Original Article

Plasma Levels of Visfatin are Associated with Periodontal Disease Severity in Coronary Artery Disease Patients

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Objectives: Periodontitis has been reported to be associated with coronary artery disease (CAD). Visfatin (also known as pre-B cell colony-enhancing factor or PBEF), which is a pleiotropic mediator that acts as growth factor, cytokine, and enzyme in energy metabolism, has recently been shown to exert a pro-inflammatory effect. This study aimed at investigating the relationship between plasma visfatin level and the severity of periodontal disease in patients with CAD. We also investigated the relationships between visfatin and traditional biomarkers associated with periodontal disease and oral health status.

Methods: Plasma visfatin concentrations were measured using an enzyme-linked immunosorbent assay in 496 consecutive patients with CAD, all of whom underwent clinical, cardiac, dental, and laboratory evaluations.

Results: The patients with CAD and periodontal disease had a higher median plasma visfatin level than that in CAD patients without periodontal disease. Patients with a community periodontal index (CPI) score of 3−4 had significantly higher levels of visfatin, high-sensitivity C-reactive protein (hs-CRP), and Framingham 10-year risk score than those in patients with a score of 1. Multivariate analysis showed that plasma visfatin level was independently associated with CPI, and also significantly associated with sex, hs-CRP, neutrophil-to-lymphocyte ratio, and the presence of missing teeth.

Conclusions: Plasma visfatin levels were elevated in patients with CAD and periodontal disease, and this increase was associated with inflammation, CPI status, and the number of missing teeth.

Key words: community periodontal index, coronary artery disease, inflammation, periodontal disease, visfatin

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Introduction

Increasing clinical and animal evidence suggests that periodontal disease (PD) is associated with cardiovascular problems, and that this association may be related to inflammatory processes.[1] Periodontal disease has also been found to contribute to elevated plasma levels of inflammatory mediators such as C-reactive protein (CRP) and interleukin 6 (IL-6), which are associated with atherosclerosis and an increased risk of acute cardiovascular events.[2] Periodontopathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum* are found in biofilm on the tooth surface, and are essential for the initiation and progression of periodontitis.[3] Several studies have shown that adipose tissue secretes mediators called adipocytokines which play important roles in immunity and inflammation.[4]

Adipose tissue is an energy-storage tissue that secretes bioactive molecules including visfatin, leptin, resistin and adiponectin, collectively called adipokines.[5] Adipokines regulate insulin sensitivity and energy expenditure as well as wound healing and inflammation. Visfatin, leptin, and resistin exert a pro-inflammatory effect, whereas adiponectin exerts an anti-inflammatory effect.

Originally called pre-B-cell colony-enhancing factor 1, visfatin is predominantly produced by macrophages and adipocytes in adipose tissue.[6] It stimulates the production of inflammatory molecules and activates nuclear factor-κB. In addition, it has also been shown to possess the enzymatic activity of nicotinamide phosphoribosyltransferase responsible for the synthesis of nicotinamide adenine dinucleotide, which is essential for cell metabolism.

Visfatin induces the production of pro-inflammatory cytokines and also acts as a chemotactic factor. Not only does it stimulate a variety of cells to synthesize inflammatory mediators and proteases, but it can also inhibit apoptosis of inflammatory cells. Increased plasma levels of visfatin have been reported in several inflammatory diseases and conditions including type 2 diabetes mellitus, obesity, metabolic syndrome, atherosclerosis, cancer, rheumatoid arthritis, and sepsis.[6-10] A recent study demonstrated that gingival fibroblasts can produce visfatin and that its synthesis is increased in inflammatory and infectious conditions.[11] Thus, it is reasonable to propose that visfatin acts as a pro-inflammatory cytokine and plays a role in chronic inflammation, thereby contributing to the pathogenesis of PD. However, few studies have investigated the association between visfatin levels and the severity or extent of PD.

The aim of this study was to investigate the associations between visfatin and selected PD risk factors by assessing plasma visfatin level, community periodontal index (CPI), and oral status in a cohort of patients with coronary artery disease (CAD).

Subjects and Methods

Study participants

Consecutive patients who were treated for CAD at the Dental and Cardiovascular Clinics of E-Da Hospital, Taiwan, between January 2010 and December 2013 were evaluated. A total of 496 patients with CAD (389 males and 107 females), including 123 without PD (87 males and 36 females, aged 28 to 96 years) and 373 with PD (298 males and 75 females, aged 31 to 97 years) were enrolled. All patients completed questionnaires regarding information on personal, medical, and dental history.

The inclusion criteria were: 1) age >18 years; 2) diagnosis of CAD made for more than one year; 3) body mass index (BMI) of 19−26 kg/m^2 in women and 20−27 kg/m^2 in men;[12] and 4) no changes in medication during the 3-month study period. The exclusion criteria were: 1) liver dysfunction; 2)

infectious disease(s); 3) inflammatory bowel disease; 4) rheumatoid arthritis; 5) granulomatous disease(s); 6) organ transplantation; and 7) cancer therapy. Those who were pregnant or lactating, needed antibiotics for infective endocarditis prophylaxis during dental procedures, had symptoms of acute illnesses (i.e., fever, sore throat, body pain, or diarrhea), used orthodontic appliances or had oral mucosal inflammatory conditions (e.g., aphthous, lichen planus, leukoplakia, or oral cancer) were also excluded. Each participant provided written informed consent before enrollment. The study protocol and procedure were approved by the Ethics Committee of I-Shou University and E-Da Hospital (EDAH IRB No. EMRP-101-050). Informed consent was obtained from all participants.

All dental examinations, which were conducted according to the World Health Organization (WHO) standardized index and the decayed, missing, and filled teeth (DMFT) index,[13] were performed using mouth mirrors, explorers, periodontal probes, and a portable dental LED light. Gingival bleeding, calculus, and periodontal pocket depths were assessed using a Williams periodontal probe according to the community periodontal index (CPI).[14] Ten index teeth (#11, #16, #17, #26, #27, #31, #36, #37, #46, and #47) were probed at six sites, including mesiobuccal, mid-buccal, distobuccal, and the corresponding lingual sites. The highest score was recorded for each sextant. Possible CPI scores were: 0 (healthy), 1 (bleeding after probing, observed directly or by mouth mirror), 2 (calculus detected during probing, but the entire black band of the probe remained visible), 3 (4−5 mm periodontal pocket depth), and 4 (≥ 6 mm periodontal pocket depth).

All blood samples were collected after overnight fasting and kept at -80°C until subsequent assay. Complete blood counts, serum creatinine and serum lipid profiles were determined in all patients. Concentrations of plasma triglycerides, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), uric acid, albumin, creatinine and glucose were measured by standard commercial methods using a parallel, multi-channel analyzer (Hitachi 7170A, Tokyo, Japan) as previously reported.[12] The concentration of plasma visfatin was determined using a commercial enzyme immunoassay (EIA) kit (Phoenix Pharmaceuticals, Belmont, CA) with a detection limit of 0.1 ng/mL, and the plasma concentration of CRP was measured using a high-sensitivity method (IMMAGE, Beckman Coulter, Immunochemistry Systems, Brea, CA) with a detection limit of 0.2 mg/L. The intra-assay coefficients of variation were 4.0−7.3% for visfatin and 4.2−8.7% for high-sensitivity CRP. The samples were measured in duplicate in a single experiment.

Statistical analysis

Data normality was analyzed using the Kolmogorov-Smirnov test. Continuous, normally distributed variables were presented as mean ± SD, while non-normally distributed variables were presented as median (inter-quartile range). Statistical differences in variables were compared using one-way analysis of variance (ANOVA) for normally distributed variables. Categorical variables were presented as frequencies and/or percentages, and inter-group comparisons were analyzed using the chi-square test. Since the distributions of plasma visfatin, triglycerides, creatinine and hs-CRP were skewed, logarithmically transformed values were used for statistical analysis with significant differences being determined using ANOVA.

The association between visfatin and PD severity was analyzed using logistic regression with those having a CPI score of 0 serving as the reference group. In stratified analysis, multivariate-adjusted odds ratios (ORs) associated with a doubling of PD severity were

calculated and presented with 95% confidence intervals (CIs). Pearson's correlation analysis was used to examine correlations between the concentration of plasma visfatin and other biomarkers. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SAS statistical software, version 8.2 (SAS Institute; Cary, NC, USA).

Results

Table 1. Baseline characteristics of the study patients with coronary artery disease (n = 496)

Characteristics	*Total (n = 496)*
Age, mean (SD), years	67.1 ± 11.8
Male, n (%)	389 (78.4)
Diabetes mellitus, n (%)	202 (40.7)
Hypertension, n (%)	370 (74.6)
Hyperlipidemia, n (%)	345 (69.6)
Smoking, n (%)	219 (44.2)
Body mass index (kg/m^2)	25.6 ± 12.4
Waist circumference (cm)	91.1 ± 9.7
Systolic blood pressure (mmHg)	134 ± 23
Diastolic blood pressure (mmHg)	77 ± 14
Fasting sugar (mg/dL)	145.4 ± 71.3
Total cholesterol (mg/dL)	176.3 ± 42.6
Triglyceride (mg/dL) (media)	142.9 ± 94.9 (117.0)
HDL-cholesterol (mg/dL)	38.8 ± 11.1
LDL-cholesterol (mg/dL)	106.0 ± 36.0
Uric acid (mg/dL) (media)	6.5 ± 1.7
Creatinine (mg/dL) (media)	1.6 ± 1.5 (1.2)
Hs-CRP (mg/L)	9.9 ± 24.1 (3.4)
White blood cell count (× 10^9/L)	8.697 ± 3.341
Visfatin (ng/mL) (media)	13.4 ± 18.1 (8.2)
Community periodontal index, n (%)	
Scores 0	123 (24.8)
Scores 1	47 (9.5)
Scores 2	221 (44.6)
Scores 3 + 4	105 (21.2)
Teeth number, n (%)	
0-16	204 (41.1)
17-24	161 (32.5)
25-32	131 (26.4)

Data are expressed as %, mean ± SD and sometimes (median) for variables with a non-normal distribution. HDL: high-density lipoprotein; LDL: low-density lipoprotein.

A total of 496 patients completed this study and their demographic and clinical characteristics are shown in Table 1. Their mean age was 67.1 ± 11.8 years (range, 28-97 years), 78 % were male, 41% had diabetes, 75% had hypertension, and 70% had hyperlipidemia. Forty-seven patients (10%) had a CPI score of 1, 221 (45%) had a CPI score of 2, and 105 (21%) had a CPI scores 3-4.

The patients with CAD and PD had a significantly higher plasma visfatin concentration than that in patients with CAD without PD (13.8 ± 19.0 ng/mL vs. 8.3 ± 3.7 ng/mL; $p = 0.002$). The association between plasma visfatin level and the risk of PD was analyzed according to CPI score. The patients with a score of 3−4 had significantly higher hs-CRP and visfatin levels and Framingham 10-year risk score than those in patients with a score of 1 (Table 2). Plasma visfatin concentrations significantly varied with CPI scores ($p < 0.0001$) (Fig. 1).

Uni- and multivariate logistic regression analyses revealed that plasma visfatin levels were positively associated with the CPI score. Multiple logistic regression analysis showed that the fully adjusted ORs for CPI score in patients with a score of 1, 2, and 3-4 were 1.058 (95% CI: 1.006−1.114), 1.170 (95% CI: 1.010−1.356) and 1.131 (95% CI: 1.054−1.214),

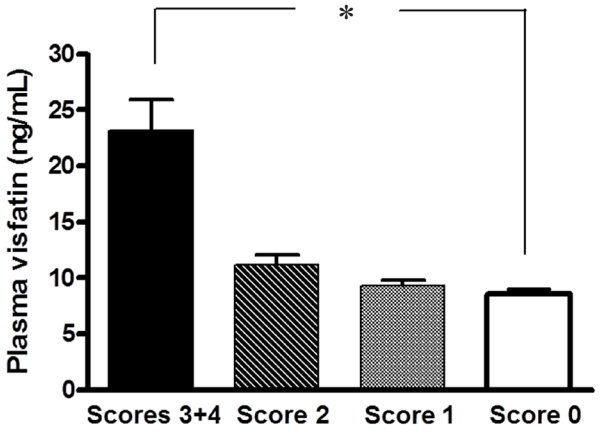

*Fig. 1 Variation in mean plasma visfatin concentrations with community periodontal index scores (*p < 0.0001). Significance of difference determined by one-way analysis of variance.*

Table 2. Comparison of clinical and biochemical characteristics by community periodontal index classes

	Community periodontal index classes			
Variable	Score 1	Score 2	Scores 3 + 4	*p*-value
No	47	221	105	
Sex (male/female)	37/10	172/49	89/16	0.347
Age (yrs)	63.7 ± 10.1	65.5 ± 10.9	67.1 ± 11.1	0.180
Body mass index (kg/m^2)	26.5 ± 6.1	25.7 ± 3.4	26.2 ± 4.1	0.350
Waist circumference (cm)	91.2 ± 10.2	90.8 ± 9.3	93.1 ± 9.9	0.138
Hypertension (n, %)	35 (74.5)	171 (77.4)	80 (76.2)	0.904
Hyperlipidemia (n, %)	34 (72.3)	158 (71.5)	75 (71.4)	0.992
Diabetes mellitus (n, %)	17 (36.2)	89 (40.3)	48 (45.7)	0.484
Current smoking (n, %)	20 (42.6)	94 (42.5)	55 (52.4)	0.472
Systolic blood pressure (mmHg)	129 ± 19	134 ± 22	133 ± 21	0.298
Diastolic blood pressure (mmHg)	75 ± 13	78 ± 15	77 ± 12	0.491
Fasting sugar (mg/dL)	129.3 ± 56.1	142.4 ± 68.8	146.6 ± 69.3	0.391
T-cholesterol (mg/dL)	184.4 ± 57.3	177.0 ± 39.0	175.4 ± 40.3	0.459
Triglyceride (mg/dL)	116.0 (94.0−177.0)	121.0 (86.5−177.5)	118.0 (90.5−190.0)	0.639
HDL-cholesterol (mg/dL)	40.0 ± 12.2	38.7 ± 11.1	38.0 ± 9.2	0.575
LDL-cholesterol (mg/dL)	111.8 ± 44.6	106.2 ± 34.9	103.7 ± 31.8	0.437
Uric acid (mg/dL)	6.3 ± 1.7	6.3 ± 1.8	6.8 ± 1.8	0.152
Albumin (g/dL)	4.1 ± 0.4	4.0 ± 0.3	4.0 ± 0.3	0.262
Creatinine (mg/dL)	1.2 (1.0−1.4)	1.3 (1.1−1.6)	1.2 (1.1−1.5)	0.528
Hs-CRP (mg/L)	2.3 (0.6−5.5)	3.3 (1.2−8.5)	3.6 (1.5−10.0)	0.025
White blood cell count (×10^9/L)	8.369 ± 3.421	8.545 ± 2.978	8.449 ± 3.095	0.923
Visfatin (ng/mL)	7.1 (5.6−11.3)	8.6 (6.3−10.2)	9.7 (7.4−20.0)	< .0001
No. of diseased vessels				
1	17 (36.2)	78 (35.3)	34 (32.4)	0.611
2	10 (21.3)	60 (27.2)	35 (33.3)	
3	20 (42.6)	83 (37.6)	36 (34.3)	
Framingham-10 year risk score	9.9 ± 8.2	13.6 ± 8.4	15.4 ± 8.8	0.039

* $p < 0.05$; HR: hazard ratio; CI: confidence interval. Hazard ratios were calculated using Cox proportional regression analysis stratified by sex, age group, and the health care use index year during the 10-year follow-up period. Adjustments were made for age, sex, occupation, living area, income, urbanization, and selected comorbidities, such as diabetes, dyslipidemia, hypertension, and coronary heart disease, in the patients. Hs-CRP: High-sensitivity C-reactive protein

respectively (Table 3).

Pearson's correlation analysis revealed that the concentration of visfatin was positively correlated with male gender, hs-CRP, neutrophil-to-lymphocyte ratio, CPI, and the presence of missing teeth (Table 4).

Discussion

In the present study, we found that visfatin levels were correlated with sex, hs-CRP, neutrophil-to-lymphocyte ratio, CPI, and the number of missing teeth. In addition, the concentration of visfatin was higher in patients with PD compared to those without. Moreover, the level of plasma visfatin was independently associated with the severity of PD. These findings are consistent with current evidence regarding the association between inflammation and PD.[15,16]

Several in vitro experiments have demonstrated that visfatin is produced in adipose tissue, and that adipokine levels are increased in patients with obesity and other systemic

Table 3. The impact of plasma visfatin level on community periodontal index classes evaluated by univariate and multivariate analyses

	Community periodontal index classes			
Factor	Score 0	Score 1	Score 2	Scores 3 + 4
Plasma visfatin				
Crude OR	1.00 (reference)	1.035	1.076	1.111
Adjusted OR[a]	1.00 (reference)	1.058	1.170	1.131
95% CI		1.006-1.114	1.010-1.356	1.054-1.214
p-value		0.030	0.036	0.001

[a]The confounders adjusted for in this model are sex, age, body mass index, fasting sugar, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride, smoking status, and coronary disease (single vs. multiple vessel disease). OR: Odd ratio; CI: Confidence interval

Table 4. Pearson's correlation coefficients between plasma visfatin and relevant parameters

Variable	Visfatin level	
	r	*p*-value
Age	0.031	0.485
Male gender	0.133	0.003
Body mass index	0.053	0.359
Systolic blood pressure	0.027	0.633
Diastolic blood pressure	0.031	0.591
Fasting sugar	0.022	0.421
Total-cholesterol	0.024	0.590
Triglyceride	0.011	0.825
HDL-cholesterol	0.027	0.549
LDL-cholesterol	0.044	0.335
Uric acid	0.058	0.247
Albumin	-0.027	0.569
Creatinine	-0.040	0.377
Hs-CRP	0.161	0.046
White blood cell count	0.087	0.062
Neutrophil-to-lymphocyte ratio	0.109	0.043
Community periodontal index	0.214	0.008
Decayed teeth	-0.032	0.612
Missing teeth	0.155	0.033
Filled teeth	-0.032	0.528
Natural teeth	-0.125	0.121

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CPI: Community periodontal index; Hs-CRP: High-sensitivity C-reactive protein

diseases. Therefore, visfatin may contribute to the detrimental effects of systemic diseases on the periodontium.[17,18] Visfatin has also been shown to induce upregulation of several genes including matrix metalloproteinase-1 (MMP-1) and chemokine (c-c motif) ligand 2 (CCL2) in periodontal ligament cells. Moreover, this visfatin-stimulated upregulation of MMP-1 and CCL2 expressions has been shown to result in increased MMP-1 and CCL2 protein levels.[17] MMP-1 plays a critical role in the modeling and remodeling of the extracellular matrix through the degradation of collagen type I and other types of collagen. Gingival levels of MMP-1, which have been reported to be enhanced at sites of periodontitis, have also been found to be reduced by periodontal treatment.[19,20] CCL2, also known as monocyte chemoattractant protein 1, is produced by a variety of cell types. Not only does it regulate the migration and infiltration of monocytes, memory T lymphocytes, and natural killer cells, but it also seems to influence T-cell immunity. Increased CCL2 levels have been found in gingival crevicular fluid and gingiva from inflamed sites.[21,22] It is therefore reasonable to suggest that visfatin may contribute to periodontal inflammation and destruction through the production of these molecules. In the present study, visfatin was correlated with CPI score, the number of missing teeth, neutrophil-to-lymphocyte ratio, and hs-CRP concentration, thereby raising the possibility that visfatin may act through an inflammatory response and may play an important role in the pathophysiology of periodontitis in CAD patients.

Periodontal disease is a common finding among patients with cardiovascular diseases.[1,23,24] We also found that patients with a CPI score of 3-4 had significantly higher plasma visfatin and hs-CRP levels, and significantly higher Framingham 10-year risk score compared to those in patients with a CPI score of 1. A previous study also suggested

that persistent infections such as chronic periodontitis may influence the changes in systemic levels of hs-CRP, LDL, and HDL, which potentially have an impact on inflammation-associated atherosclerotic processes such as CAD.[25] Janket et al. reported that the number (i.e., quantity) of remaining teeth and their maintenance (i.e., quality), and removing potential inflammatory foci such as pericoronitis or retained root tips may positively impact cardiovascular survival.[26] Furthermore, Mahendra et al. suggested a possible relationship between periodontal infection and atherosclerosis that may help to develop preventive treatment strategies.[27] Taken together, these findings support the link between inflammation, PD, and cardiovascular disease.

Further supporting the role of visfatin in the relationship between inflammation and PD, previous studies have demonstrated that visfatin can induce the production of pro-inflammatory cytokines such as tumor necrosis factor-α and IL-8 by peripheral mononuclear cells. Visfatin has also been shown to promote macrophage survival and inhibit neutrophil apoptosis. In addition, it has been shown to affect leukocyte recruitment by upregulating cell adhesion molecules including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin. Furthermore, visfatin has been shown to stimulate endothelial cells to release various mediators such as IL-6, IL-8, and monocyte chemotactic protein-1.[28] It is, therefore, reasonable to suggest that visfatin may act as a pro-inflammatory cytokine that plays a role in chronic inflammation, thereby contributing to the pathogenesis of PD and cardiovascular disease.[25] Our findings support the hypothesis that visfatin may act through an inflammation response and that it plays an important role in the pathophysiology of PD in patients with CAD.[1,25]

There are several limitations to this study. First, it has a cross-sectional design. Second, the blood samples were collected from patients with PD in the chronic stage of the illness. Both limit the ability to infer a causal relationship between increased plasma visfatin concentrations and PD. Lastly, our analyses were based on single measurements of visfatin, that may not reflect the relationship between visfatin levels and PD over time.

In conclusion, we found elevated plasma levels of visfatin in PD patients with CAD, suggesting a close relationship between visfatin and chronic inflammation. Visfatin may also play a role in complex interactions involving the immune system, adipose tissue, and inflammation. However, a large-scale prospective cohort study is still necessary to determine the potential causal relationship between visfatin and the development of PD and CAD.

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