

# Serum visfatin in chronic renal failure patients on maintenance hemodialysis: a correlation study

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## Background and aim of work

Endothelial dysfunction, atherosclerosis, and cardiovascular disease are strongly linked to chronic kidney disease. It has been hypothesized that visfatin may play an important role in uremia-related atherosclerosis and the relation between visfatin and endothelial dysfunction has been proved. We aimed to study and characterize the relation of visfatin to some clinical and biochemical parameters among chronic renal failure (CRF) patients on regular hemodialysis.

## Patients and methods

This study was carried out on a total of 90 individuals, divided into two groups: group A included 68 patients with CRF on regular hemodialysis (44 men and 24 women) and group B included 22 healthy individuals as controls (four men and 18 women). All participants were subjected to the following: full clinical assessment, BMI assessment, FBS (Fasting blood sugar), PPBS (postprandial blood sugar), Hb level, lipid profile, serum urea, creatinine, potassium, phosphorus, and serum visfatin.

## Results

Serum visfatin concentration was significantly high in group A (uremic on hemodialysis) compared with group B (control) (48.95 ng/ml  $\pm$  11.62 compared with 22.65 ng/ml  $\pm$  5.24;  $P < 0.001$ ); a highly significant positive correlation was found between serum visfatin and serum low-density lipoprotein ( $r = 0.39$ ;  $P < 0.001$ ) and a significant positive correlation between serum visfatin and serum triglycerides and serum uric acid ( $r = 0.28$ ;  $P < 0.05$  and  $r = -0.24$ ;  $P < 0.05$ ), respectively, whereas a highly significant negative correlation between serum visfatin and Hb ( $r = -0.43$ ;  $P < 0.001$ ) and a significant negative correlation between serum visfatin and serum urea ( $r = -0.25$ ;  $P < 0.05$ ), blood sugar, both fasting and postprandial ( $r = -0.34$ ;  $P < 0.001$  and  $r = -0.39$ ;  $P < 0.001$ ), respectively, were found in the patients in group A, without a significant correlation either to high-density lipoprotein, serum creatinine, the etiology of CRF, or to the duration of dialysis in the patients in group A.

## Conclusion

This study proves the association of serum visfatin with CRF, unrelated to the biochemical parameter of kidney functions; however, further studies to examine visfatin expression within renal tissue may clarify its definitive role in CRF.

## Keywords:

chronic renal failure, hemodialysis, visfatin

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## Introduction

Intense research has been carried out in recent years on the pathophysiology of adipokines in renal disease and their relationship with the risk of cardiovascular disease in patients with renal failure. The direct association between some proinflammatory cytokines and cardiovascular morbidity and mortality seems clear, but the pathophysiological role and potential implications of other adipokines, such as visfatin, remain unclear [1].

Visfatin is an adipokine identified in 2004 and thus named for the suggestion that it would be predominantly produced and secreted in visceral fat [2]. It has a molecular weight of 52 kDa and its gene encodes 491 amino acids. It is identical to pre-B cell colony-enhancing factor, described in 1994

as a cytokine produced by lymphocytes, acting on lymphocyte maturation and inflammatory regulation. Visfatin was also recognized recently as the formerly described nicotinamide phosphoribosyltransferase, the limiting enzyme in nicotinamide adenine dinucleotide biosynthesis, and is thus involved in the production of reactive oxygen species [3,4].

This interesting adipocytokine has been the subject of extensive research studies because of its pleiotropic action. Interestingly, it acts as an inflammatory cytokine and its levels are elevated in a number of acute and chronic inflammatory diseases including sepsis, acute lung injury, rheumatoid arthritis, and inflammatory bowel disease [5]. Axelsson *et al.* [6], in 2007, for the first time reported an increased serum level of visfatin in chronic kidney disease (CKD) and later on, several other studies reported a similar relationship between

visfatin and CKD [7–9]. Moreover, Axelsson *et al.* [6] also found visfatin to be associated with soluble vascular adhesion molecule 1, which is a biomarker of endothelial damage in CKD. Proteinuria is an important predictor of endothelial dysfunction (ED) in early diabetic nephropathy and an association has been observed between proteinuria and visfatin level [10].

Song *et al.* [11] studied visfatin at the molecular level as they cultured mesangial cells with recombinant visfatin and found a marked increase in the synthesis of profibrotic molecules including transforming growth factor- $\beta$ , plasminogen activation inhibiting factor 1, and type 1 collagen, which are well known to contribute toward the pathogenesis of diabetic nephropathy. Thus, the fibrotic buildup observed by Song *et al.* [11] and the possibility of reactive oxygen species through its activity as a nicotinamide phosphoribosyltransferase strongly support the concept that visfatin could be one of the cytokines responsible for renal damage in diabetic nephropathy.

Considerable progress has been made in identifying the association of visfatin with visceral adipose tissue, diabetes, and inflammation, but the maintenance of visfatin elevation among patients with chronic renal failure (CRF) has not been proven. In this study, we investigated the state of serum visfatin among patients with CRF on maintenance hemodialysis, and its relation to some clinical and biochemical parameters.

## Patients and methods

A total of 90 individuals were included in this study, divided into two groups: group A included 68 patients with end-stage renal disease on hemodialysis of a duration ranging from 7 months to 15 years, mean  $\pm$  SD  $5.57 \pm 3.55$  years (44 men and 24 women); their ages ranged from 23 to 75 years, mean  $\pm$  SD  $51.24 \pm 11.55$  years. Group B included 22 healthy controls (four men and 18 women); their ages ranged from 46 to 48 years, mean  $\pm$  SD  $46.67 \pm 1.03$  years. Patients were recruited from the Internal Medicine Department, Al-Zahraa University Hospital, Cairo, Egypt. The patients fulfilled the criteria for diagnosis of renal failure.

All patients were subjected to a detailed assessment of history and a thorough physical examination, including ECG, was performed to exclude coronary heart disease.

Exclusion criteria were as follows: type 1 diabetes mellitus, urinary tract infection, renal stones, rheumatoid arthritis, recent cerebrovascular stroke, liver cirrhosis, recent surgical, or vascular maneuvers.

BMI was calculated as body weight (kg) divided by the square of height (m).

Fasting (12–16 h) venous blood samples (5 ml) were drawn from each individual participating in the study and divided into two parts: the first part, 2 ml, was added to a tube containing EDTA for the determination of hemoglobin using Beckman Coulter, inc. T 890 (Coulter Counter; Harpenden, UK). The second part was placed in a plain tube and left to clot; the serum was separated by centrifugation at 3000g for 5 min and fasting blood glucose was determined immediately using the colorimetric technique on a Hitachi 912 auto analyzer (Roche Diagnostics, Auckland City, Germany). The rest of the serum was stored at  $-20^{\circ}\text{C}$  for determination of the following: urea, creatinine, calcium, phosphorous, potassium, sodium, uric acid, total cholesterol, and triglyceride using colorimetric techniques on a Hitachi 912 auto analyzer and ion selective electrodes for sodium and potassium determination on a Hitachi 912 auto analyzer.

For the determination of high-density lipoprotein-cholesterol (HDL-C), phosphotungstic acid and magnesium ions were used for precipitating all lipoproteins, except the HDL fraction, which was present in the supernatant and measured using a Hitachi 912 auto analyzer. Low-density lipoprotein-cholesterol (LDL-C) was measured using the Friedwald formula [12].

Two hours after a meal, 2 ml of blood was drawn from each individual participating in the study and added to a tube containing fluoride for the determination of PPBG (Postprandial blood sugar) using colorimetric kits on a Hitachi 912 auto analyzer.

Serum visfatin was determined using a competitive enzyme immunoassay and the kit was supplied from Phoenix Pharmaceutical Inc. (Burlingame, California, USA) [13]. The results of visfatin were expressed as ng/ml and the detection range was 0.1–1000 ng/ml.

## Statistical analysis

Data were analyzed using the Microsoft Office 2003 (Excel) and Statistical Package for Social Science (SPSS) version 16. (SPSS Inc., 233 South Wacker)

Parametric data were expressed as mean  $\pm$  SD and nonparametric data were expressed as number and percentage of the total. Comparison of the mean  $\pm$  SD of two groups was carried out using an unpaired Student's *t*-test.

Measurement of the mutual correspondence between two values was carried out using a correlation

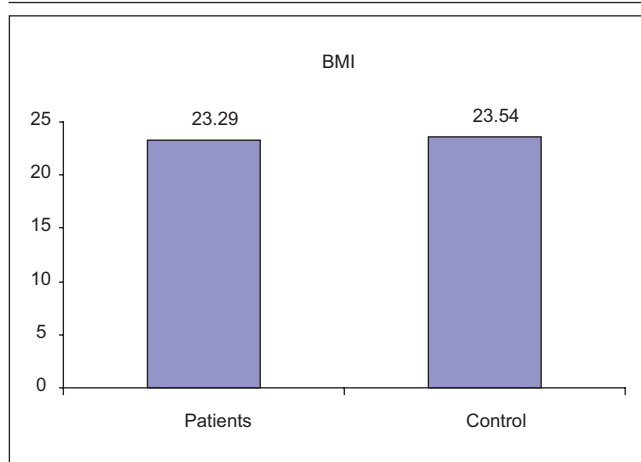
coefficient. A *P* value greater than 0.05 was considered nonsignificant, *P* value less than 0.05 was considered significant, and *P* value less than 0.01 was considered highly significant.

## Results

We carried out this study on two groups; group A included 68 patients with end-stage renal disease on hemodialysis of a duration ranging from 7 months to 15 years (mean 5.57 years) (44 men and 24 women); their ages ranged from 23 to 75 years (mean 51.24 years); and group B included 22 healthy controls (four men and 18 women); their ages ranged from 46 to 48 years (mean 46.67 years) (Table 1).

Our results showed that BMIs were within the normal range in both groups (23.29 vs. 23.54) and there were no significant statistical differences between them (Fig. 1). In terms of the serum visfatin concentration, there was a highly significant statistical difference between group A (uremic on hemodialysis) and group B (control) ( $48.95 \text{ ng/ml} \pm 11.62$  compared with  $22.65 \text{ ng/ml} \pm 5.24$ ;  $P < 0.001$ ; Table 2 and Fig. 2). In terms of the correlations between serum visfatin and the different parameters in the renal failure group on hemodialysis, the results showed a significant positive correlation between serum visfatin and LDL ( $r = 0.39$ ;  $P < 0.001$ ; Table 3 and Fig. 3), serum triglycerides ( $r = 0.28$ ;  $P < 0.05$ ; Table 3 and Fig. 4), and serum uric acid ( $r = -0.24$ ;  $P < 0.05$ ), respectively (Table 3), whereas significant negative correlations were found between serum visfatin and Hb ( $r = -0.43$ ;  $P < 0.001$ ; Table 3 and Fig. 3), blood sugar both fasting and postprandial ( $r = -0.34$ ;  $P < 0.001$  and  $r = -0.39$ ;  $P < 0.001$ ), respectively (Table 3), and blood urea ( $r = -0.25$ ;  $P < 0.05$ ; Table 3) in group A.

Figure 1



Mean BMI in the uremic and control groups (mean  $\pm$  SD). A nonsignificant difference in BMI was found in both groups as BMI was within normal in both groups.

No significant correlation was found between visfatin and serum creatinine in group A ( $r = -0.38$ ;  $P > 0.05$ ; Table 3 and Fig. 5), and no significant correlation was found between serum visfatin and HDL ( $r = -0.22$ ;  $P > 0.05$ ; Table 3 and Fig. 6).

## Discussion

Visfatin has been hypothesized to be involved in the complex interactions between ED, inflammation, and atherosclerosis and their major clinical consequences in CRF, suggesting that visfatin is an important promising surrogate biomarker for the prediction of ED and future cardiovascular risk in CKD patients [14,15].

In this work, we aimed to study the relation of serum visfatin to some clinical and biochemical parameters

Table 1 Laboratory parameters of the uremic group compared with the control group (mean  $\pm$  SD)

	Patients	Control	<i>P</i> value
Age	51.24	46.67	—
Sex (M/F)	44/24	4/26	—
Hemoglobin (g/dl)	10.05 $\pm$ 1.92	13.23 $\pm$ 0.80	<0.001
Blood urea (mg/dl)	143.21 $\pm$ 26.70	28.00 $\pm$ 7.07	<0.001
Serum creatinine (mg/dl)	8.94 $\pm$ 2.95	1.01 $\pm$ 0.13	<0.001
FBS (mg/dl)	84.35 $\pm$ 17.47	94.44 $\pm$ 9.77	0.0004
PP (mg/dl)	127.97 $\pm$ 26.80	119.00 $\pm$ 14.21	0.0336
TG (mg/dl)	173.18 $\pm$ 88.59	76.87 $\pm$ 16.37	<0.001
Cholesterol (mg/dl)	255.97 $\pm$ 39.02	212.74 $\pm$ 28.26	<0.001
HDL (mg/dl)	33.68 $\pm$ 16.01	53.87 $\pm$ 7.95	<0.001
LDL (mg/dl)	187.85 $\pm$ 29.45	134.07 $\pm$ 5.64	<0.001
Ca (mg/dl)	8.17 $\pm$ 1.03	8.95 $\pm$ 0.53	<0.001
K (mEq/l)	6.03 $\pm$ 1.28	4.02 $\pm$ 0.38	<0.001
Phosphorous (mg/dl)	5.52 $\pm$ 1.42	2.91 $\pm$ 0.15	<0.001
Na (mEq/l)	138.68 $\pm$ 4.27	146.67 $\pm$ 3.63	<0.001
Uric acid (mg/dl)	7.03 $\pm$ 1.36	4.24 $\pm$ 0.56	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

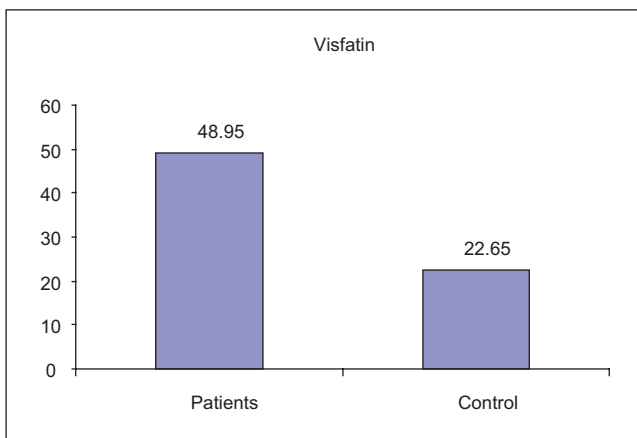
Table 2 Serum visfatin level in the uremic group compared with the control group (mean  $\pm$  SD)

	Patients	Control	<i>P</i> value
Visfatin (ng/dl)	48.95 $\pm$ 11.62	22.65 $\pm$ 5.24	<0.001

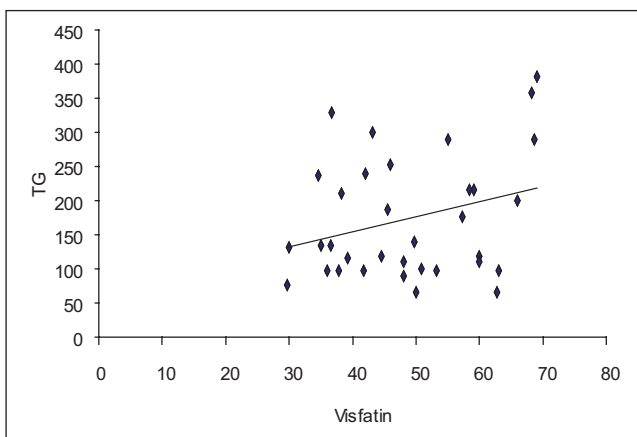
Table 3 Correlation between visfatin and other parameters in the patient group

	Visfatin ( <i>r</i> value)	<i>P</i> value
Visfatin	1.000	
BMI	0.539	<0.01
Hb	-0.432	<0.01
Blood urea	-0.252	<0.05
Serum creatinine	0.038	>0.05
FBS	-0.342	<0.01
PP	-0.390	<0.01
TG	0.286	<0.05
Cholesterol	-0.001	>0.05
LDL	0.397	<0.01
HDL	0.224	>0.05
Ca	-0.225	>0.05
K	-0.035	>0.05
Phosphorous	-0.174	>0.05
Na	-0.084	>0.05
Uric acid	0.248	<0.05
Age	0.079	>0.05
Duration of dialysis	0.171	>0.05

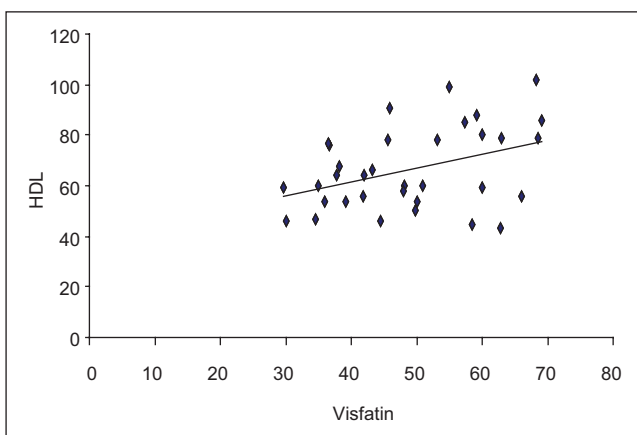
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**Figure 2**

Serum visfatin level in the uremic group compared with the control group (mean  $\pm$  SD).

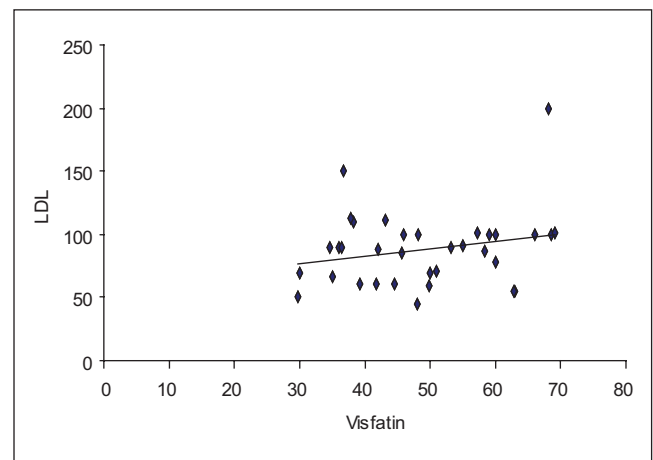
**Figure 4**

A significant positive correlation between visfatin and TG in the uremic group.

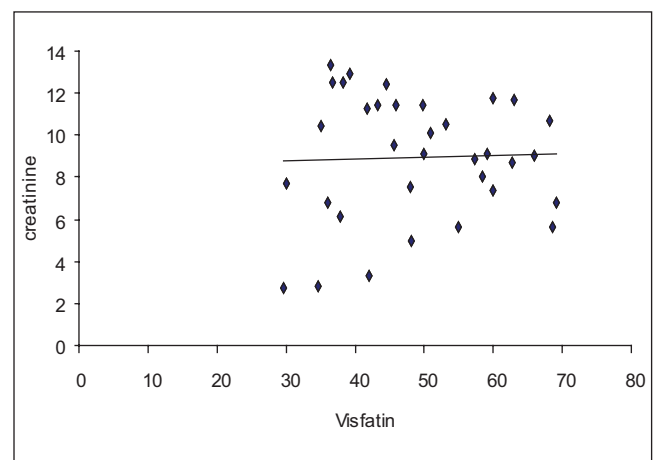
**Figure 6**

A nonsignificant correlation between visfatin and high-density lipoprotein in the uremic group.

in chronic renal patients treated by hemodialysis and compare them with a control group. BMIs were within the normal range in all patients as obesity and high

**Figure 3**

A significant positive correlation between visfatin and low-density lipoprotein in the uremic group.

**Figure 5**

Nonsignificant correlation between visfatin and creatinine in the uremic group.

BMI have an influence on serum visfatin [16] and a positive association between high BMI and risk for CKD has been reported [17,18]. Furthermore, a high BMI is associated with glomerular hyperperfusion and hyperfiltration, resulting in renal injury with proteinuria obesity-related glomerulopathy [19,20]. BMI has been considered as a common, strong, and potentially modifiable independent risk factor for CKD [18].

Obesity is also a risk factor for progressive renal function loss in patients with known renal disease [21]. BMI is an appropriate, simple, and cheap measurement, and a low BMI value is closely associated with mortality in HD patients [22]. Also, BMI is a simple method and reliable indicator to estimate fat mass in dialysis patients [23].

This study showed a highly significant increase in serum visfatin in the CRF group on hemodialysis in



comparison with the healthy control participants; this result in agreement with different studies on CKD from different perspectives [6,24,25].

Axelsson *et al.* [6] reported an elevated serum level in visfatin in CKD and later on, several other studies reported a similar relationship between visfatin and CKD [24,25]. Also, Axelsson *et al.* [6] found visfatin to be associated with soluble vascular adhesion molecule 1, which is a biomarker of endothelial damage in CKD. Moreover, as proteinuria is an important predictor of ED in early diabetic nephropathy, interestingly, an association has been observed between proteinuria and visfatin level [10]. However, our results are in disagreement with the results of Nüsken *et al.* [26], who found decreased serum visfatin among end stage renal disease (ESRD) patients treated by hemodialysis, and this may be attributed to the fact that their patients showed a reduction in body fat mass with increased insulin levels. This increase in insulin level in the study of Nüsken and colleagues may explain the highly significant negative correlation between visfatin and blood sugar (both fasting and postprandial) in the patient group in our study. However, further correlation study is needed to investigate the relation of visfatin to glycemic state with the simultaneous measurement of insulin in normal BMI patients as insulin is known to suppress visfatin level [27]; moreover, an explanation for low blood sugar could be the glucose-lowering effect of visfatin as has been suggested by Naz *et al.* [28]. Also, there may be other factors that have an effect on the visfatin level such as appetite of patients as well as hydration status as has been studied by Chumlea *et al.* [29]. Time of dialyses and dialysis adequacy may also affect visfatin levels in dialyzed patients because of the decreased clearance of visfatin [30].

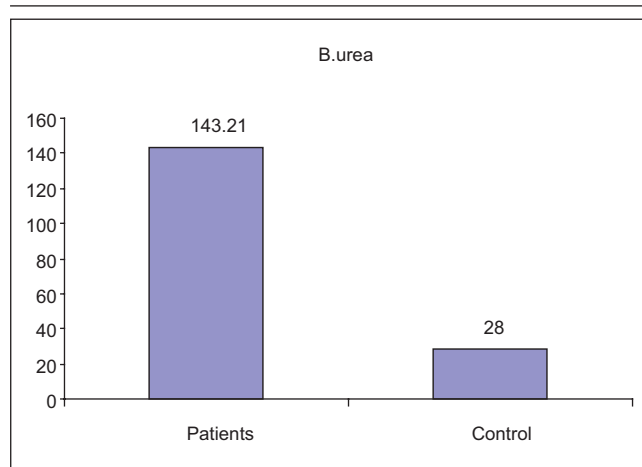
Interestingly, no significant correlation was found between serum visfatin and serum creatinine in our study as well as a significant negative correlation with blood urea (Fig. 7). These results may raise a question: is elevated visfatin because of diminished visfatin clearance or because of an ongoing inflammatory process as has been suggested by Malyszko *et al.* [30]? Our results may, in part, answer this, as we found a lack of correlation between serum visfatin and creatinine and an inverse correlation with urea despite high serum creatinine and urea in the patients in the uremic group (Fig. 8). This hypothesis is also supported by normalization of ED following renal transplantation that is accompanied by a reduction in circulating visfatin [31].

This directs us to the fact that visfatin is primarily an inflammatory cytokine [32] and the role of low-grade inflammation in CKD is no longer unclear [33].

As our results showed a positive correlation between serum visfatin and serum uric acid, taking into consideration that uric acid is an inflammatory marker, Ruggiero *et al.* [34] confirms the association between uric acid and visfatin as an inflammatory marker that plays a role in inflammation and atherosclerosis in HD patients and answers the question of Lobo *et al.* (2013): Is there an association between uric acid and inflammation in hemodialysis patients? Moreover, our results are in agreement with their previous results, which showed that uric acid levels correlate with inflammatory markers and adhesion molecules in hemodialysis patients [35].

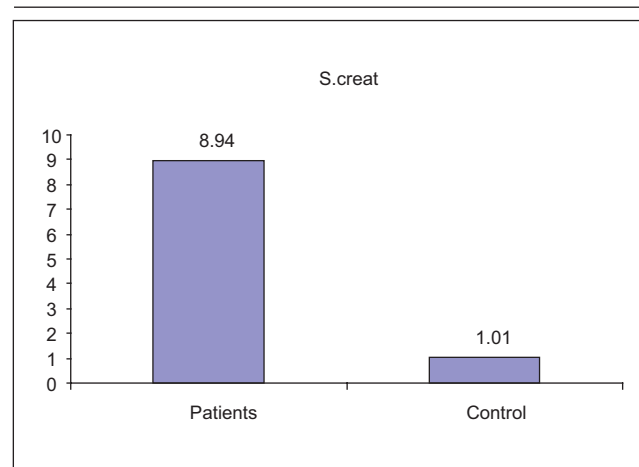
Anemia develops early in the course of CKD and is almost universal in patients with CKD stage 5 [36]; our results showed a highly significant negative correlation with serum visfatin. This relation led

Figure 7



Mean ± SD of blood urea of both groups.

Figure 8



Serum creatinine in the uremic group compared with the control group (mean ± SD).

us to hypothesize that visfatin may have an effect on the pathogenesis of anemia in CRF; thus, further work is needed to examine the relation. Is it just an association, as Orasan *et al.* [37], found that administration of L-carnitine to CRF patients on hemodialysis led to a reduction in visfatin and improvement in ED, but induced no improvement in hemoglobin level, or does it have a causal relation to anemia as has been suggested by Kaygusuz *et al.* [38], that high levels of visfatin may interact with iron parameters. Another explanation could be that visfatin may play a role in erythropoietin insensitivity in addition to reduced erythropoietin production in renal failure patients [39].

In terms of the correlation between serum visfatin and lipid profile, our results showed a significant positive correlation between serum visfatin and serum triglycerides among patients with CRF and this is in agreement with the results of Mu *et al.* [15]; also, the results of Mu and colleagues showed a positive correlation with serum LDL and a negative correlation with serum HDL, and this is in agreement with our results, which showed that serum visfatin is correlated positively with serum LDL and showed no correlation with serum high density lipoprotein (HDL). This supports the role, at least in part, of visfatin in uremia-related atherosclerosis.

## Conclusion

This study concluded that serum visfatin is upregulated in patients with CRF on maintenance hemodialysis; however, further investigations on the relationship between serum visfatin and the various pathophysiological aspects of renal disease are warranted, and we recommend the study of serum visfatin before and after a hemodialysis session. Moreover, serial measurements at the onset of CKD and then during progressively declining stages of renal dysfunction may be more useful to determine the causal relationship between visfatin and CRF and also to study visfatin expression within renal tissues, may clarify its definite role in CRF. Finally, the question of whether visfatin can be used as a surrogate marker in CRF patients may be answered in future studies.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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