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ORIGINAL ARTICLE

Associations between plasma nesfatin-1 levels and the presence and severity of coronary artery disease

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Abstract

Nesfatin-1 is a recently identified anorexigenic peptide mainly secreted from the brain and adipose tissue. Although nesfatin-1 may have pro-inflammatory and apoptotic properties, the association between plasma nesfatin-1 levels and coronary artery disease (CAD) has not been clarified yet. We investigated plasma nesfatin-1 levels in 302 patients undergoing elective coronary angiography. Of the 302 study patients, CAD was present in 172 (57%), of whom 67 had 1-vessel, 49 had 2-vessel, and 56 had 3-vessel disease. Compared with 130 patients without CAD, 172 with CAD had higher plasma nesfatin-1 levels (median 0.21 vs. 0.17 ng/mL, $P<0.01$). A stepwise increase in nesfatin-1 levels was found depending on the number of > 50% stenotic coronary vessels: 0.17 in CAD(−), 0.20 in 1-vessel, 0.21 in 2-vessel, and 0.22 ng/mL in 3-vessel disease ($P<0.05$). A high nesfatin-1 level (> 0.19 ng/mL) was found in 43% of patients with CAD(−), 55% of those with 1-vessel, 55% of those with 2-vessel, and 68% of those with 3-vessel disease ($P<0.05$). Nesfatin-1 levels significantly correlated with the number of > 50% stenotic coronary segments ($r=0.14$, $P<0.02$). In multivariate analysis, plasma nesfatin-1 levels were a significant factor for CAD independent of atherosclerotic risk factors. The odds ratio for CAD was 1.71 (95% CI 1.01–2.91) for high nesfatin-1 level of > 0.19 ng/mL ($P<0.05$). Thus, plasma nesfatin-1 levels were found to be high in patients with CAD and were associated with CAD independent of atherosclerotic risk factors, suggesting that high nesfatin-1 levels in patients with CAD may play a role in the development of coronary atherosclerosis.

Keywords Atherosclerosis · Biomarker · Coronary artery disease · Nesfatin-1

Introduction

Nesfatin-1 is a recently identified anorexigenic peptide derived from nucleobindin 2 (NUCB2), which is mainly secreted by the brain and adipose tissue [1, 2]. Nesfatin-1 is recognized to play a role in energy and glucose homeostasis as well as regulating food intake [3, 4]. However, studies on the association between diabetes mellitus (DM) and blood nesfatin-1 levels have reported conflicting results. Some studies reported high nesfatin-1 levels in patients with type 2 DM [5], whereas others reported low nesfatin-1 levels in such patients [6, 7]. Interestingly, nesfatin-1 was suggested to have anti-inflammatory and anti-apoptotic effects on subarachnoid hemorrhaging brain injury [8] and traumatic brain injury [9] in rat models. However, nesfatin-1 was recently reported to induce pro-inflammatory mediators [10] and to promote apoptosis [11] in vitro. High nesfatin-1 levels in blood were also reported in patients with several inflammatory diseases, such as osteoarthritis and chronic obstructive pulmonary disease (COPD) [12–14]. Thus, nesfatin-1 may have pro-inflammatory and apoptotic properties.

The role of nesfatin-1 in the process of atherosclerosis has not been elucidated yet. Regarding blood nesfatin-1 levels in patients with atherosclerotic diseases, one study [15] reported that plasma nesfatin-1 levels were low in patients with acute myocardial infarction (AMI). However, low

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nesfatin-1 levels in AMI patients may be probably due to reduced food intake after AMI. To elucidate the association between plasma nesfatin-1 levels and the presence and severity of CAD, we investigated plasma nesfatin-1 levels in 302 patients undergoing elective coronary angiography.

Methods

Study patients

We investigated plasma nesfatin-1 levels in 302 consecutive patients undergoing elective coronary angiography for suspected CAD at Tokyo Medical Center from June 2009 to September 2016. Patients with acute coronary syndromes, such as AMI and unstable angina, were excluded from this study. Patients with a history of percutaneous coronary intervention or cardiac surgery were excluded. Patients with heart failure or those with malignancy were also excluded from this study. Hypertension was defined as blood pressures ≥ 140/90 mmHg or on drugs, and 185 (61%) patients were taking anti-hypertensive drugs. Hyperlipidemia was defined as an LDL cholesterol level of > 140 mg/dL or on drugs, and 118 (39%) patients were taking statins. Diabetes mellitus (DM) [fasting plasma glucose (FPG) level ≥ 126 mg/dL or on treatment] was present in 80 (26%) patients, and 125 (41%) were smokers (≥ 10 pack-years). Our study was approved by the institutional ethics committee of our hospital (R07-054/R15-056). After written informed consent was obtained, overnight-fasting blood samples were taken on the morning of the day when coronary angiography was performed.

Measurements of plasma nesfatin-1 and C-reactive protein (CRP) levels

Blood samples were collected in EDTA-containing tubes, and plasma was stored at − 80 °C. Plasma nesfatin-1 levels were measured in one batch by an enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (LifeSpan BioScience, Seattle, USA) at Ochanomizu University according to the manufacturer's instructions. The intra- and inter-assay coefficients of variation were < 10% and < 12%, respectively. Plasma high-sensitivity C-reactive protein (hsCRP) levels were also measured using a BNII nephelometer (Dade Behring, Tokyo, Japan).

Coronary angiography

Angiograms were recorded on a cineangiogram system (Philips Electronics Japan, Tokyo, Japan). The presence of CAD was defined as at least one coronary artery having > 50% luminal diameter stenosis on angiograms. The severity of CAD was represented as the numbers of > 50% stenotic vessels and stenotic segments and the severity score of stenosis. The degree of coronary stenosis in each segment was scored from 0 to 4 points (0, ≤ 25%; 1, 26–50%; 2, 51–75%; 3, 76–90%; 4, > 90% stenosis), and the severity score was defined as the sum of scores of all segments. Coronary artery segments were defined as 29 segments according to the Coronary Artery Surgery Study (CASS) classification. All angiograms were evaluated by a single cardiologist (Y.M.), blinded to the clinical and laboratory data.

Statistical analysis

Differences between 2 groups were evaluated by unpaired *t* test for parametric variables, by Mann–Whitney *U* test for nonparametric variables, and by Chi squared test for categorical variables. Differences among ≥ 3 groups were evaluated by an analysis of variance with Scheffe's test for parametric variables, by Kruskal–Wallis test for nonparametric variables, and by Chi squared test for categorical variables. Correlations between nesfatin-1 levels and the severity of CAD were evaluated by Spearman's rank correlation test and by multiple linear regression analysis. To determine the cut-off point of plasma nesfatin-1 levels for CAD, a relative cumulative frequency distribution curve was created, and then the optimum cut-off point was determined to be 0.19 ng/mL. A multiple logistic regression analysis was used to determine the independent association between nesfatin-1 levels and the presence of CAD. The variables included in this analysis were age, gender, body mass index (BMI), hypertension, hyperlipidemia, statin use, DM, and HDL cholesterol (< 40 mg/dL) and nesfatin-1 (> 0.19 ng/mL) levels. A P value of < 0.05 was considered to be statistically significant. Results are presented as the mean ± SD or the median value. Statistical procedures were performed using the IBM SPSS Statistics version 25 software (IBM, Chicago, IL, USA).

Results

Among the 302 study patients, CAD was present in 172 patients (57%) [1-vessel disease (1-VD), $n = 67$; 2-vessel disease (2-VD), $n = 49$; 3-vessel disease (3-VD), $n = 56$]. Compared with 130 patients without CAD, 172 patients with CAD were older and had a male predominance; higher prevalence of hypertension, hyperlipidemia, DM, and smoking; and lower HDL cholesterol levels (Table 1). Plasma hsCRP levels were higher in patients with CAD than in those without CAD (median 0.62 vs. 0.46 mg/L, $P < 0.02$). Notably, plasma nesfatin-1 levels were significantly higher in patients with CAD than in those without CAD (median 0.21 vs. 0.17 ng/mL, $P < 0.01$) (Fig. 1). A stepwise increase

Table 1 Clinical characteristics and plasma nesfatin-1 levels of patients with and without CAD

	CAD(−) ($n=130$)	*P* value CAD(−) vs. CAD	CAD ($n=172$)	1-VD ($n=67$)	2-VD ($n=49$)	3-VD ($n=56$)	*P* value among 4 groups
Age (years)	65 ± 11	< 0.001	70 ± 9	68 ± 9	69 ± 10	72 ± 8	< 0.001
Gender (male)	78 (60%)	< 0.001	137 (80%)	55 (82%)	35 (71%)	47 (84%)	< 0.005
BMI (kg/m^2)	24.5 ± 4.8	NS	24.0 ± 3.2	24.2 ± 3.4	24.1 ± 3.1	23.6 ± 3.2	NS
Hypertension	80 (62%)	< 0.001	137 (80%)	50 (75%)	38 (78%)	49 (88%)	< 0.005
SBP (mmHg)	130 ± 21	NS	132 ± 21	130 ± 19	135 ± 20	132 ± 25	NS
Diabetes mellitus	20 (15%)	< 0.001	60 (35%)	19 (28%)	18 (37%)	23 (41%)	< 0.001
HbA1c (%)	5.9 ± 0.7	< 0.002	6.3 ± 0.9	6.1 ± 0.8	6.4 ± 0.9	6.4 ± 1.0	< 0.005
Smoking	41 (32%)	< 0.01	84 (49%)	36 (54%)	23 (47%)	25 (45%)	< 0.025
Hyperlipidemia	57 (44%)	< 0.025	101 (59%)	35 (52%)	32 (65%)	34 (61%)	< 0.05
Statin	37 (28%)	< 0.005	81 (47%)	29 (43%)	24 (49%)	28 (50%)	< 0.01
LDL-C (mg/dL)	114 ± 28	NS	114 ± 30	109 ± 30	117 ± 32	119 ± 29	NS
HDL-C (mg/dL)	59 ± 15	< 0.001	50 ± 12	51 ± 12	51 ± 11	48 ± 12	< 0.001
hsCRP (mg/L)	0.46 (0.25, 1.19)	< 0.02	0.62 (0.35, 1.37)	0.64 (0.32, 1.33)	0.57 (0.30, 1.19)	0.70 (0.42, 1.74)	NS
Nesfatin-1 levels (ng/mL)	0.17 (0.12, 0.28)	< 0.01	0.21 (0.15, 0.32)	0.20 (0.16, 0.32)	0.21 (0.15, 0.32)	0.22 (0.15, 0.37)	< 0.05
Nesfatin-1 > 0.19 ng/mL	56 (43%)	< 0.01	102 (59%)	37 (55%)	27 (55%)	38 (68%)	< 0.025

Data represent the mean ± SD or the number (%) of patients, with the exception of hsCRP and nesfatin-1 levels which are presented as the median value and interquartile range

BMI body mass index, *SBP* systolic blood pressure, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol

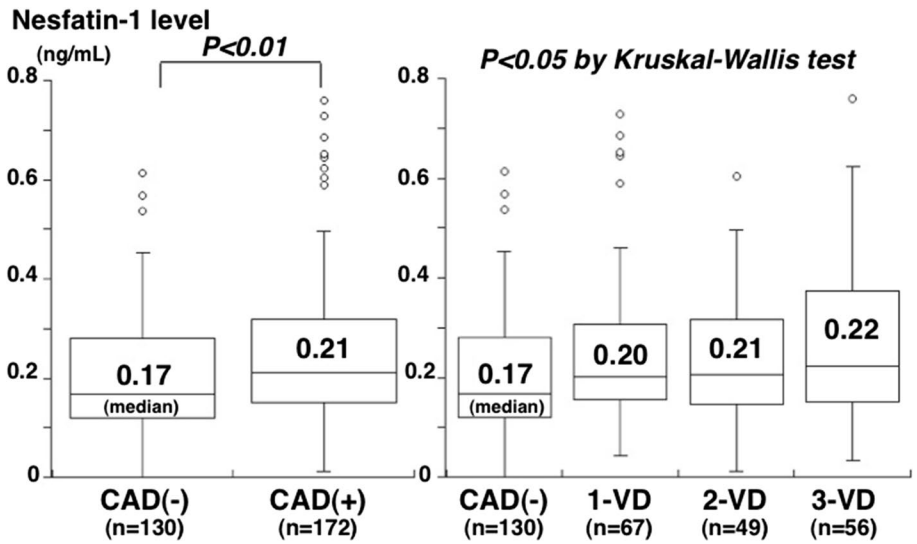

Fig. 1 Plasma nesfatin-1 levels and the presence of CAD or the number of stenotic coronary vessels. Plasma nesfatin-1 levels were significantly higher in CAD than in CAD(−) (left). Furthermore, nesfatin-1 levels in 4 groups of CAD(−), 1-VD, 2-VD, and 3-VD were 0.17, 0.20, 0.21, and 0.22 ng/mL, respectively, and were highest in 3-VD ($P<0.05$ by Kruskal–Wallis test) (right). The central line represents the median, and the box represents the 25th–75th percentiles. The whiskers represent the lowest and highest value in the 25th percentile minus 1.5 IQR and 75th percentile plus 1.5 IQR, respectively

in nesfatin-1 levels was found depending on the number of > 50% stenotic coronary vessels: 0.17 in CAD(−), 0.20 in 1-VD, 0.21 in 2-VD, and 0.22 ng/mL in 3-VD ($P<0.05$) (Fig. 1). A high nesfatin-1 level (> 0.19 ng/mL) was present in 43% of patients with CAD(−), 55% of those with 1-VD, 55% of those with 2-VD, and 68% of those with 3-VD ($P<0.025$). Furthermore, nesfatin-1 levels significantly, but weakly, correlated with the number of > 50% stenotic coronary segments and the severity score (rs = 0.14 and rs = 0.13, $P<0.02$ by Spearman's rank correlation test) (Table 2). However, in the multiple linear regression analysis which included age, BMI, blood pressures, and LDL cholesterol, HDL cholesterol, HbA1c, and nesfatin-1 levels, no significant correlation was found between nesfatin-1 levels and the number of > 50% stenotic segments or the severity score (Table 3).

Of the 302 study patients, 80 (26%) had DM, of whom 54 were receiving treatment (insulin or anti-diabetic

Table 2 Correlations of plasma nesfatin-1 levels with the severity of CAD and atherosclerotic risk factors

	rs[a]	*P* value
The number of > 50% stenotic coronary segments	0.14	< 0.02
The severity score of stenosis	0.13	< 0.02
Age (years)	0.05	NS
Systoric blood pressure (mmHg)	0.01	NS
BMI (kg/m^2)	− 0.07	NS
HbA1c (%)	0.09	NS
LDL cholesterol level (mg/dL)	− 0.01	NS
HDL cholesterol level (mg/dL)	− 0.10	NS
hsCRP level (mg/L)	0.02	NS

[a]By Spearman's rank correlation test

Table 3 Factors associated with the severity of CAD (multiple linear regression analysis of the 302 study patients)

	β	*P* value
The number of > 50% stenotic coronary segments		
Age (years)	0.16	< 0.01
BMI (kg/m^2)	− 0.14	< 0.02
HbA1c (%)	0.13	< 0.05
HDL cholesterol level (mg/dL)	− 0.27	< 0.001
The severity score of stenosis		
Age (years)	0.18	< 0.01
BMI (kg/m^2)	− 0.14	< 0.02
HbA1c (%)	0.13	< 0.05
HDL cholesterol level (mg/dL)	− 0.28	< 0.001

The analysis included age, BMI, systolic blood pressure, and HbA1c, LDL cholesterol, HDL cholesterol and nesfatin-1 levels

drugs). Notably, patients with DM had higher prevalence of CAD than those without DM (75% vs. 50%, $P < 0.001$). However, nesfatin-1 levels did not significantly differ between patients with and without DM (median 0.23 vs. 0.19 ng/mL) or between DM patients receiving and not receiving treatment (0.24 vs. 0.22 ng/mL). Furthermore, nesfatin-1 levels did not significantly correlate with BMI, HbA1c or hsCRP levels (Table 2). To elucidate the independent associations between nesfatin-1 levels and the presence of CAD, variables (age, gender, hypertension, smoking, DM, BMI, hyperlipidemia, statin use, and HDL cholesterol and nesfatin-1 levels) were entered into a multiple logistic regression model. Plasma nesfatin-1 levels were found to be a significant factor associated with the presence of CAD independent of atherosclerotic risk factors. The odds ratio for CAD was 1.71 (95% CI 1.01–2.91) for high nesfatin-1 level of > 0.19 ng/mL ($P < 0.05$) (Table 4).

Table 4 Factors associated with the presence of CAD (multiple logistic regression analysis of the 302 study patients)

	Odds ratio	95% CI	*P* value
Age (per 10-year increase)	1.41	1.08–1.86	< 0.02
Male gender	3.11	1.69–5.73	< 0.001
Statin use	2.92	1.63–5.23	< 0.001
Diabetes mellitus	2.20	1.15–4.23	< 0.02
Low HDL-C level (< 40 mg/dL)	2.73	1.18–6.31	< 0.02
High nesfatin-1 level (> 0.19 ng/mL)	1.71	1.01–2.91	< 0.05

The dependent variable was the presence of CAD. The analysis included age, gender, hypertension, hyperlipidemia, statin use, DM, BMI, and HDL cholesterol (< 40 mg/dL) and nesfatin-1 (> 0.19 ng/mL) levels

Discussion

In the present study, plasma nesfatin-1 levels were significantly higher in patients with CAD than in those without CAD, but they did not correlate with BMI, HbA1c, or hsCRP levels. High plasma nesfatin-1 levels were a significant factor associated with the presence of CAD independent of atherosclerotic risk factors. However, nesfatin-1 levels only weakly correlated with the severity of CAD, defined as the numbers of stenotic vessels and segments, and no significant correlation was found in multiple linear regression analysis.

Although nesfatin-1 was previously suggested to have anti-inflammatory and anti-apoptotic effects on brain injury in rats [8, 9], nesfatin-1 has recently been reported to induce pro-inflammatory mediators and to promote apoptosis in vitro [10, 11]. Blood nesfatin-1 levels were reported to be high in patients with inflammatory diseases, such as COPD, osteoarthritis, and major depressive disorders [12–14], and to correlate with hsCRP and interleukin-6 levels [12–14, 16]. These findings suggest that nesfatin-1 may have pro-inflammatory and apoptotic properties in humans, in contrast to anti-inflammatory and anti-apoptotic properties on rat brain injury. Furthermore, nesfatin-1 was demonstrated to promote the proliferation and migration of vascular smooth muscle cells in vitro [17] and to increase neointimal hyperplasia and vascular remodeling in rats [17, 18]. Nesfatin-1 was also reported to increase sympathetic nerve activity, thereby increasing blood pressures in rats [3, 19]. Blood nesfatin-1 levels correlated with blood pressures in 54 patients with polycystic ovary syndrome [16]. In addition, stress was shown to increase plasma levels and hypothalamic mRNA expression of nesfatin-1 in rats, thus suggesting some role of nesfatin-1 in the stress response [20]. Therefore, nesfatin-1 may have a promoting effect on the progression of atherosclerosis.

The role of nesfatin-1 in the progression of atherosclerosis remains unclear. Regarding blood nesfatin-1 levels in patients with atherosclerotic disease, one study [15] investigated plasma nesfatin-1 levels in 48 patients with AMI, 74 with stable CAD, and 34 controls. They reported nesfatin-1 levels to be low in AMI patients, but no significant difference was found in nesfatin-1 levels between stable CAD and controls. Recently, Robinson et al. [21] measured plasma nesfatin-1 levels in 232 patients with rheumatoid arthritis and evaluated carotid atherosclerosis using ultrasonography, of whom 40% had plaque. They reported that nesfatin-1 levels negatively correlated with carotid intima-media thickness ($\beta = -0.02$, $P < 0.05$), but nesfatin-1 levels tended to positively correlate with carotid plaque ($\beta = +0.81$, $P = $ NS). In the present study, we measured plasma nesfatin-1 levels in 172 patients with stable CAD and 130 without CAD. We found that nesfatin-1 levels were significantly higher in patients with stable CAD than in those without CAD. In the multivariate analysis, nesfatin-1 levels were found to be a significant factor for the presence of CAD independent of atherosclerotic risk factors. Our findings thus suggest that high plasma nesfatin-1 levels may play a role in the development of CAD. Furthermore, we showed that nesfatin-1 levels significantly correlated with the severity of CAD, defined as the numbers of stenotic vessels and segments and the severity score by Spearman's rank correlation test. However, the correlations between plasma nesfatin-1 levels and the severity of CAD were weak. In the multiple linear regression analysis, no significant correlation was found. Moreover, as shown in Fig. 1, there was a substantial overlap in nesfatin-1 levels between patients with and without CAD. Therefore, plasma nesfatin-1 levels in patients with CAD may reflect not only coronary atherosclerosis but also the degree of atherosclerosis in other vascular beds.

Blood nesfatin-1 levels in patients with DM remain controversial, with some studies indicating high nesfatin-1 levels [5] and others indicating low levels [6, 7]. Zhang et al. [5] reported nesfatin-1 levels to be higher in patients with newly diagnosed DM than in controls and to correlate with HbA1c levels. A meta-analysis of 7 studies reported no obvious difference in nesfatin-1 levels between patients with and without DM [22]. However, a subgroup analysis showed higher nesfatin-1 levels in patients with newly diagnosed DM and lower nesfatin-1 levels in DM patients on treatment than in controls [22]. Regarding the association with BMI, Tsuchiya et al. [23] reported that nesfatin-1 levels correlated negatively with BMI, whereas others showed a positive correlation with BMI [5, 16]. In our study, 26% of patients had DM. Plasma nesfatin-1 levels did not differ markedly between patients with and without DM despite receiving anti-diabetic treatment. Moreover, nesfatin-1 levels did not correlate with HbA1c level or BMI, as shown in Table 2. Of note, nesfatin-1 levels were found to be a significant factor associated with CAD independent of DM, BMI, and other atherosclerotic risk factors.

Our study has several limitations. First, in our study, angiography was used to evaluate coronary atherosclerosis. Coronary angiography cannot visualize plaques and only shows lumen characteristics. However, IVUS, which can visualize coronary plaques, was not always performed in our patients. Second, no patient with acute coronary syndrome was included in our study. A further study in patients with acute coronary syndrome, such as unstable angina, is needed to elucidate the potential role of nesfatin-1 in this syndrome. Third, our study was cross-sectional in nature and was unable to establish causality since it only depicted some associations and proposed some hypotheses. Finally, our study was performed in Japanese patients undergoing coronary angiography, who are generally considered to be a highly select population at high risk for CAD. Our results, therefore, may not be applicable to the general or other ethnic populations.

Conclusion

Plasma nesfatin-1 levels in patients with CAD were found to be high, but they did not correlate with BMI or HbA1c levels. High plasma nesfatin-1 levels were a significant factor for the presence of CAD independent of DM and other atherosclerotic risk factors, thus suggesting that nesfatin-1 may play a role in the development of coronary atherosclerosis.

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Compliance with ethical standards

Conflict of interest Our study has no conflicts of interest to disclose.

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