Correlation of serum visfatin level with chest pain scoring as an indication of myocardial ischemia in chronic kidney disease patients

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Background
Nicotinamide phosphoribosyltransferase (Visfatin), an enzyme involved in the NAD+ salvage pathway, has been shown to help in the regulation of glucose homeostasis. It is a highly conserved, 52 kDa protein found in living species from bacteria to humans. It is an adipokine produced and secreted primarily by adipose tissue. Chronic kidney disease (CKD) and end-stage renal disease patients showed increased cardiovascular mortality, and vascular events account for more than half of the deaths in this population. Myocardial ischemia is a consequence of coronary heart disease. Recent studies found that with increasing visfatin levels, CKD patients have a larger number of vessels with stenosis and a higher likelihood of coronary artery disease.

Research design and methods
The current prospective study includes 137 CKD patients and patients with chest pain (CP), as well as 20 patients as controls. Patient data included age, sex, comorbidities, smoking status, weight, height, and BMI, calculated using the equation: BMI = weight (kg)/height (m^2). Estimated glomerular filtration rate was calculated using the modified Modification of Diet in Renal Disease equations; in addition, enzyme-linked immunosorbent assay was used to estimate serum visfatin levels, and CP was assessed through a modification of the master questionnaire.

Results
All patients had significantly ($P < 0.05$) higher serum visfatin levels compared with controls. Patients who had typical anginal CP had significantly ($P < 0.05$) higher serum visfatin levels compared with those who had atypical anginal or nonanginal CP, with nonsignificantly ($P > 0.05$) higher serum visfatin levels in patients with atypical anginal CP compared with those with nonanginal CP. Moreover, patients with stage 4 CKD had a significantly ($P < 0.05$) higher serum visfatin level compared with patients with stage 3 CKD.

Conclusion
It could be concluded that patients with CKD are at an actual risk of developing CP secondary to myocardial ischemic attack, presenting either as typical or as atypical anginal pain. Elevated serum visfatin levels may be the cornerstone for the relationship between CKD and coronary heart disease. Serum visfatin levels in range of 12.4–16.4 ng/ml could predict the possibility of developing an anginal attack in patients with atypical anginal CP, with high sensitivity and specificity for diagnosis.

Keywords:
CKD-chronic kidney disease, CP-chest pain, CA-coronary angiography, eGFR-estimated glomerular filteration rate

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Introduction

The adipose tissue secretes several bioactive mediators that influence inflammation, insulin resistance, diabetes, atherosclerosis, and several other pathologic states besides the regulation of body weight. These mediators are mostly proteins and are termed 'adipocytokines' comprising adiponectin, resistin, visfatin, retinol binding protein-4, and leptin [1,2].

Nicotinamide phosphoribosyltransferase (visfatin), an enzyme involved in the NAD+ salvage pathway, has been shown to help in the regulation of glucose homeostasis. It is a highly conserved, 52 kDa protein found in living species from bacteria to humans. It is an adipokine produced and secreted primarily by visceral white adipose tissue. Visfatin is also produced by endotoxin-stimulated neutrophils and inhibits neutrophil apoptosis through its antiapoptotic activity mediated by caspase 3 and caspase 8. Nicotinamide phosphoribosyltransferase is a pleotropic protein with multiple functions in a variety of physiological processes; their dysregulations have been implicated in the pathogenesis of a number of human diseases or conditions such as acute lung injury, aging, atherosclerosis, cancer, diabetes, rheumatoid arthritis, and sepsis [3,4].

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients showed increased cardiovascular mortality, and vascular events account for more than half of the deaths in this population [5]. Myocardial ischemia, a consequence of coronary artery disease, is a major cause of death among patients with ESRD. The pathophysiology and clinical presentation of coronary artery disease in ESRD patients seem to differ from those in non-ESRD patients, with a higher implication of myocardial microvascular disease, a higher mortality rate, fewer myocardial infarctions, less significant coronary stenosis, and low efficacy of well-established drugs such as statins and angiotensin-converting enzyme inhibitors. Traditional risk factors fail to explain the increased risk for cardiovascular morbidity and mortality in ESRD patients [6].

The current prospective study aimed to estimate the serum visfatin level in CKD patients and in patients who complained of chest pain (CP) and to correlate serum visfatin levels with clinical CP scoring.

Patients and methods

The current prospective double-blinded study was conducted at the Departments of Nephrology and Cardiology, Ibn Sina College of Medicine, Jeddah, KSA, from June 2009 until August 2013. After approval of the study protocol by the local ethical committee and obtaining the patients' consent, 137 CKD patients and those who complained of CP were enrolled in the study.

Exclusion criteria included a history of congestive heart failure, defined as dyspnea in addition to any two of the following conditions — raised jugular venous pressure, bilateral basilar crackles, pulmonary venous hypertension, interstitial edema on chest radiography (requiring hospitalization or extra-ultrafiltration), left ventricular ejection fraction less than 35%, and intercurrent or terminal illnesses; history of coronary artery bypass graft surgery; inflammatory diseases such as infection, sepsis, liver disease, and collagen disease; or steroid use or surgery within 1 month before admission.

The study also included 20 age-matched age and sex-matched volunteers free of any form of renal impairment due to cardiac diseases, chosen from among those attending the hospital blood bank for blood donation after passing the preliminary laboratory investigations required for blood donation according to hospital protocol, who served as a control group for serum visfatin levels.

Patient data included age, sex, comorbidities, smoking status, weight and height, and BMI, calculated according to the equation: BMI = weight (kg)/height (m^2) [7]. Estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease equation as follows: eGFR (ml/min/1.73 m^2) = 186.3 × (serum creatinine in mg/dl)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 for female patients). Thereafter, patients were categorized according to eGFR into five stages of CKD: stage 1 with a GFR of 90 ml/min/1.73 m^2 or higher, stage 2 with a GFR of 60–89 ml/min/1.73 m^2, stage 3 with a GFR of 30–59 ml/min/1.73 m^2, stage 4 with a GFR of 15–29 ml/min/1.73 m^2, and stage 5 with GFR of less than 15 ml/min/1.73 m^2 [8].

All laboratory investigations were performed before the angiographic procedure. After a 12-h fasting period, whole blood samples (10 ml) were obtained from patients and controls, which were collected in a plain tube and allowed to clot; the samples were centrifuged at 5000 rpm for 10 min and serum was separated into two parts: the first part was put in an Eppendorf tube and stored at -80°C until quantitative ELISA estimation of serum visfatin levels (Visfatin C-terminal ELISA kit; Phoenix Pharmaceuticals Inc., Burlingame, California, USA) [9]; the other part of the serum was used for estimation of serum levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL), uric acid, albumin, creatinine, and glucose by standard commercial methods on a parallel, multichannel analyzer (Hitachi 7170A; Hitachi, Tokyo, Japan).

CP was assessed on the basis of a modification of the Master questionnaire (Fig. 1). Typical anginal pain was diagnosed if the following criteria were fulfilled: Pain is described as a constricting discomfort in the front of the chest or in the neck, shoulders, jaw, or arms; pain is precipitated by physical exertion and relived by rest or glycerin trinitrite administration within about 5 min; patients with typical angina. Patients with pain fulfilling two of these three criteria were diagnosed as having atypical anginal pain. Patients fulfilling one criterion or none of the three criteria were diagnosed as having nonanginal pain [10].

All patients with atypical anginal pain and nonanginal pain were assessed for the risk of developing coronary artery disease within the next 10 years using the Framingham database [11,12]. Patients with nonanginal pain or atypical anginal pain with a CP score of 10 or lower were assessed for causes of CP other than coronary heart disease (CHD), and those with persistent pain after exclusion or treatment of other

causes of CP were assessed using functional imaging or coronary angiography (CA). Patients with typical or atypical anginal pain who had CP scores in range of 11–59 were assigned for functional imaging using MRI. Patients with typical or atypical anginal pain with scores from 60 to 90 were assigned for diagnostic CA. Patients with typical anginal pain who scored greater than 90 were assigned to receive treatment for angina until they were stabilized and to undergo diagnostic CA for planning of revascularization (Table 1) [13,14].

Results

The study included 137 CKD patients: 82 male (59.9%) and 55 female (40.1%), with a mean age of 53.1 ± 7 years, range: 37–65 years. The mean BMI of the studied patients was 30.9 ± 3.3 kg/m^2, range: 25.2–34.1 kg/m^2. Forty-seven patients (34.3%) were overweight and 90 patients (65.7%) were obese. Thirty-six patients were current smokers, 47 patients were ex-smokers, and 54 patients were nonsmokers. The mean duration of dialysis among dialysis patients was 11 ± 2.8 months, range: 8–15 months. Diabetes was the underlying cause of nephropathy in 41 patients, hypertension in 37 patients, glomerulonephritis in 14 patients, diabetes and hypertension in 20 patients, and other causes in nine patients; the underlying disease was unknown in 16 patients. The mean systolic blood pressure was 137.7 ± 23 mmHg, range: 110–175 mmHg, whereas the mean diastolic blood pressure was 84.5 ± 3.8 mmHg, range: 75–90 mm Hg (Table 2). The mean levels of laboratory data of studied patients are shown in (Table 3).

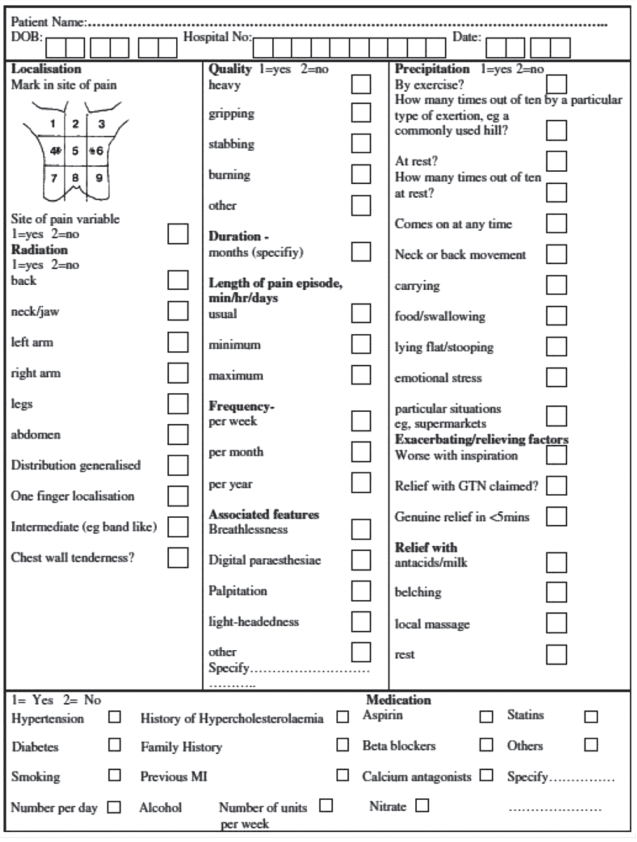
The mean serum creatinine (S. Cr) level was 2.39 ± 0.53 mg/dl, range: 1.3–4.27 mg/dl; 69 patients (50.6%) had S. Cr levels in the range of 2–2.5 mg/dl; 32 patients had S. Cr levels in the range of 1.5–2 mg/dl, 30 patients had S. Cr levels higher than 2.5 mg/dl, whereas only six patients had S. Cr levels less than 1.5 mg/dl. Forty-seven patients (34.4%) had a mean eGFR of 36.7 ± 6.6 ml/min/1.73 m^2, range: 30–59 ml/min/1.73 m^2 (CKD stage 3), whereas 90 patients (65.6%) had a mean eGFR of 22.9 ± 4.5 ml/min/1.73 m^2, range: 15–29 ml/min/1.73 m^2 (CKD stage 4; Table 4 and Fig. 2).

Table 1 Scoring levels of the CP questionnaire and corresponding management [13,14]

Pain character	CP score level	Management
Typical anginal pain	<60	Functional imaging using MRI to assess for wall motion abnormalities or myocardial ischemia
	≥60–90	Diagnostic CA to assess for obstructive CAD and, if confirmed, to plan for revascularization
	≥90	Management of angina and CA later on to plan for revascularization
Atypical anginal pain	≤10	Evaluation of other causes for chest pain
	11–59	Functional imaging
	≥60	Diagnostic chest pain
Nonanginal pain		Evaluation of other causes for chest pain

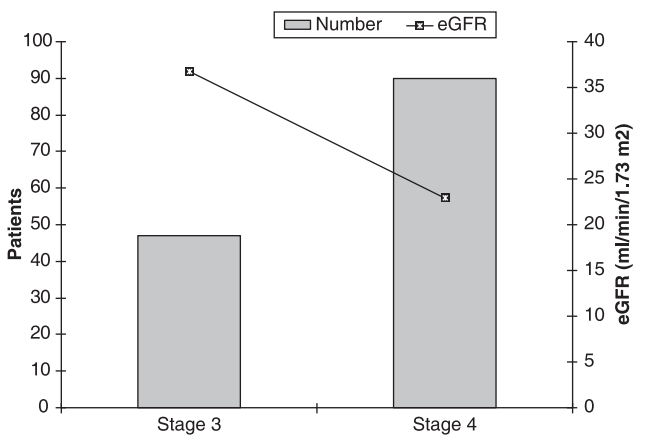
CA, coronary angiography; CAD, coronary artery disease; CP, chest pain; CT, computed tomography.

Figure 1



Chest pain questionnaire [10].

Figure 2



Patients distribution according to stage of CKD and their eGFR. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Patients were categorized according to character of CP as follows: 11 patients (8%) had typical anginal pain, 95 patients (69.4%) had atypical anginal pain, and 31 patients (22.6%) had nonanginal pain. CP scoring of patients with typical anginal pain defined two patients with scores less than 60, who were assigned for functional imaging using MRI, five patients with scores in range of 60–90, who were assigned for diagnostic invasive CA, and four patients with scores of 90 or higher, who were managed as anginal patients and received appropriate management to be further evaluated later using invasive CA to prepare for revascularization surgery (Table 5).

CP scoring of patients with atypical anginal pain defined 12 patients with scores of 10 or lower, who were further evaluated for causes other than CAD for their CP, 55 patients with scores in the range of 11–59, who were assigned for functional imaging using MRI, and 28 patients with a score of 60 or higher, who were assigned for diagnostic invasive CA. Patients with nonanginal pain showed mosaic scores, with a mean of 22.4 ± 18.9, range: 5–69, and all were further evaluated for causes other than CAD for their CP. Thus, 57 patients were assigned for functional imaging, 33 patients were assigned for diagnostic invasive CA, 43 patients were evaluated for causes other than CAD for their CP, and four patients were managed as anginal patients (Table 5).

All patients with atypical anginal or nonanginal CP were subjected to evaluation of future CHD risk, which was found to be correlated with the scores of the CP questionnaire, with a possible higher risk for developing CHD within 10 years among those had CP scores of 60 or higher compared with those who had atypical anginal pain with CP scores of less than 60 and those who had nonanginal CP (Table 6 and Fig. 3).

All patients had significantly ($P < 0.05$) higher serum visfatin levels compared with controls. Patients with typical anginal CP had significantly ($P < 0.05$) higher serum visfatin levels compared with those with atypical anginal or nonanginal CP, with nonsignificantly

Table 2 Enrollment data of studied patients

Data		Findings
Age (years)		
<40	11 (8)	38.4 ± 0.8 (37–39)
40–49	32 (23.4)	46.9 ± 1 (46–49)
50–54	31 (22.6)	52.3 ± 1.3 (50–54)
55–59	42 (30.7)	57.5 ± 1 (55–59)
≥60	21 (15.3)	62.8 ± 1.8 (60–65)
Total		53.1 ± 7 (37–65)
Sex		
Males		82 (59.9)
Females		55 (40.1)
BMI data		
Weight (kg)		88.2 ± 8.6 (79–102)
Height (cm)		169.1 ± 14.9 (162–178)
BMI		
Strata		
Overweight	47 (34.3)	28.7 ± 4.3 (25.2–29.8)
Obese	90 (65.7)	32 ± 3.6 (30.1–34.1)
Total		30.9 ± 3.3 (25.2–34.1)
Smoking		
Current smoker		36 (26.3)
Ex-smoker		47 (34.3)
Nonsmoker		54 (39.4)
Underlying kidney disease		
Diabetes mellitus		41 (29.9)
Hypertension		37 (27)
Hypertension+diabetes mellitus		20 (14.6)
Glomerulonephritis		14 (10.2)
Others		9 (6.6)
Unknown		16 (11.7)
Blood pressure measures (mmHg)		
SBP		137.7 ± 23 (110–175)
DBP		84.5 ± 3.8 (75–90)

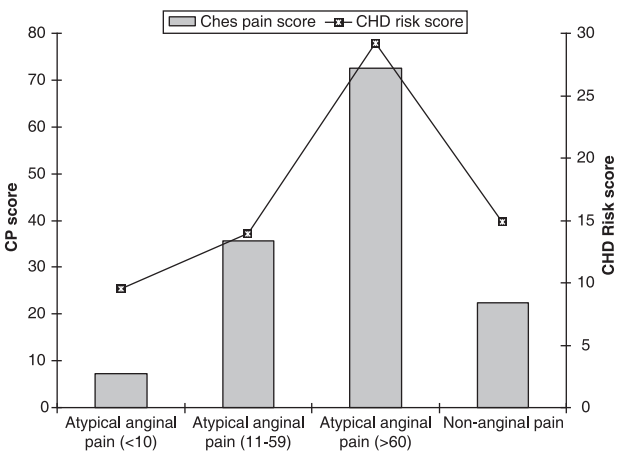
Data are presented as means ± SD and number; ranges and percentages are in parenthesis. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3 Patients' laboratory data at enrollment

Chemistry results	Early
Hemoglobin concentration (%)	9.4 ± 1.1
Serum uric acid (mg/dl)	6.9 ± 2.3
Serum calcium (mg/dl)	12.27 ± 8.4
Serum phosphate (mg/dl)	4.34 ± 1.8
Serum total cholesterol (mg/dl)	228.5 ± 31.8
Serum triglyceride (mg/dl)	111.8 ± 15
Serum HDL (mg/dl)	37.5 ± 5.3
Serum LDL (mg/dl)	168.7 ± 32.7

Data are presented as means ± SD; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Figure 3



CP questionnaire and CHD risk scoring of studied patients categorized according pain characters. CHD, chronic heart disease; CP, chest pain.

(P > 0.05) higher serum visfatin levels in patients with atypical anginal CP compared with those with nonanginal CP (Fig. 4). Moreover, patients with stage 4 CKD had significantly (P<0.05) higher serum visfatin levels compared with patients with stage 3 CKD (Table 7 and Fig. 5).

The calculated CP score showed a significant positive correlation with age, male sex, presence of diabetes mellitus, and serum visfatin level, whereas it showed a significant negative correlation with the serum HDL level. The serum visfatin level of the studied patients showed a significant positive correlation with male sex, whereas it showed a significant negative correlation with eGFR (Table 8).

Table 4 Serum creatinine levels and eGFR of studied patients

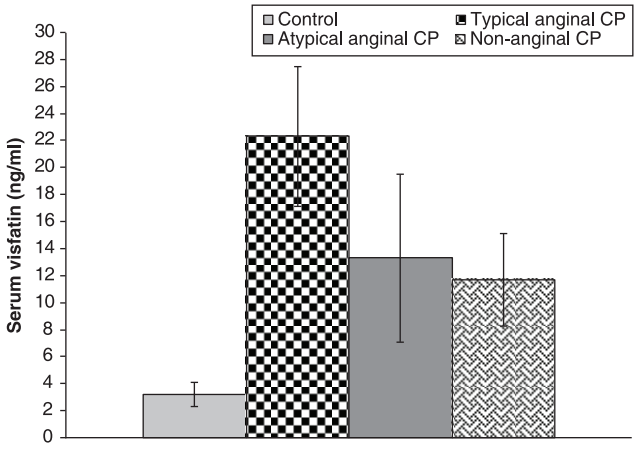
Laboratory results	*N* (%)	Value
Serum creatinine (mg/dl)		
<1.5	6 (4.4)	1.38 ± 0.06 (1.3–1.46)
1.5–2	32 (23.4)	1.86 ± 0.11 (1.57–2)
>2–2.5	69 (50.4)	2.41 ± 0.13 (2.1–2.45)
>2.5–3	16 (11.6)	2.76 ± 0.13 (2.6–3)
>3–3.5	8 (5.8)	3.27 ± 0.15 (3.1–3.43)
>3.5	6 (4.4)	3.82 ± 0.29 (3.57–4.27)
Total	137 (100)	2.39 ± 0.53 (1.3–4.27)
Estimated GFR (ml/min/1.73 m²)		
Stage 3 (30–59)	47 (34.4)	36.7 ± 6.6 (30–59)
Stage 4 (15–29)	90 (65.6)	22.9 ± 4.5 (15–29)
Total	137 (100)	27.6 ± 8.5 (15–59)

Data are presented as means ± SD and number; ranges and percentages are in parenthesis; eGFR, estimated glomerular filtration rate.

Evaluation of the serum visfatin level as a hazard function for the possibility of getting a high CP score showed progressively increased cumulative hazard with increasing levels of visfatin (Fig. 6). Evaluation of the 50th and 75th percentiles of serum visfatin levels (12.4 and 16.4 ng/ml, respectively) as cutoff points for prediction of high CP scores using receiver-operating characteristic curve analysis showed a wider area under the curve (0.715) for the 50th percentile compared with the 75th percentile (0.661; Fig. 7a and b, respectively).

Evaluation of both cutoff points revealed a high sensitivity and a negative predictive value for the cutoff

Figure 4



Serum (± SD) visfatin levels estimated in studied patients categorized according to character of CP and compared with controls. CP, chest pain.

Table 5 Patients categorization and scoring according to CP pain questionnaire and their management

Pain character	Score level	*N* (%)	Score	Management
Typical anginal pain	<60	2 (1.5)	48.5 ± 12 (40–57)	Functional imaging using MRI to assess for wall motion abnormalities or myocardial ischemia
	≥60–90	5 (3.5)	80 ± 7.8 (69–89)	Invasive CA to assess for obstructive CAD and, if confirmed, to plan for CABG surgery
	≥90	4 (3)	91.3 ± 1.5 (40–93)	Management of angina and CA later on to plan for CABG surgery
Total		11 (8)	78.4 ± 17 (90–93)	
Atypical anginal pain	≤10	12 (8.8)	7.3 ± 2.1 (4–10)	Evaluation of other causes for CP
	11–59	55 (40.1)	35.6 ± 16 (11–59)	Functional imaging
	≥60	28 (20.4)	72.6 ± 7.5 (61–85)	Invasive CA
Total		95 (69.3)	42.9 ± 24.9 (4–85)	
Nonanginal pain		31 (22.6)	22.4 ± 18.9 (5–69)	Evaluation of other causes for CP

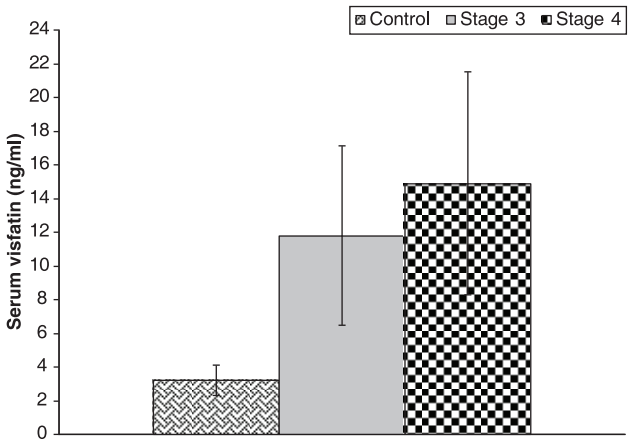
Data are presented as numbers and mean ± SD; percentages and ranges are in parenthesis; CA, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CP, chest pain; CT, computed tomography.

Table 6 CHD risk scores of patients with atypical anginal and nonanginal pain according to the CP questionnaire

	CP questionnaire data			
Pain character	Score level	*N* (%)	Score	CHD risk score
Atypical anginal pain	≤10	12 (8.8)	7.3 ± 2.1 (4–10)	9.5 ± 5.7 (3–20)
	11–59	55 (40.1)	35.6 ± 16 (11–59)	13.9 ± 6.3 (3–27)
	≥60	28 (20.4)	72.6 ± 7.5 (61–85)	29.2 ± 10.2 (13–53)
Nonanginal pain		31 (22.6)	22.4 ± 18.9 (5–69)	14.9 ± 7.6 (5–31)

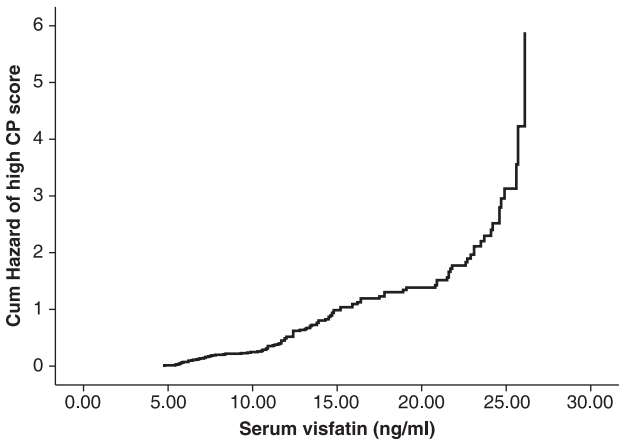
Data are presented as numbers and mean ± SD; percentages and ranges are in parenthesis; CHD, coronary heart disease; CP, chest pain.

Figure 5



Mean (± SD) serum visfatin levels estimated in studied patients categorized according to CKD stage and compared with levels in controls. CKD, chronic kidney disease.

Figure 6



Cumulative hazard function of serum visfatin for the possibility of high CP scores of studied patients. CP, chest pain.

Table 7 Serum visfatin levels of the studied patients categorized according to pain character on the CP questionnaire and stage of CKD

Categorization data	*N* (%)	Serum visfatin level (ng/ml)
Control	20 (100)	3.2 ± 0.9 (2.1–5.4)
Pain character on CP questionnaire		
Typical anginal pain	11 (8.1)	22.3 ± 5.2 (11.9–26.1)[a]
Atypical anginal pain	95 (69.3)	13.3 ± 6.2 (4.7–26.9)[a,b]
Nonanginal pain	31 (22.6)	11.7 ± 3.4 (5.6–18.9)[a,b]
CKD staging		
Stage 3 (30–59)	47 (34.4)	11.8 ± 5.3 (4.7–23.1)[a,c]
Stage 4 (15–29)	90 (65.6)	14.9 ± 6.6 (5.6–26.9)[a]

Data are presented as numbers and mean ± SD; percentages and ranges are in parenthesis; CKD, chronic kidney disease; CP, chest pain; [a]Significant versus controls; [b]Significant versus patients who had typical anginal CP; [c]Significant versus patients with CKD stage 3.

Table 8 Correlation coefficient '*r*' between CP score and serum visfatin levels and demographic, clinical, and laboratory data

	CP score		Serum visfatin (ng/ml)	
	r	*P*	*r*	*P*
Age (years)	0.379	<0.001	0.160	>0.05
Duration of dialysis	0.125	>0.05	0.139	>0.05
Male sex	0.718	<0.001	0.222	0.009
Smoking	0.105	>0.05	0.073	>0.05
Serum total cholesterol (mg/dl)	0.107	>0.05	0.071	>0.05
Serum HDL level (mg/dl)	–0.203	0.017	–0.154	>0.05
CP score			0.398	<0.001
Presence of DM	0.482	<0.001	0.259	0.002
Serum Cr (mg/dl)	0.156	>0.05	0.131	>0.05
eGFR (ml/min/1.73 m^2)	0.073	>0.05	–0.220	0.010

CP, chest pain; Cr, creatinine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

point 12.4 ng/ml, whereas the cutoff point 16.4 ng/ml had a high specificity and a positive predictive value, with higher likelihood ratios (Table 9). Thus, serum visfatin level in range of 12.4–16.4 ng/ml is suspicious of having a CHD necessitating either functional imaging or invasive CA.

Discussion

The current study provided interesting data on patients with CKD and presenting with CP; first, ~8% of the studied patients had typical anginal pain that required treatment, without invasive investigations being required in ~30% of these patients. Second, ~65% of the studied patients required investigations for possible myocardial ischemia, and 35% of these patients were assigned for invasive CA directly and 65% were assigned for preliminary functional imaging. These findings highlight the necessity for monitoring the myocardial status and function of CKD patients, irrespective of the severity of the disease, as evidenced by the positive nonsignificant correlation between CP score, serum creatinine, and eGFR.

Third, serum levels of visfatin were significantly higher in studied patients compared controls and were significantly higher in patients with stage 4 CKD compared with those with stage 3 CKD. These findings indicate concomitant elevation of serum visfatin levels with increasing severity of CKD. In contrast, significantly higher serum levels of visfatin were observed in patients with typical anginal CP compared with those with atypical or nonanginal pain, suggesting a relation between elevated serum visfatin levels and an increased risk for myocardial ischemia.

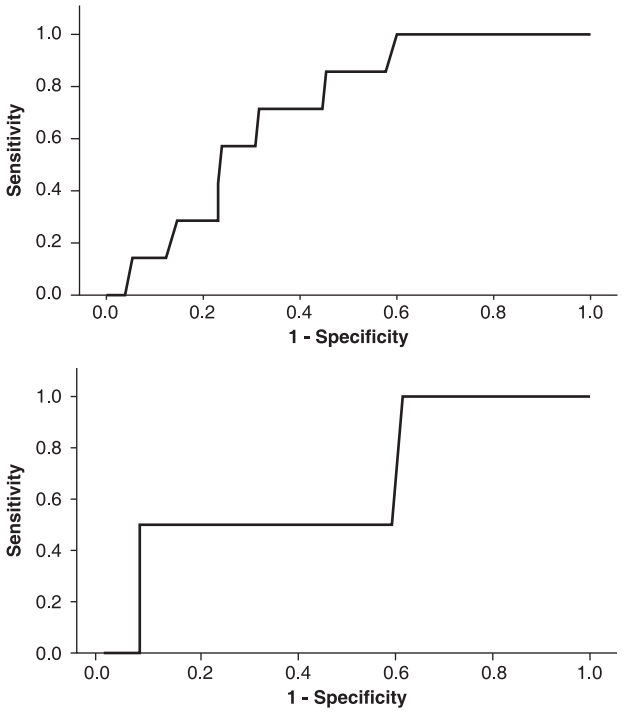
Thus, high serum visfatin levels may be a connecting channel between CKD and CHD, as evidenced by the significant negative correlation between eGFR and serum visfatin levels and the significant positive correlation with CP scores and serum HDL levels, a cardiovascular risk factor. In accordance with this

Table 9 Correlation coefficient '*r*' between CP score and serum visfatin levels and demographic, clinical, and laboratory data

	50th percentile (12.4 ng/ml)	75th percentile (16.4 ng/ml)
Sensitivity	71.43% (95% CI: 55.41–84.27%)	53.66% (95% CI: 37.43–69.34%)
Specificity	63.16% (95% CI: 52.64–72.83%)	87.5% (95% CI: 79.18–93.36%)
Positive likelihood ratio	1.94% (95% CI: 1.4–2.68)	4.29 (95% CI: 2.35–7.83)
Negative likelihood ratio	0.45% (95% CI: 0.27–0.75)	0.53% (95% CI: 2.35–7.83)
Positive predictive value	46.15% (95% CI: 33.7–58.97%)	64.71% (95% CI: 46.49–80.24%)
Negative predictive value	83.33% (95% CI: 72.69–91.07%)	81.55% (95% CI: 72.7–88.51%)

CI, confidence interval; CP, chest pain.

Figure 7



ROC curve analysis of two cutoff points of serum visfatin level as predictors of a high CP score. CP, chest pain; ROC, receiver-operating characteristic.

suggestion, Nüsken *et al.* [15] reported that serum visfatin levels were increased in hemodialysis patients compared with controls and dialysis patients; only plasma HDL levels and insulin-treated diabetes mellitus were independently associated with serum visfatin levels. Bessa *et al.* [16] reported that serum visfatin is strongly associated with endothelial adhesion molecules and the percentage of flow-mediated dilatation, thus suggesting that visfatin is an important promising biomarker for the prediction of endothelial dysfunction. In addition, they suggested that the relationship between visfatin and IL-6 indicates that circulating visfatin may reflect the subclinical inflammatory status, thus concluding that visfatin might be involved in the complex interactions between endothelial dysfunction, inflammation, and atherosclerosis, leading to future cardiovascular risk in CKD patients.

Recently, Lu *et al.* [17] found that with increasing visfatin levels, CKD patients had a larger number of vessels with stenosis and a higher likelihood of coronary artery disease, as well as incrementally lower eGFR and serum albumin levels and higher high-sensitivity C-reactive protein and brain natriuretic peptide levels, and concluded that significantly higher plasma visfatin levels in the presence of coronary artery disease suggests that increased plasma visfatin levels may be involved in the pathogenesis of coronary atherosclerosis in CKD patients. Tang *et al.* [18] found that serum levels of visfatin, IL-6, and CRP were significantly increased in CKD patients compared with age-matched healthy controls, serum visfatin levels increased with the progression of renal dysfunction, patients with carotid artery plaques showed significantly higher levels of visfatin compared with those without plaques, and they showed using multiple regression analysis that the serum visfatin level is an independent risk factor for carotid atherosclerosis; they concluded that the serum level of visfatin should be considered to be a new risk factor for atherosclerosis in CKD.

Statistical analysis of diagnostic cutoff points of serum visfatin levels defined a high sensitivity and negative predictive value for the cutoff point 12.4 ng/ml and a high specificity and positive predictive value with higher likelihood ratios for the cutoff point 16.4 ng/ml. Thus, patients with serum visfatin levels in range 12.4–16.4 ng/ml are suspected of having a CHD, necessitating further evaluation. In support of the applicability of serum visfatin levels as predictors for cardiovascular lesions, Gunes *et al.* [19] found that the mean visfatin level was significantly higher in hypertensive patients and in the prehypertensive group than in participants with normal blood pressure, with a significantly positive correlation between visfatin levels and systolic and diastolic blood pressure. Karakan *et al.* [20] found that the left ventricular mass index was correlated with BMI, systolic blood pressure, and serum visfatin levels, and that on regression analysis, systolic blood pressure and serum visfatin levels were independent variables affecting the left ventricular mass index, but serum visfatin levels might be a more sensitive marker than other evaluations for cardiac performance in nondiabetic peritoneal dialysis

patients. Moreover, Mazaherioun and colleagues found significantly higher serum visfatin levels in patients with acute myocardial infarction (12.77 ± 8.06 ng/ml) compared with controls (6.57 ± 2.96 ng/ml), and a visfatin level greater than 7.244 ng/ml was found to have a sensitivity of 70% and a specificity of 75% for predicting acute myocardial infarction.

It could be concluded that patients with CKD are at an actual risk of developing CP secondary to myocardial ischemic attack, presenting either as typical or as atypical anginal pain. Elevated serum visfatin levels may be the cornerstone of the relationship between CKD and CHD. Serum visfatin levels in range 12.4–16.4 ng/ml could predict the possibility of having an anginal attack in patients with atypical anginal CP, with high sensitivity and specificity for diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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