and periodontal status varies according to the presence or absence of obesity and the severity of periodontitis. Thus, the effect of periodontal treatment on cardiovascular diseases may be observable in subjects with obesity and severe periodontitis.

Cross-sectional studies have reported that elevated CRP levels are positively associated with cigarette smoking [37,38] and elevated liver enzyme, such as ALT [39]. These observations are consistent with the present findings, which showed that the elevation of CRP levels was associated with smoking habit and serum ALT level in non-obese participants. On the other hand, although it is known that CRP is also associated with diabetes mellitus [40], only univariate logistic regression analysis using all participants showed the correlation between elevation of CRP and HgA1c levels in our study. In the present study, the prevalence of participants with poor glycemic control (HbA1c ≥ 6.5% [41]) was only 3% (data not shown). The association between CRP and HbA1c might not have reached the level of significance, since almost all of the current study participants had good glycemic control.

After adjusting BMI, self-reported current medical history, AST, ALT, HbA1c, HDL cholesterol, and PPD ≥ 6 mm, $p < 0.05$ variables were reduced to BMI and PPD ≥ 6 mm in the logistic regression analysis (Table 4). In the current data, the Spearman's correlation analysis showed that BMI was associated with self-reported current medical history, AST, ALT, HbA1c, and HDL cholesterol (data not shown). In addition, having PPD ≥ 6 mm was associated with HgA1c. These indicate that BMI and PPD ≥ 6 mm overwhelmed the effects of self-reported current medical history, AST, ALT, HbA1c, and HDL cholesterol on elevated CRP levels.

In this study, the prevalence of CRP > 3 mg/L was 5.8%. It is reported that the prevalence of CRP > 3 mg/L was 21.4% and 10.1% in healthy people with and without excessive visceral adiposity, respectively [42]. It is also known that the prevalence of CRP > 3 mg/L for the age groups 25 to 39, 40 to 59, and 60 to 84 years old were 15.7%, 20.6%, and 38.7%, respectively, in men; and 21.2%, 22.1%, and 33.7%, respectively, in women not on hormone therapy among the general population [43]. These data indicate that the current prevalence of elevated CRP levels was low compared to previous studies. In addition, the prevalence of PPD ≥ 6 mm in this study was 10.2% (data not shown). In a study of Japanese adults, the prevalence of PPD ≥ 6 mm was reported as 43.1% [44]. Therefore, the prevalence of severe periodontitis was also low compared to previous reports. In this study, Japanese adults who underwent oral health check-ups were recruited at the Asahi University Hospital. As the present study population was highly health conscious, the prevalence of CRP > 3 mg/L and severe periodontitis might be low. This would limit the ability to extrapolate our findings to the general population.

The present study has other limitations. First, information on sociological factors was not collected, which may have an influence on serum CRP levels [45]. Second, we measured only BMI to evaluate presence or absence of obesity. Additional measurements of waist circumference and waist-hip ratios will improve the reliability of our diagnostics of obesity. Third, this was a cross-sectional study, which does not permit conclusions regarding causal relationships. Further prospective studies, investigating longitudinal relationships among CRP, periodontal status, and obesity, are needed. Fourth, although self-reported current medical history did not correlate with elevation of CRP levels, it is possible that inflammatory diseases other than periodontitis had an influence on our data. In future, it will be necessary to clarify the effects of inflammatory diseases besides periodontitis on the current association. Fifth, periodontal status was evaluated using the CPI, which assesses in a categorized manner only PPD. However, because the present study was combined with routine health check-up, our data obtained were limited and we were not able to secure enough time to measure clinical attachment level and alveolar bone level.

Conclusions

Within the limits of the current study, severe periodontitis is associated with elevated CRP levels in Japanese adults with obesity, but not in those without obesity.

Conflicts of Interest

The authors declare no conflict of interest.

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