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Association of Serum Visfatin and Vaspin with the Severity of Coronary Artery Disease

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Abstract

Adipose tissues or adipocytes releases signaling proteins called adipokines. Certain adipokines appear to have cardio protective function against myocardial ischaemia/ reperfusion (I/R) injury while others participate in cardiac remodeling. Visfatin also known as nicotinamide phosphoribosyl- transferase, is a cytokine that is highly expressed in visceral fat. The involvement of the levels of this adipokine in cardiovascular disease is still controversial. Similarly low concentration of vaspin levels is associated with the severity of coronary artery disease. The aim of our study was to identify the concentration of the adipokines visfatin and vaspin in patients with coronary artery disease across the spectrum of the disease. A significant difference was observed in visfatin concentration between STEMI and NSTEMI patients. Similarly when vaspin concentration was compared, a remarkable difference was observed between STEMI and NSTEMI groups. There was a significant correlation between vaspin and Left ventricular ejection fraction. In conclusion, visfatin and vaspin concentration are elevated in acute myocardial infarction and could be involved in the pathogenesis of coronary artery disease. More fundamental research on the role of these adipokines in the pathophysiology of the disease is warranted.

Keywords: Adipokines; Adipocytes; Leptin; Visfatin; Vaspin; Cardioprotective.

Introduction

Adipokines also called as adipocytokines are signaling proteins secreted by adipose tissues or adipocytes [1]. Adipocytes (30–50%), pre adipocytes and fibroblasts, collagen fibre matrix, blood vessels and immune cells together constitute adipose tissue. Our understanding of adipocytes physiology began with the discovery of leptin in 1994 [2]. Over the last two decades several other adipokines have been discovered such as adiponectin, resistin, visfatin, apelin, omentin, chemerin, nesfatin and other cytokines, e.g. interleukin-6 (IL6), plasminogen activator inhibitor (PAI-1), monocyte chemoattractant protein 1 (MCP-1) and tumour necrosis factor-a (TNFa) [3]. By distinctive means of signaling pathways and chemical inhibitors, the adipokines performs their function. Adipokines can be a friend or a foe to cardiovascular physiology. For instance, some adipose tissue-derived molecules plays a role as cardioprotective agents against myocardial ischaemia/ reperfusion (I/R) injury while other adipokines may participate in cardiac remodeling [4].

Visfatin, one of the more recently known adipokine, is also known as nicotinamide phosphoribosyl- transferase or Nampt [5, 6]. It is a pre-B cell colony-enhancing factor (PBEF) and a 52- to 55-kDa protein claimed to be a cytokine that is highly expressed in visceral fat [7]. It synergizes with IL-7 and stem cell factors to promote the growth of B cell precursors [8]. It plays a role in mimicking

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insulin by bringing down the blood glucose level. It also actively participates in the pathophysiology of type 2 diabetes mellitus (T2DM), liver disease and chronic kidney disease.yu et al [9]. The role of visfatin in cardiovascular disease is still controversial. Visfatin levels were positively associated with cardiac enzymes in IRA occlusion which suggests the possibility of association of visfatin level in coronary artery disease. In contrast, the visfatin level was also found to be reduced in CAD and HF patients from other reports [10, 11].

Similarly vaspin is also a new adipokine derived from visceral adipose tissue also known as serine protease inhibitor. Data from previous study demonstrated a strong relationship between vaspin and metabolic syndrome in humans. It improves insulin resistance and also plays role in exerting anti-inflammation and anti-apoptotic effects [12]. Studies have shown that low concentration of vaspin levels is associated with the severity of coronary artery disease [13, 14]. There are no studies done in the Indian population using these biomarkers. The main aim of the study was to identify the concentration of the adipokines visfatin and vaspin in patients with coronary artery disease across the spectrum of the disease. We also wanted to determine the clinical characteristics of the patient that have a relationship with the concentration of these adipokines.

Materials and Methods

The study protocol was approved by the Institution Ethics Committee, SRM Medical College Hospital and Research Centre, Kancheepuram, and was conducted between November 2014 and July 2015. Written informed consent was obtained from all patients who participated in the study. Patients with prior HF, severe valvular heart disease, coexisting cancers, connective tissue diseases and cirrhosis were excluded from the study. Demographic characteristics, clinical variables and patient history were obtained from patient interviews and medical records. A total of 5ml of peripheral blood was collected in ethylenediamine tetra acetic acid (EDTA) coated vacutainer tubes from each patient within 48 hours of admission to the cardiac intensive care unit (ICU). Plasma visfatin and vaspin levels were assessed using an enzyme linked immunosorbent assay (ELISA) (RAY BIOTECH, USA). Patients were followed up at 6 months through telephonic interview by investigators blinded to the biomarker levels to assess major adverse cardiovascular events that include all cause mortality, rehospitalizations and coronary artery bypass graft surgery (CABG).

Data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). The differences in the patient characteristics between the three study groups were compared using one way analysis of variance (ANOVA) for continuous variables or Pearson's chi-squared test for variables with frequency distribution. Pearson correlation was used to measure correlation between different variables. A p value of <0.05 was considered as statistically significant. Statistical analysis was performed using computer software programs such as Statistical Package for Social Scientists, SPSS version. 16 (Chicago, IL, USA) and Graph Pad Prism version 5.01 for Windows (San Diego, CA, USA).

Results

The study subjects comprised of patients with STEMI (n = 39), NSTEMI (n = 32), Effort Angina (n= 54) and healthy controls (n = 12). The baseline characteristics of the population were compared with respect to age, gender, body mass index (BMI), left ventricular ejection fraction (LVEF), waist hip ratio (WHR) and risk factors such as diabetes, hypertension and dyslipidemia. Family history of coronary artery disease (CAD) and their smoking status were also recorded and compared between the groups. Their past previous history of stroke and past history of ACS were also compared. Between the four groups gender, hypertension, family history of CAD, history of stroke, past history of ACS, LVEF and visfatin emerged as variables that were different and statistically significant (Table 1).

A significant difference was observed in visfatin concentration between STEMI and NSTEMI patients ($P<.05$) (Figure1a). Similarly when vaspin concentration was compared, a remarkable difference was observed between STEMI and NSTEMI groups (Figure 1b). A significant correlation was seen between vaspin and BMI (P value =0.03, r = - 0.22) (Figure 2a) as well as with vaspin and LVEF (P value = 0.04, r= - 0.19) (Figure 2b).The cut offs derived from receiver operating characteristic (ROC) curves for visfatin to predict MI is 18.63 ng/ml with a AUC of 0.751; p=0.001; sensitivity= 82%, and specificity of 67.2% (Fig.3a) and for vaspin is 201.52 ng/ml with a AUC of 0.66; p=0.003, sensitivity 61% and specificity of 60%) (Fig 3b). When visfatin and vaspin concentration were compared among patients with and without risk factors, no significant difference was observed (Table 2).

Fig. 1a: Visfatin levels in study patients

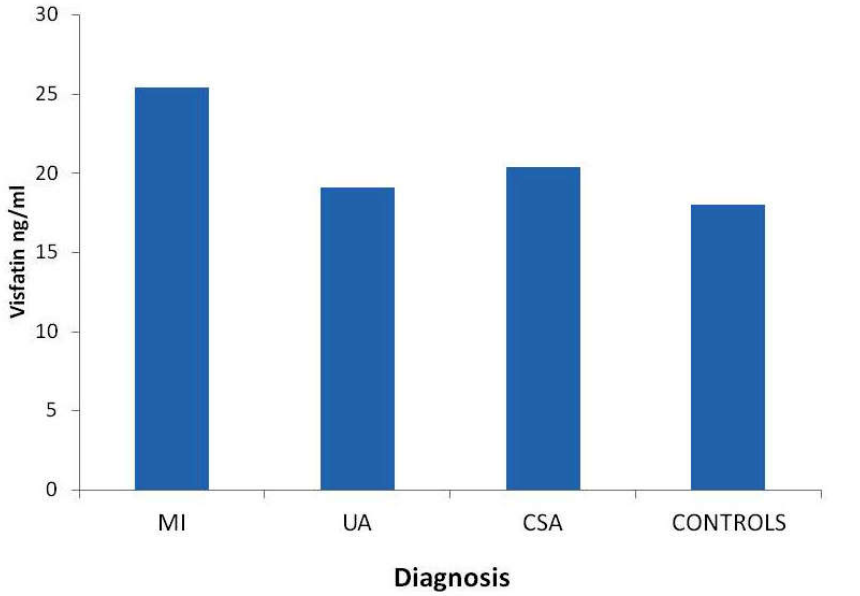
Parameters	STEMI (n=39)	Unstable Angina (n=32)	Effort Angina (n=54)	Controls (n=12)	P Value
Age	50.5±11.3	51.3±9.0	57.5±9.1	51.3±14.7	0.07
Male	32 (84.2%)	25 (78.1%)	32 (59.3%)	10 (83.3%)	0.03
Diabetes mellitus	15(38.5%)	14(43.8%)	28(51.9%)	1(8.3%)	0.04
Hypertension	11 (28.2%)	17(53.1%)	33 (61.1%)	8(66.7%)	0.02
Smoking	10 (25.6%)	10 (31.2%)	7 (13.0%)	3(25.0%)	0.08
Dyslipidemia	5 (12.8%)	3 (9.4%)	4 (7.4%)	NA	0.73
Family history CAD	7 (17.9%)	12 (37.5%)	7 (13.0%)	1 (8.3%)	0.02
History of stroke	5 (12.8%)	3 (9.4%)	9 (16.7%)	4(33.3%)	0.28
Past history of ACS	5 (12.8%)	9 (28.1%)	20(37.0%)	6(50.0%)	0.02
BMI	29.0 ± 22.6	25.9±4.7	29.0±6.4	23.6±2.6	0.53
WHR	1.0±0.08	0.9±0.07	0.9±0.1	0.9±0.09	0.63
Cpk	803.1±0.24	635.5±1780.5	1260.2±2649.7	NA	0.76
Cpk MB	110.3±158.7	75.5±159.9	22.5±7.9	NA	0.69
Urea	26.1±9.2	27.6±15.6	26.0±15.5	22.7±10.2	0.76
Creatinine	1.0±0.24	1.5±3.2	1.6±3.5	1.1±0.2	0.79
LVEF	47.8±11.0	58.3±8.9	55.4±11.5	57.3±11.9	0.001
VISFATIN	23.9(18.8-31.8)	16.90(14.4-21.1)	18.4(14.1-23.4)	18.1(14.2-22.85)	0.001
VASPIN	259.7(129.0-455.5)	112.5(78.0-374.3)	197.3(82.9-333.2)	95.9(15.0-202.5)	0.002

ACS- Acute Coronary Syndrome BMI- Body Mass Index , CAD- Coronary Artery Disease, Cpk MB - Creatine phosphokinase-MB , WHR – Waist Hip Ratio, LVEF – Left Ejection Fraction

Table 2: Visfatin & Vaspin levels in presence of risk factor

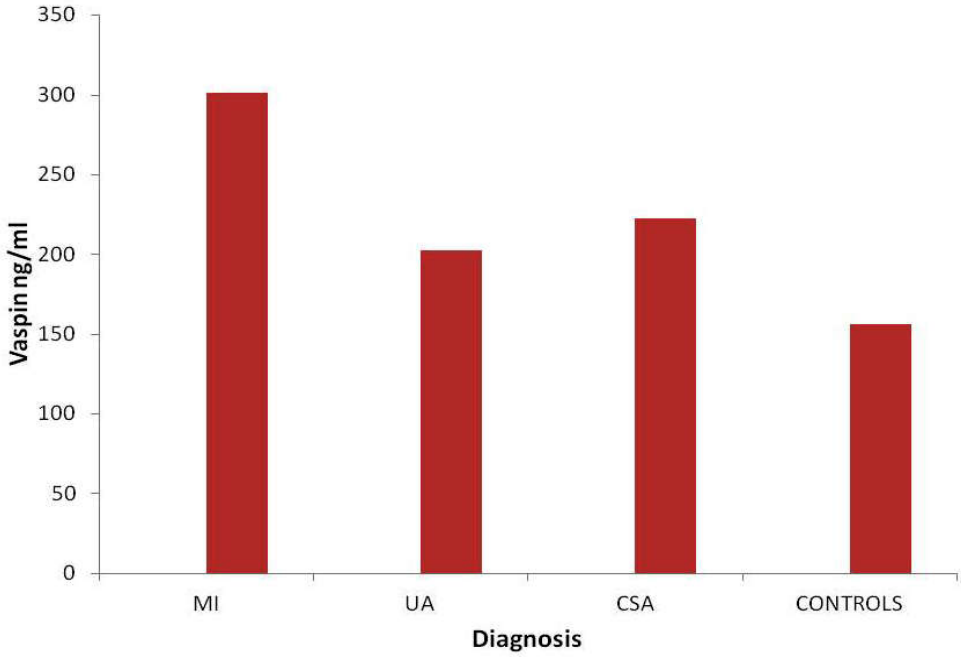
Risk factors	Visfatin(ng/ml)		Vaspin ng/ml		P value	
	Present	Not present	Present	Not present	Visfatin ng/ml	Vaspin ng/ml
Diabetes mellitus	19.5(15.0-23.6)	17.7(13.9-23.6)	183.8(85.8-340.2)	195.5(83.7-328.8)	0.31	0.69
Hypertension	19.6(14.9-23.6)	18.8(14.3-24.1)	129.0(76.5-294.4)	210.7(112.5-344.0)	0.91	0.56
Smoking	22.0(17.8.-29.0)	19.1(14.4-23.6)	182.7(83.0-397.3)	183.4(82.9-331.5)	0.11	0.86
Dyslipidemia	22.3(18.4-28.0)	20.8(14.2-23.8)	171.3(94.3-428.3)	179.8(80.6-280.3)	0.20	0.65
Family history of CAD	22.1(16.8-25.9)	19.3(14.6-23.5)	129.0(77.5-418.6)	195.5(87.1-303.3)	0.28	0.46
History of Stroke	17.7(13.9-23.6)	19.6(14.9-25.1)	196.0(77.6-234.5)	195.5(84.8-339.6)	0.16	0.84
Past History of ACS	16.5(13.6-23.0)	21.8(16.9-26.4)	168.7(80.5-277.2)	186.6(86.5-358.8)	0.00	0.45

ACS- Acute Coronary Syndrome, CAD- Coronary Artery Disease



MI- Myocardial Infarction, UA-Unstable Angina , CSA-Chronic Stable Angina

Fig. 1a: Visfatin levels in study patients



MI- Myocardial Infarction, UA-Unstable Angina , CSA-Chronic Stable Angina

Fig. 1b: Vaspin level in study patients

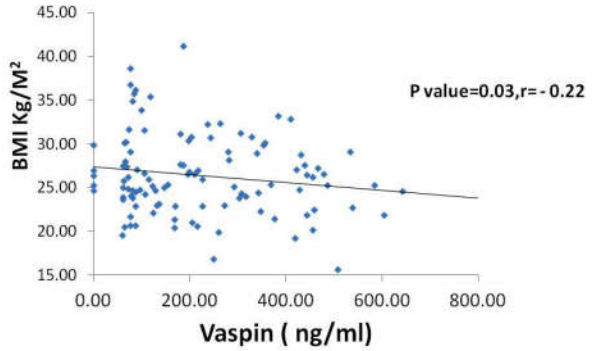


Fig. 2a: Correlation of Vaspin with BMI

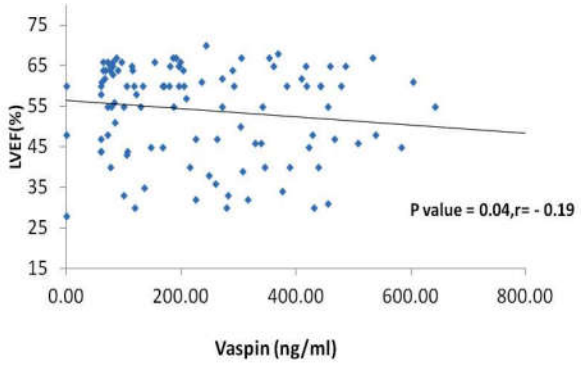


Fig. 2b: Correlation of Vaspin and LVEF

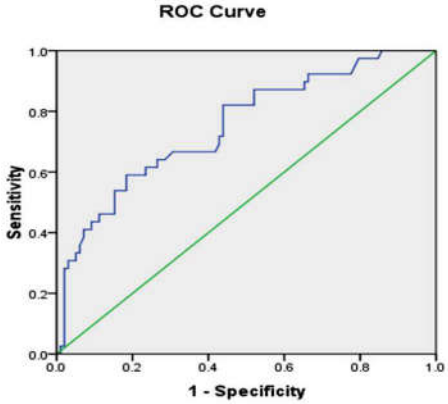


Fig. 3a: Visfatin in acute myocardial infraction. (AUC-0.751; p=0.000; Cut off value for MI=18.63ng/ml, sensitivity=82%, specificity=67.2%)

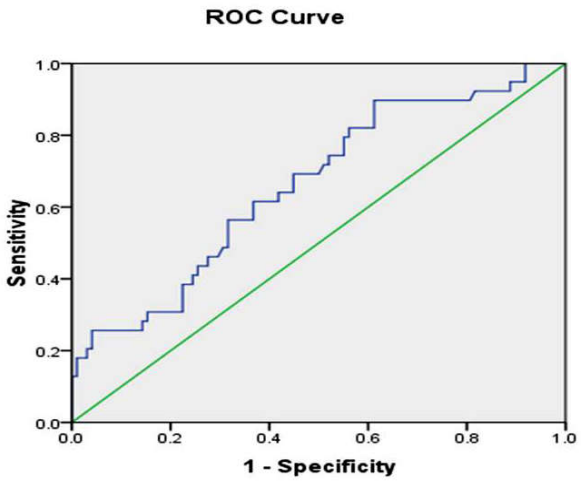


Fig. 3b: Vaspin in Acute Myocardial infraction. (AUC-0.66; p=0.003; Cut off value for MI=201.52 ng/ml, sensitivity=61%, specificity=60%)

Discussion

We have explored the concentration of two novel adipokine visfatin and vaspin in patients with acute myocardial infarction. There are no earlier studies where these adipokine levels were measured in Indian population. The concentration of visfatin is significantly higher in patients with MI as compared with NSTEMI or controls. These findings are in consistent with the study done by Mariyam et al in which the concentration of visfatin was higher in patients with acute myocardial infarction compared to controls [15]. However, this study did not measure visfatin level in patients with NSTEMI. Meta analysis by Yang et al also showed that elevated level of visfatin could increase the risk of MI.

In our study the mean concentration of visfatin was 25.49 ng/ml in patients with MI [16]. In a study performed in the Polish population, the mean visfatin concentration among MI patients was 12.2 ng/ml [17]. There are no published reports on the assessment of visfatin concentration in NSTEMI patients. Our study showed the concentration of visfatin to be higher in STEMI than in NSTEMI. In contrast the study by Hua et al showed the concentration of visfatin to be higher in unstable angina compared to STEMI. (20.4 vs. 17.9 ng/ml) [18] .

When plasma concentration of vaspin was measured in our study it was high in MI patients as compared to subjects with NSTEMI and controls. In a study they measured fasting plasma vaspin levels in 81 subjects with the metabolic syndrome and 241 age and sex matched control subjects without the metabolic syndrome using the enzyme-linked immunosorbent assay. They also analysed sex-specific plasma vaspin concentrations according to the presence of the metabolic syndrome and the severity of coronary atherosclerosis. The result showed that elevated plasma vaspin level was significantly correlated with coronary atherosclerosis in women. Serum vaspin also had a significant correlation with metabolic syndrome in men [19].

The mean concentration of vaspin in our study was 201.52 ng/ml which was a contrast when compared with results of other studies where the plasma concentration of vaspin was found to be less in MI patients. A study done by Zhang et al showed that the levels of plasma vaspin were significantly lower in the CAD group (0.47 ± 0.63 μg/L) than those in the healthy group and CAG group [13]. Similarly in another study the levels of plasma vaspin were low in patients with CAD than age-matched subjects with normal coronary anatomy [20]. The serum levels of vaspin were significantly lower in subjects with CAD [0.91 (0.44–1.29) ng/ml] [14]. The difference in results could arise due to various factors such as timing of blood sampling, severity of CAD, the type of kit used and biological variability.

Our study results showed a moderate negative correlation ($p<0.005$) between vaspin and BMI. Similarly Caramin et al in his study said that when there is a weight loss, level of serum vaspin increases [21]. Results from other studies also showed that elevated level of serum vaspin is highly associated with obesity [22]. Higher waist circumference is also correlated with higher vaspin level but low visfatin level. Derosa et al evaluated the levels of some inflammatory adipocytokines in 363 obese and 365 non-obese subjects and observed high level of vaspin concentration in obese subjects [23].

We did not find any correlation between visfatin and BMI. However there are studies showing elevated level of serum visfatin are associated with obesity. In a study done by Indulekha et al subjects were divided into four groups metabolically healthy no obese (MHNO, n = 462), metabolically healthy obese (MHO, n = 192), metabolically obese non obese (MONO, n = 315), and metabolically obese, obese (MOO, n = 335) to find out association of adipokines, inflammatory and oxidative stress markers. It was observed that visfatin levels were shown to be higher in obese group [24]. Similarly in a study comprising of 90 subjects from the pediatric age group (60 controls and 30 obese) between the ages of 5 and 18 years, visfatin was found to be higher in obese subjects when compared with the control group [25].

Our study showed a negative correlation between Vaspin and LVEF. These findings were in contrast to an earlier study where it was observed that patients with high vaspin had a greater improvement in left ventricular ejection fraction after 24 months [12]. This study suggested that vaspin could also play a contributory role in the ventricular remodeling process. Since our study was cross sectional in nature we could not ascertain if the change in LVEF had any relationship with the baseline vaspin levels. Future studies should be performed that assesses serial measurement of vaspin along with change in LVEF to make definite conclusions on whether vaspin could play a strong role in the pathogenesis of ventricular remodeling.

Conclusion

High visfatin and vaspin concentration are found to be associated with myocardial infarction. Vaspin

was also observed to have a negative correlation with BMI and left ventricular ejection fraction. More fundamental and mechanistic studies that address the role of these adipokines in the pathogenesis of CAD is warranted.

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Conflict of Interest

We declare that we do not have any conflict of interest.

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