Evaluation of serum YKL-40 and cardiovascular risk in chronic kidney disease

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Background Chronic kidney disease (CKD) is a worldwide health problem. Patients with end-stage renal disease have high prevalence of atherosclerosis and consequently development of cardiovascular disease resulting in elevated mortality rates. YKL-40 has been shown to play a role in the pathogenesis of endothelial dysfunction, atherosclerosis, and abnormal angiogenesis. It is closely related to the early and late phases in the development of atherosclerosis.

Aim To study serum YKL-40 levels in patients with CKD and to assess its correlation with high-sensitive C-reactive protein (Hs-CRP) and carotid intima-media thickness (CIMT) as a predictor for early atherosclerosis.

Patients and methods A cross-sectional study included 40 CKD patients. Group I was classified into: Ia which 20 patients on regular hemodialysis and Ib which included 20 predialysis patients' CKD (stages 4–5), compared with 40 healthy controls of the same age and sex (group II). Routine laboratory investigations were done and serum Hs-CRP and YKL-40 level were measured in both groups and healthy controls. CIMT was measured by B-mode ultrasound.

Results There were a highly significant increase of serum YKL-40 and Hs-CRP levels and intima-media thickness of carotid artery in group I when compared with the control group and a highly significant increase in group Ia in comparison to group Ib. There were highly significance positive correlations between YKL-40 level and Hs-CRP, CIMT in groups Ia and Ib.

Conclusion The study concluded that the serum level of YKL-40 is significantly elevated in patients with chronic renal failure both hemodialysis and predialysis and there was significant positive correlation between YKL-40 and CIMT as well as Hs-CRP in all patients with chronic renal failure. We suggest that YKL-40 had a role as an inflammatory marker and for early detection of atherosclerosis.

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Keywords: carotid intima-media thickness, chronic kidney disease, cardiovascular disease, hemodialysis, high-sensitive C-reactive protein, YKL-40

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Introduction

Chronic renal failure (CRF) is a worldwide public health problem [1]. Patients with CRF have significantly increased risk of atherosclerosis and development of cardiovascular disease (CVD) resulting in increased mortality rates [2]. Atherosclerosis in patients with chronic kidney disease (CKD) has many contributing factors: one of them is chronic inflammation which has an important effect on the vascular endothelium leading to the development of CVD in patients with CRF [3]. Acute-phase protein and proinflammatory mediators are increased, maybe, due to impaired renal functions or dialysis per se [2]. A wide array of inflammatory mediators serve as indexes of inflammation and are also related to the development of atherosclerotic CVD [4]; high-sensitive C-reactive protein (Hs-CRP) is one of the inflammatory biomarkers that is used to assess inflammation in CRF patients. YKL-40 is one of the inflammatory biomarkers, which is expressed by several cell types of the immune system. It has an important role in the pathogenesis of endothelial dysfunction, atherosclerosis, and abnormal angiogenesis [5]. YKL-40 is expressed by macrophage and the highest expression was found in macrophages in early atherosclerotic lesions, suggesting that early atherosclerosis can be detected by measurement of serum YKL-40 [6]. Since the atherosclerotic changes in the carotid artery are the mirror reflection of pathological events of generalized atherosclerosis, measurements of intima-media thickness of carotid arteries by ultrasound can be used as an indicator of atherosclerosis [7]. Carotid intima-media thickness (CIMT) has proved to be a noninvasive, sensitive, and specific quantitative measure of early atherosclerosis. An increment of 0.1 mm in IMT is associated with 24–31% increased risk of cardiovascular mortality in dialysis patients.

Aim

This work was carried out to evaluate serum YKL-40 level in patients with CKD and to assess its correlation with Hs-CRP (as established by inflammatory and cardiovascular markers) and CIMT as a predictor for early atherosclerosis [7].

Patients and methods

Patients

This study included 40 patients with CKD (group I), they were 19 men and 21 women and their ages ranged between 25 and 65 years with a mean±SD of 42.05 ±11.36. The duration of CKD ranged between 12 and 60 months), with a mean±SD of 41.85±10.57 months and age-matched 40 apparently healthy participants as a control (group II)

The patients were recruited from Internal Medicine Department and Nephrology Unit in Al-Zahraa University Hospital during the period from April 2014 to January 2015. From all participants participating in the study an oral consent was taken. Also approval of the ethics committee of Faculty of Medicine, Al-Azhar University was obtained.

We classified our patients (group I) into two subgroups: group Ia included 20 patients on regular hemodialysis (HD) (10 men and 10 women); their ages ranged between 25 and 65 years with mean±SD of 41.70±11.31 years. The duration of HD ranged between 36 and 60 months with mean±SD of 36.30 ±8.14 months and group Ib included 20 predialysis patients' CKD (stages 4–5), they were nine men and 11 women, their ages ranged between 25 and 65 years with mean±SD of 42.40±11.68 years.

Inclusion criteria

Adult patients with CKD with age more than 18 years, not diabetic, or hypertension, or ischemic heart disease, and with body mass index of less than 35 kg/m^2.

Exclusion criteria

Patients with acute or chronic known infection other than pyelonephritis, CVD, diabetes mellitus, hypertension, autoimmune disease, malignancy, chronic liver disease (hepatitis B or C), or HIV infection were excluded from the study.

All patients and control were subjected to the following:

(1) Full history taking and full clinical examination.
(2) Five milliliters of fasting (12–16 h) venous blood samples were collected from each participants participating in the study and were divided into two parts: The first part was 4 ml of blood collected in an EDTA containing tubes for the determination of complete blood count on Coulter counter-T890 (Coulter Counter, Harpenden, UK). The second part was 4 ml of venous blood and was left to clot. Serum should be separated from the cells as soon as possible by centrifugation at 3000*g* for 5 min. The separated serum was stored at −20°C until analysis of fasting blood glucose (immediately), kidney function tests, albumin, lipid profile, Hs-CRP, and YKL-40.
(3) Determination of kidney function tests, albumin, fasting blood glucose, and lipid profile were carried out on Dimension RxL Max analyzer (Siemens Healthcare GmbH – Henkestr, Erlangen, Germany) by colorimetric techniques.
(4) Determination of Hs-CRP was performed by a solid-phase immunosorbent assay (ELISA) [8] and the kit was supplied by DRG International Inc. (841 Mountain Avenue, Springfield, New Jersey, USA).
(5) Estimated glomerular filtration rate (eGFR) using modification of diet in renal disease formula [9]:

$$\begin{aligned}\text{eGFR} = {} & 186 \times \text{serum creatinine} \\ & (\text{mg/dl})^{-1.154} \times \text{age}^{-0.203} \\ & \times (1.212 \text{ if black}) \times (0.742 \text{ if female}).\end{aligned}$$

or

$$\begin{aligned}\text{eGFR} = {} & \text{eGFR} \\ & = 170 \times \text{serum creatinine}(\text{mg/dl})^{-0.999} \\ & \times \text{age}^{-0.176} \times (0.762 \text{ if female}) \\ & \times (1.180 \text{ if black}) \times \text{BUN}(\text{mg/dl})^{-0.170} \\ & \times \text{albumin}^{0.318}.\end{aligned}$$

Determination of serum YKL-40 was performed using enzyme immunoassay method [10] and the kit was supplied from MicroVue (Quidel Corporation, San Diego, California, USA).
(6) CIMT of carotid artery measurement was done by using B-mode ultrasound with a high definition L12-5 linear wideband probe (Philips HDI 5000, Bothell, Washington, USA). Common carotid artery IMT measurements of the proximal and distal common carotid artery posterior wall were done manually by the provided distance measurement system of the sonography device after magnification of the images.

Statistical analysis

Data were analyzed by Microsoft Office 2003 (Excel) (Impressa Systems, Santa Rosa, California, USA) and statistical package for social sciences, version 10. Parametric data were expressed as mean±SD and nonparametric data were expressed as number and percentage of the total. Comparing (mean±SD) of the two groups was done using the paired and

unpaired Student's *t* test. Determining the extent that a single observed series of proportions differs from a theoretical or expected distribution was done using the χ^2test. The correlation between different studied parameters was done using Pearson's correlation coefficient. A *P* value more than 0.05 is considered nonsignificant; *P* value less than 0.05 is considered significant; and a *P* value less than 0.01 is considered highly significant.

Results

The causes of CKD in 40 patients studied: in group Ia 20 patients on regular HD. There were nine (45%) patients who had bilateral small contracted kidneys, five (25%) patients who had recurrent pyelonephritis, four (20%) patients who had urinary tract blockages and reflux, and two (10%) patients who had polycystic kidneys, while in group Ib predialysis patients, there were 10 (50%) patients who had urinary tract blockages and reflux obstructive uropathy; seven (35%) patients who had bilateral small contracted kidneys; and three (15%) patients who had polycystic kidney (Table 1).

There were a highly significant increases in the mean ±SD of serum urea, creatinine in group I (122.68 ±43.41, 5.45±2.10) when compared with group II (19.55±4.89, 0.85±0.19), respectively (*P*<0.01). Also there were a highly significant increase in the mean ±SD of serum low-density lipoprotein (LDL), cholesterol, triglyceride (TG) in group I (126.83 ±18.78, 189.73 ±26.92, 115.58±39.15) when compared with group II (10528±11.22, 165.83 ±19.22, 87.48±17.66), respectively (*P*<0.01). There was a significant increase in the mean±SD of white blood cells in group I (6.88±1.92) when compared with group II (6.05± 0.94) (*P*<0.05), while there was a highly significant decrease in the mean±SD of red blood cells (RBCs), hemoglobin (Hb) in group I (3.61±1.00, 9.90±1.91) when compared with group II (4.14±0.35, 12.17±0.71), respectively (*P*<0.01). There was a highly significant decrease in the mean ±SD of eGFR, serum high-density lipoprotein (HDL), serum albumin in group I (14.08±3.45, 43.85 ±14.04, 3.72±0.38) when compared with group II (110.44±19.38, 56.33±11.52, 4.50 ±0.45), respectively (*P*<0.01) (Table 2).

There was a highly significant increase in mean±SD of serum YKL-40, serum Hs-CRP, and CIMT in group I (286.45±44.60, 23.16±9.3, 0.72±0.14) when compared with group II (62.19±14.11, 5.93±2.45, 0.26±0.13), respectively (*P*<0.01) (Table 2, Fig. 1).

There was a highly significant decrease in the mean ±SD of RBCs, Hb in group Ia (20 patients on regular HD) (3.22±1.18, 8.60±1.76) when compared with group Ib (20 predialysis patients) (4.04±0.45, 11.20 ±0.97), respectively (*P*<0.01). There was a highly significant increase in the mean±SD of serum urea, creatinine in group Ia (142.60±48.16, 6.70±2.21) when compared with group Ib (102.75±26.68, 4.20±0.91), respectively (*P*<0.01), while there was a highly significant decrease in the mean±SD of eGFR, serum HDL, in group Ia (11.12±2.49, 38.10±8.86)

Table 1 Causes of chronic renal failure in group I (40 patients with chronic kidney disease)

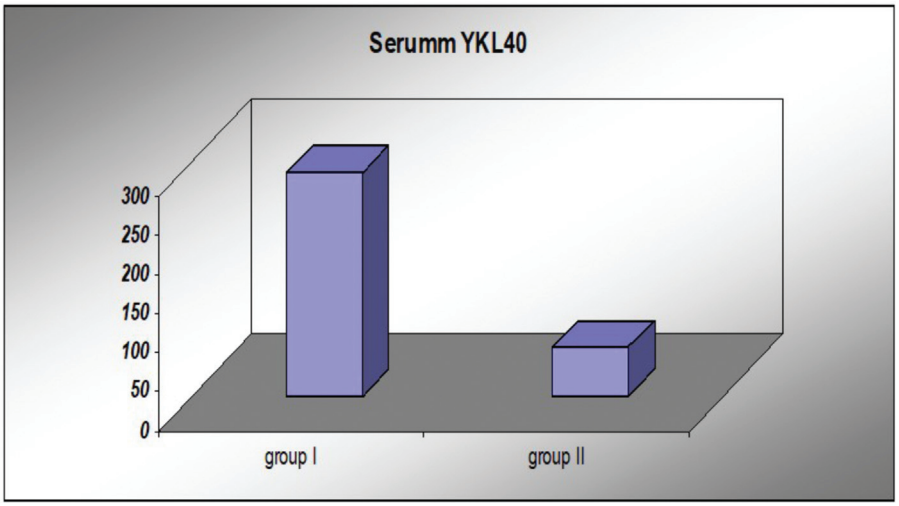
Causes of renal failure	Total patients (*N*=40) [*n* (%)]	Group Ia (*N*=20) [*n* (%)]	Group Ib (*N*=20) [*n* (%)]
Small sized kidneys	16 (40)	9 (45)	7 (35)
Urinary tract blockages	14 (35)	4 (10)	10 (50)
Polycystic kidneys	5 (12.5)	2 (10)	3 (15)
Recurrent pyelonephritis	5 (25)	5 (25)	–

Table 2 Comparison between groups I and II

Parameters	Group I	Group II	*P* value	S
WBCs (/cmm)	6.88±1.92	6.05±0.94	<0.05	S
RBCs (/cmm)	3.61±1.00	4.14±0.35	<0.01	HS
Hb (g/dl)	9.90±1.91	12.17±0.71	<0.01	HS
Serum urea (mg/dl)	122.68 ±43.41	19.55±4.89	<0.01	HS
Serum creatinine (mg/dl)	5.45±2.10	0.85±0.19	<0.01	HS
eGFR (ml/min)	14.08±3.45	110.44 ±19.38	<0.01	HS
LDL (mg/dl)	126.83 ±18.78	105.28 ±11.22	<0.01	HS
HDL (mg/dl)	43.85 ±14.04	56.33 ±11.52	<0.01	HS
Serum cholesterol (mg/dl)	189.73 ±26.92	165.83 ±19.22	<0.05	HS
Serum TG (mg/dl)	115.58 ±39.15	87.48 ±17.66	<0.01	HS
ALB (g/dl)	3.72±0.38	4.50±0.45	<0.01	HS
FBG (mg/dl)	94.92 ±13.93	94.32 ±10.47	>0.05	NS
Serum YKL-40 (ng/l)	286.45 ±44.60	62.19 ±14.11	<0.01	HS
Serum Hs-CRP (mg/l)	23.16±9.33	5.93±2.45	<0.01	HS
CIMT (mm)	0.72±0.14	0.26±0.13	<0.01	HS

Data are presented as mean±SD. ALB, serum albumin; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; Hb, hemoglobin; HDL, high-density lipoproteins; HS, highly significant; Hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoproteins; RBC, red blood cell; S, significant; S. TG, serum triglyceride; WBC, white blood cell.

Figure 1



Comparison between groups I and II as regards serum YKL-40.

Table 3 Comparison between groups Ia and Ib

Parameters	Group Ia	Group Ib	*P* value	S
WBCs (/cmm)	7.75±2.20	6.00±1.05	>0.05	NS
RBCs (/cmm)	3.22±1.18	4.04±0.45	< 0.01	HS
Hemoglobin (mg/dl)	8.60±1.76	11.20±0.97	<0.01	HS
Serum urea (mg/dl)	142.60 ±48.16	102.75 ±26.68	<0.01	HS
Serum creatinine (mg/dl)	6.70±2.21	4.20±0.9 1	< 0.01	HS
eGFR (ml/min)	11.12±2.49	19.42±7.01	<0.01	HS
HDL (mg/dl)	38.10±8.86	49.70 ±15.85	<0.01	HS
Cholesterol (mg/dl)	204.15 ±28.00	175.30 ±16.30	<0.01	HS
TG (mg/dl)	134.20 ±35.76	96.95 ±33.73	<0.01	HS
LDL (mg/dl)	132.05 ±19.76	121.88 ±17.15	>0.05	HS
ALB (g/dl)	3.74±0.24	3.82±0.36	>0.05	NS
FBG (mg/dl)	95.48±9.50	94.37 ±17.53	>0.05	NS
Serum YKL-40	321.80 ±25.46	249.24 ±25.78	<0.01	HS
Serum Hs-CRP (mg/l)	30.55±7.84	15.78±1.59	<0.01	HS
CIMT	0.80±0.10	0.63±0.12	<0.01	HS

Data are presented as mean±SD. ALB, albumin; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL, high-density lipoprotein; HS, highly significant; Hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; RBC, red blood cell; S, significant; TG, triglyceride; WBC, white blood cell.

when compared with group Ib (19.42±7.01, 49.70 ±15.85), respectively (P<0.01) (Table 3).

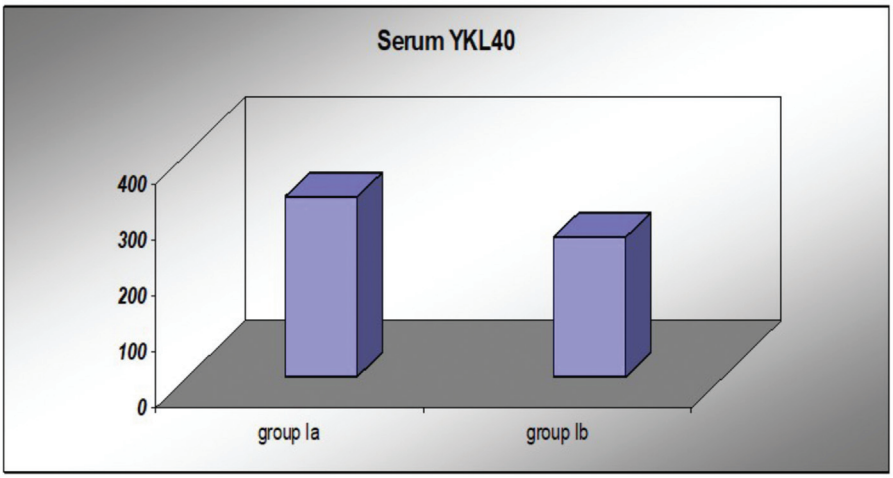
There was a highly significant increase in the mean ±SD of serum cholesterol, TG, LDL in group Ia (204.15±28.0, 134.20±35.76, 132.05±19.76) when compared with group Ib (175.30±16.3, 96.95 ±33.73, 121.88±17.15), respectively (P<0.01) (Table 3). Also there was a highly significant increase in the mean±SD of serum YKL-40, serum Hs-CRP (CIMT), in group Ia (321.80±25.46, 30.55 ±7.84, 0.80±0.10) when compared with group Ib (249.24±25.78, 15.78±1.59, 0.63±0.12), respectively (P<0.01) (Table 3, Figs 2–4).

In group I (40 patients with chronic kidney), there was a significant positive correlation between serum YKL-40 level and each of serum urea (P<0.05), serum creatinine (P<0.01), total serum cholesterol (P<0.01), serum TG (P<0.01) serum LDL (P<0.01), serum Hs-CRP (P<0.01), and CIMT (P<0.01), While there was significant negative correlation between serum YKL-40 level and each of eGFR (P<0.01), Hb level (P<0.01) and serum HDL (P<0.01). Also there was nonsignificant negative correlation between YKL-40 level and serum albumin (P>0.05) (Table 4, Figs 5 and 6).

Regarding the correlation of serum YKL-40 level and studied parameters in group Ia (20 patients with CRF on regular dialysis), there was positive correlation between serum YKL-40 level and with each of serum albumin (P<0.01), Hb level (P<0.01), and), and a nonsignificant negative correlation was noted of serum urea (P<0.05), serum creatinine (P<0.05), total serum cholesterol (P<0.01), serum TG (P<0.01), serum Hs-CRP (P<0.01), and CIMT (P<0.05). However, there was negative significant correlation between serum YKL-40 and each of eGFR and LDL (P>0.05) (Table 5).

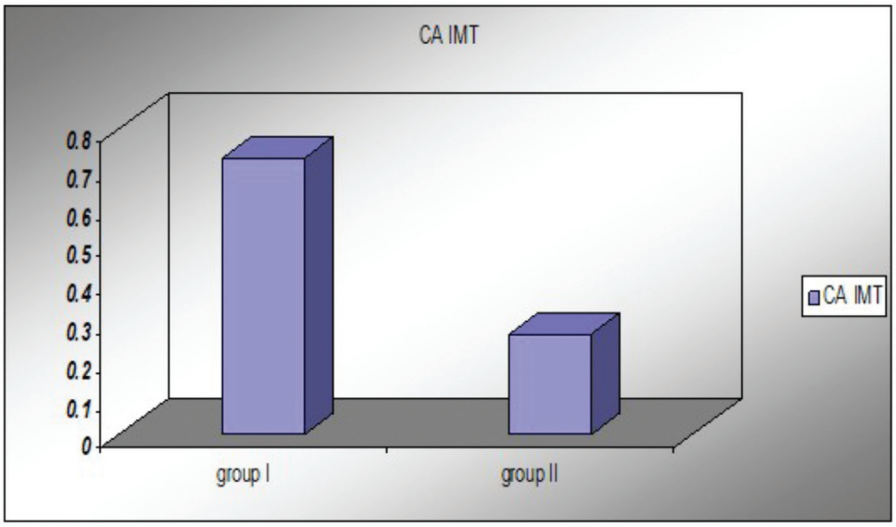
Among patients with CKD (predialysis group Ib) there was positive correlation between serum YKL-40 and each

Figure 2



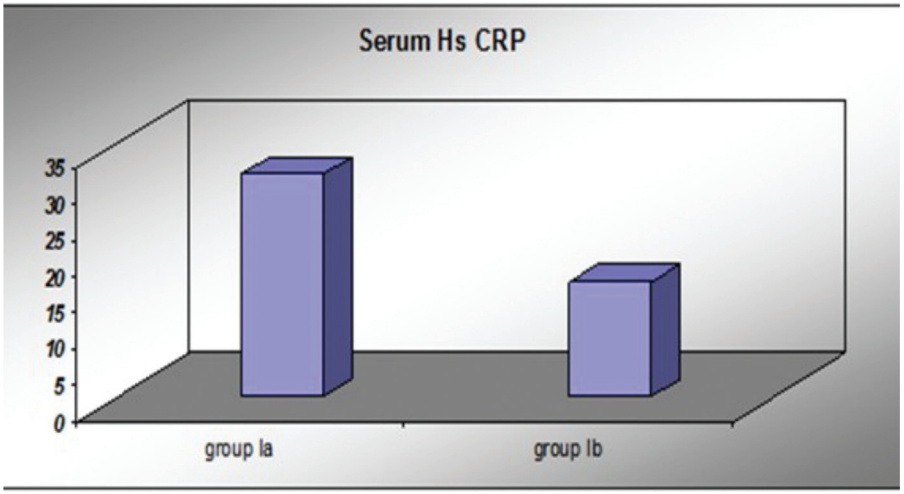
Comparison between groups Ia and Ib as regards serum YKL-40

Figure 3



Comparison between groups Ia (under hemodialysis) and Ib (predialysis) as regards CIMT. CIMT, carotid intima-media thickness.

Figure 4



Comparison among groups Ia (under hemodialysis) and Ib (predialysis) as regards serum Hs-CRP. Hs-CRP, high-sensitive C-reactive protein.

of serum urea ($P<0.05$), serum creatinine ($P<0.05$), serum Hs-CRP ($P<0.01$), and CIMT ($P<0.05$), while a negative correlation was noted between serum YKL-40 and Hb level ($P<0.05$) (Table 6).

A nonsignificance correlation was noted between serum YKL-40 and each of eGFR, lipid profile (total serum cholesterol, serum TG, LDL, HDL), and serum albumin ($P>0.05$) (Table 6).

Discussion

In the present study, there is a high significant elevation of serum level of both YKL-40 and Hs-CRP in all patients with CKD (group I) compared with the control (group II) and this elevation was more significant in HD patients (group Ia) than in the predialysis (group Ib).

Table 4 Correlation between YKL-40 level and some studied parameters of group I

Parameters	YKL-40 (*r*)	*P* value	S
eGFR	−0.435	<0.01	HS
Serum urea	0.334	<0.05	S
Serum creatinine	0.449	<0.01	HS
LDL	0.330	<0.05	HS
HDL	−0.455	<0.01	HS
Cholesterol	0.478	<0.01	HS
TG	0.343	<0.01	HS
ALB	−0.345	>0.05	NS
Hb	−0.487	<0.01	HS
Serum Hs-CRP	0.938	<0.01	HS
CIMT	0.347	<0.05	S

ALB, albumin; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL, high-density lipoprotein; HS, highly significant; Hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; S, significant; TG, triglyceride.

Moreover, there was high significant positive correlation between YKL-40 and Hs-CRP in all patients with CKD either in the predialysis or the HD group.

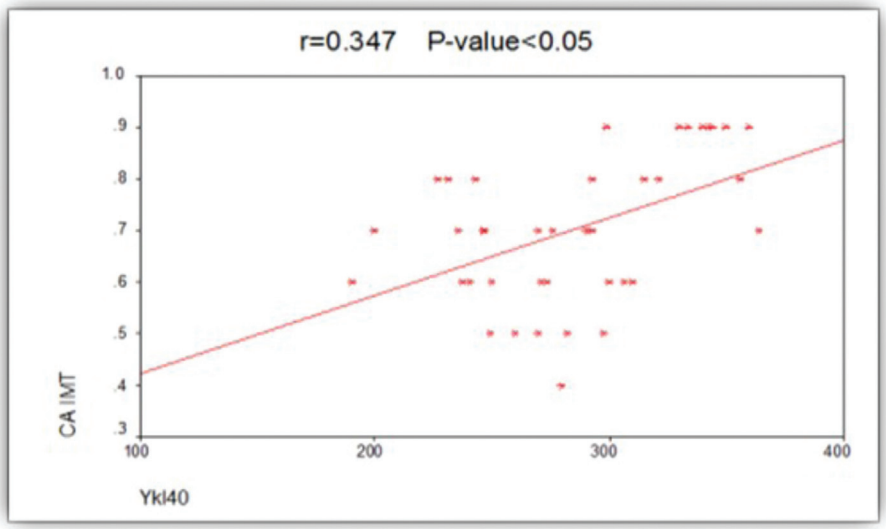
Johansen *et al.* [11] reported that plasma YKL-40 concentrations was decreased the renal vein compared with the femoral artery. This finding supports the renal clearance of YKL-40. Therefore, it is reasonable to speculate that an increased level of this glycoprotein may be due to decreased renal clearance or dialysis procedure per se [12].

Schiavon *et al.* [13] and Lee and Elias [14] demonstrated that YKL-40 is excreted by the kidney and elevated serum YKL-40 level may be a consequence of impaired clearance or catabolism of YKL-40 in the kidney which may lead to the accumulation of YKL-40 in the blood. This suggests that elevated serum YKL-40 level was significantly associated with elevated serum creatinine and urea in predialysis and HD patients.

Pawlak *et al.* [15] found a fivefold higher YKL-40 levels in HD, especially in those with CVD.

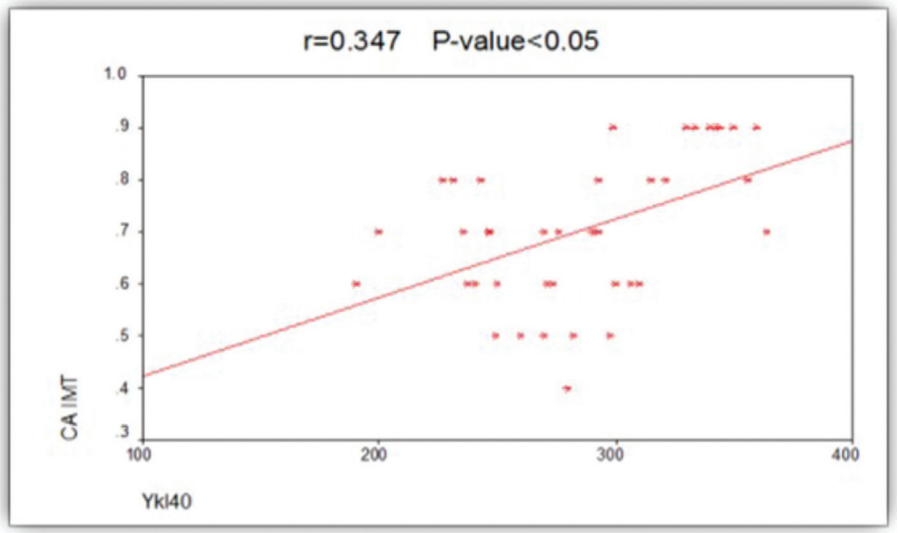
Razeghi *et al.* [16] reported that increased marker of inflammation in patients on regular dialysis has increased the risk of cardiovascular events and death. The high levels of CRP in HD patients become a strong determinant of mortality and morbidity as shown in many studies.

Figure 5



Correlation between YKL-40 level and CIMT level in group I. CIMT, carotid intima-media thickness.

Figure 6



Correlation between YKL-40 level and Hs-CRP in group I. Hs-CRP, high-sensitive C-reactive protein.

Table 5 Correlation between YKL-40 level and some studied parameters of group Ia

Parameters	YKL-40 (*r*)	*P* value	S
eGFR	–0.166	>0.05	NS
Serum urea	0.456	<0.05	S
Serum creatinine	0.450	<0.05	S
LDL	0.153	>0.05	NS
HDL	–0.047	<0.05	S
Serum cholesterol	0.009	<0.01	HS
TG	0.153	>0.05	NS
ALB	–0.486	<0.01	HS
Hb	–0.452	<0.01	HS
Serum Hs-CRP	0.983	<0.01	HS
CIMT	0.475	<0.05	S

ALB, albumin; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL, high-density lipoprotein; HS, highly significant; Hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; S, significant; TG, triglyceride.

Table 6 Correlation between YKL-40 level and some studied parameters of group Ib

Parameters	YKL-40 (*r*)	*P* value	S
eGFR	–0.310	>0.05	NS
Serum urea	0.468	<0.05	S
Serum creatinine	0.477	<0.05	S
LDL	0.200	>0.05	NS
HDL	–0.170	>0.05	NS
Serum cholesterol	0.093	>0.05	NS
TG	0.091	>0.05	NS
ALB	–0.137	>0.05	NS
Hb	–0.462	<0.05	S
Hs-CRP	0.955	<0.01	HS
CIMT	0.444	<0.05	S

ALB, albumin; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL, high-density lipoprotein; HS, highly significant; Hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; S, significant; TG, triglyceride.

According to many studies CRP could be a powerful predictor of mortality in dialysis patients; this finding obtained from the study done by Zimmermann *et al.* [17], revealed that patients with a CRP of more than 10 mg/l have higher mortality rate when compared with patients having a CRP of less than 10 mg/l, according to a 7-year follow-up. Moreover, another study showed that the patients' CRP level of 7.5 mg/l have 2.7 times higher mortality risk than patients with a CRP level less than 3.3 mg/l [18].

Our study has shown that serum YKL-40 has positively correlated CRP level. In dialysis patients Hs-CRP is the most powerful predictor of mortality [18].

Kanwar *et al.* [19] showed that Hs-CRP is the major acute-phase protein and an established nonspecific marker of inflammation. A number of epidemiological studies have shown that Hs-CRP is an important risk factor for atherosclerosis and coronary heart disease. Pasceri *et al.* [20] reported that Hs-CRP directly increased vascular cell adhesion molecules and intercellular adhesion molecule in human endothelial cells demonstrating the direct proinflammatory effect of Hs-CRP.

Ridker [21] identified CRP as a marker of inflammation and predictive factor for coronary artery disease in patients with CKD and in general population. This finding suggesting that inflammation is an additional mechanism contributing to the development of atherosclerotic disease.

One of the proinflammatory cytokines, interleukin-6 (IL-6) which has an important role in chronic

inflammation, leads to the accumulation of mononuclear cell at the site of injury and also CRP, which is produced by the liver is regulated by IL-6 [22]. Another study reported that elevated IL-6 concentrations lead to increased concentrations of YKL-40 [23].

IL-6 and YKL-40 are released from activated macrophages at the site of inflammation, before the appearance of the central inflammatory response and then rapidly decline after beginning of antibiotic therapy while the CRP remains high for a longer time when compared with the results of Nordenbaek *et al.* [24]. Studies evaluating its place in chronic inflammatory states revealed different results, some manifested positive correlations of YKL-40 with Hs-CRP [25], while some did not [26].

Our study has shown high significant increase of CIMT in group I in comparison to group II, particularly in the HD group compared with the predialysis one.

Early vascular changes in patients with CKD could be obtained by measurement of IMT of carotid arteries and can predict patients with high risk factor [27].

Another study done by Szeto *et al.* [28] found that decreased kidney function is associated strongly with faster change in CIMT. In this study, a higher value of mean carotid CIMT was observed in patients with CKD on HD and predialysis.

Our study is in agreement with Trimarchi *et al.*[29]; who showed that increased carotid artery IMT is considered as a marker of early atherosclerotic changes in CRF and has significantly increased CVD risk in any age group.

Our study has shown that there is a positive correlation between serum YKL-40 and CIMT; this result is in agreement with Libby and Braunwald [30]; who reported that some of the key elements in the early development of atherosclerosis in humans are increased transport of lipids across the endothelial vessel wall and maturation of monocytes to macrophage in the arterial intima layer. The activated macrophages secrete inflammatory mediators that stimulate vascular smooth muscle cells (VSMC) migration and proliferation and participate in plaque development and thrombus formation [30,31]. Therefore, one of the indicators of the risk of developing an acute coronary syndrome or death in CRF patients could be the measure of the inflammatory activity in coronary artery plaques [32].

As regards lipid profile, our results have shown a highly significant increase in serum cholesterol, TG, LDL levels in group I when compared with group II, and also a highly significant increase in group Ia (HD patients) when compared with group Ib (predialysis) for both.

Lipid abnormalities have been postulated to contribute to the high incidence of CVD and they are common in patients with CRF. Generally, uremia is accompanied with elevated levels of TGs, total cholesterol, and LDL cholesterol while usually with decreased HDL cholesterol levels. This pattern of lipid abnormalities is associated with accelerated atherosclerosis [3].

Lipid parameters of our CRF patients were consistent with the previous findings including a high significant increase in serum cholesterol, TG, LDL cholesterol in group I compared with the control, while HDL cholesterol was significantly decreased, putting in mind the significant increase was more in HD patients than the predialysis group. We also observed inverse relationships of HDL cholesterol with Hs-CRP, YKL-40 as well as CIMT which is in agreement with Keane *et al.* [33].

In agreement with our results, Nassiri *et al.* [34]; found that more than 90% of HD patients were suffering from dyslipidemia manifested by high levels of cholesterol, TG, or both, and low levels of HDL cholesterol. Also, our result agree with Liu *et al.* [35], who reported that lipid abnormalities start early in patients with CRF and progress with declining of renal function and this leads to cardiovascular disorders which may be the leading cause of death in these patients.

Mora *et al.* [36] found that patients receiving dialysis have elevated TG and more atherogenic lipid profile. The majority of these patients have significantly elevated levels of total and LDL cholesterol markedly elevated apolipoprotein B and low level of HDL cholesterol

Many studies have shown that with decreasing of GFR there is an elevation of lipoproteins in both predialysis and HD patients [37]. These results could be due to increased synthesis by the liver or due to its decreased catabolism in the kidneys. This decreased clearance could be the result of loss in kidney function, in HD patients.

Our results agree with Lowrie and Lew [38], who found that there is a highly significant increase of serum total cholesterol levels in HD patients compared with the controls.

In our study, there was a significant decrease of serum albumin levels in all patients with CRF, particularly in the HD group. Moreover, there was significant negative correlation between serum albumin and Hs-CRP, YKL-40 as well as CIMT.

Malnutrition and hypoalbuminemia have been shown to be important predictors of mortality and hospitalization in patients with CRF, and an association between the presence of cardiac disease and hypoalbuminemia in HD patients has been reported [39].

In agreement with our results Kaysen [40] found that there was a negative correlation between acute-phase proteins, such as Hs-CRP and serum albumin. Low serum albumin concentration was used as an index of malnutrition and was associated with increased mortality risk in patients with renal replacement therapy.

It is notable that most CKD patients with malnutrition had signs of acute-phase response and/or carotid plaques, suggesting that malnutrition is closely associated with both atherosclerotic vascular disease and inflammatory response. This could be the result of acute-phase response in the liver induced by the proinflammatory mediators leading to increase albumin degradation. Accordingly, malnourished patients had significantly elevated CRP indicating an inflammatory process [41].

In CKD patients, an inverse correlation between CRP level and serum albumin has been noticed and also an association between CVD development and low serum albumin levels has been shown. This can be explained by the increased proinflammatory cytokines which inhibit appetite, decrease albumin synthesis in the liver, and decreased erythropoiesis in the bone marrow [33].

Owen *et al*. [42] demonstrated that hypoalbuminemia was a strong predictor of mortality in dialysis patients.

Also Kalantar-Zadeh *et al*. [43] showed higher mortality in dialysis patients with lower albumin. Many studies have shown that serial measurement of serum albumin can even better predict chronic inflammation and clinical events.

Looking at the results of all these studies, it is clear that hypoalbuminemia is adversely associated with CVD in end-stage renal disease. Stenvinkel *et al*. [39] were the first to demonstrate that patients in predialysis CRF with carotid plaque have lower serum albumin level. Joki *et al*. [44] demonstrated that even in the predialytic phase of CRF, hypoalbuminemia is an excellent reflection of CVD.

These results indicate that elevated serum markers of inflammation are associated with poor nutritional outcome in end-stage renal disease patients resulting in increased morbidity and mortality.

Our results have shown a highly significant reduction of RBCs and Hb in group I when compared with group II, also a highly significant reduction of RBCs and Hb in group Ia when compared with group Ib for both.

The hemopoietic response to inflammation includes anemia secondary to reduced erythropoiesis. This has been attributed to the inhibition of erythropoietin secretion by proinflammatory cytokines [45].

Inflammation can also induce a functional iron deficiency, as cytokines can inhibit the delivery of iron from reticuloendothelial cells to hematopoietic cells. Also, patients with high Hs-CRP levels showed poor response to erythropoietin therapy meaning that the patients had a low rise in Hb for the same dose of erythropoietin. It has been reported that the dose of erythropoietin required for maintaining a certain Hb level in dialysis patients may be increased by 30 to 70% in those individuals who have high Hs-CRP levels as compared with those having lower values [46].

Francisco *et al*. [47] reported that blood loss either occult or overt occurs in frequent blood sampling, blood loss during HD, and gastrointestinal bleeding due to increased bleeding tendency and gastritis caused by uremia while Stenvinkel *et al*. [39] reported that infection and inflammation to be another cause of anemia in CRF.

Eschbach *et al*. [48] explained that bone marrow suppression may also be present as a result of uremic toxins as well as proinflammatory cytokines. Also Macdougall [49] reported that the presence of uremic inhibitors, for example, parathyroid hormone, spermine, and aluminum toxicity is another cause of anemia in CRF.

Levin *et al*. [50] reported that anemia leads to left ventricular dilatation and/or left ventricular hypertrophy.

Many studies found anemia in renal impairment patients and HD patients due to decreased erythropoietin (the most important factor), iron deficiency, folate deficiency, hemolysis, and bone marrow fibrosis due to the shortened life span of RBCs.

Fishbane *et al*. [51] reported that anemia is a predictable consequence of CRF and generally develops long before the end-stage renal disease and the main cause of anemia is erythropoietin deficiency which is responsible for maintaining the proliferation and differentiation of erythroid cell growth in the bone marrow.

Conclusion

The study concluded that the serum level of YKL-40 is significantly elevated in patients with CKD both HD or predialysis and there was significant positive correlation between YKL-40 and CIMT as well as Hs-CRP in all patients with CKD. The association between YKL-40 and the standard inflammatory parameter, CIMT, and low serum albumin suggest that YKL-40 had a role as inflammatory marker and in the early detection of atherosclerosis.

Recommendation

Further studies are recommended to study the relationship between serum YKL-40 concentration and other early markers of kidney diseases as cystatin C and neutrophil gelatinase associated lipocalin and relation of it to the causes of CKD.

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Conflicts of interest

There are no conflicts of interest.

References

1 O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, *et al.* Age affects outcome in chronic kidney disease. *J Am Doc Nephrol* 2007; **18**:2758–2765.

2 Recio-Mayoral A, Banerjee D, Streather C, Kaski JC. Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease – a cross-sectional study of pre dialysis, dialysis and kidney-transplantation patients. *Atherosclerosis* 2011; **216**:446–451.

3 Nusair MB, Rajpurohit N, Alpert MA. Chronic inflammation and coronary atherosclerosis in patients with end-stage renal disease. *Cardiorenal Med* 2012; **2**:117–124.

4 Davis R, Bansal V, Litinas E, Hoppensteadt D, Thethi I, Nelson K, Fareed J. Up regulation of inflammatory mediators in end-stage renal disease as measured using biochip array technology. *Clin Appl Thromb Hemost* 2011; **17**:218–223.

5 Takahashi R, Ito Y, Takahashi H, Ishii H, Kasuga H, Mizuno M, *et al.* Combined values of serum albumin, C-reactive protein and body mass index at dialysis initiation accurately predicts long-term mortality. *Am J Nephrol* 2012; **36**:136–143.

6 Kastrup J. Can YKL-40 be a new inflammatory biomarker in cardiovascular disease? *Immunobiology* 2012; **217**:483–489.

7 Michelsen AE, Rathcke CN, Skjelland M, Holm S, Ranheim T, Krohg-Sørensen K, *et al.* Increased YKL-40 expression in patients with carotid atherosclerosis. *Atherosclerosis* 2010; **211**:589–595.

8 Grad E, Pachino RM, Fitzgerald GA, Danenberg HD. Role of thromboxane receptor in C-reactive protein-induced thrombosis. *Arterioscler Thromb Vasc Biol* 2012; **32**:2468–2474.

9 Kallner A, Ayling PA, Khatami Z. Does eGFR improve the diagnostic capability of S-Creatinine concentration results? A retrospective population based study. *Int J Med Sci* 2008; **5**:9–17.

10 Wang X, Xing GH. Serum YKL-40 92 concentrations are elevated and correlated with disease severity in patients with obstructive sleep apnea syndrome. *Scand J Clin Lab Invest* 2014; **74**:74–78.

11 Johansen JS, Møller S, Price PA, Bendtsen F, Junge J, Garbarsch C, Henriksen JH. Plasma YKL-40: a new potential marker of fibrosis in patients with alcoholic cirrhosis? *Scand J Gastroenterol* 1997; **32**:582–590.

12 Okyay GU, Er RE, Tekbudak MY, Paşaoğlu Ö, Inal S, Öneç K, *et al.* Novel inflammatory marker in dialysis patients: YKL-40. *Ther Apher Dial* 2013; **17**:193–201.

13 Schiavon LL, Narciso-Schiavon JL, Carvalho Filho RJ, Sampaio JP, Medina-Pestana JO, Lanzoni VP, *et al.* Serum levels of YKL-40 and hyaluronic acid as noninvasive markers of liver fibrosis in haemodialysis patients with chronic hepatitis C virus infection. *J Viral Hepat* 2008; **15**:666–667.

14 Lee CG, Elias JA. Role of breast regression protein-39/YKL-40 in asthma and allergic responses. *Allergy Asthma Immunol Res* 2010; **2**:20–27.

15 Pawlak K, Rozkiewicz D, Mysliwiec M, Pawlak D. YKL-40 in hemodialyzed patients with and without cardiovascular complications the enhancement by the coexistence of the seropositivity against hepatitis C virus infection. *Cytokine* 2013; **62**:75–80.

16 Razeghi E, Omati H, Maziar S, Khashayar P, Mahdavi-Mazdeh M. Chronic inflammation increases risk in hemodialysis patients. *Saudi J Kidney Dis Transpl* 2008; **19**:785–789.

17 Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 2015; **55**:648–658.

18 Usta S, Basbug HS, Cakiroglu Y. High sensitivity C-reactive protein: could it be used as a cardiovascular risk predictor in hemodialysis patients?. *Appl Med Res* 2015; **1**:12–15.

19 Kanwar M, Hashem M, Rosman H, Kamalakannan D, Cheema A, Ali A, *et al.* Usefulness of clinical evaluation, troponins, and C-reactive protein in predicting mortality among stable hemodialysis patients. *Am J Cardiol* 2006; **98**:1283–1287.

20 Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000; **102**:2165–2168.

21 Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001; **103**:1813–1818.

22 Atreya R, Mudter J, Finotto S, Müllberg J, Jostock T, Wirtz S, *et al.* Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in Crohn's disease and experimental colitis in vivo. *Nat Med* 2000; **6**:583–588.

23 Nielsen AR, Plomgaard P, Krabbe KS, Johansen JS, Pedersen BK. IL-6, but not TNF-a, increases plasma YKL-40 in human subjects. *Cytokine* 2011; **55**:152–155.

24 Nordenbaek C, Johansen JS, Junker P. YKL-40, a matrix protein of specific granules in neutrophils, is elevated in serum of patients with community-acquired pneumonia requiring hospitalization. *J Infect Dis* 1999; **180**:1722–1726.

25 Johansen JS, Lottenburger T, Nielsen HJ. Diurnal, weekly, and long-time variation in serum concentrations of YKL-40 in healthy subjects. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:2603–2608.

26 Catalán V, Gómez-Ambrosi J, Rodríguez A, Ramírez B, Rotellar F, Valentí V, *et al.* Increased circulating and visceral adipose tissue expression levels of YKL-40 in obesity-associated type 2 diabetes are related to inflammation: impact of conventional weight loss and gastricbypass. *J Clin Endocrinol Metab* 2011; **96**:200–209.

27 Lubomirova M, Djerassi R, Bogov B. Common carotid artery thickness in chronic kidney disease. *Macedonian J Med Sci* 2014; **2**:257–260.

28 Cheuk-Chun S, Kai-Ming C, Kam-Sang W, Ping C, Bonnie C, Chi-Bon L, Philip K. Carotid intima media thickness predicts cardiovascular diseases. *J Am Soc Nephrol* 2014; **18**:1966–1972.

29 Trimarchi H, Muryan A, Dicugno M, Young P, Forrester M, Lombi F, *et al.* Proteinuria: an ignored marker of inflammation and cardiovascular disease in chronic hemodialysis. *Int J Nephrol Renovasc Dis* 2012; **5**:1–7.

30 Libby P, Braunwald E. *Braunwald's heart disease: a textbook of cardiovascular medicine*. 8th ed. Philadelphia, PA: Saunders/Elsevier 2012.

31 Swirski FK, Libby P, Aikawa EE. Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. *J Clin Invest* 2007; **117**:195–205.

32 Baeten D, Boots AM, Steenbakkers PG, Elewaut D, Bos E, Verheijden GF, *et al.* Human cartilage gp-39+, CD16+ monocytes in peripheral blood and synovium. Correlation with joint destruction in rheumatoid arthritis. *Arthritis Rheum* 2000; **43**:1233–1243.

33 Keane WF, Tomassini JE, Neff DR. Lipid abnormalities in patients with chronic kidney disease: implications for the pathophysiology of atherosclerosis. *J Atheroscler Thromb* 2013; **20**:123–133.

34 Nassiri AA, Hakemi MS, Asadzadeh R, Faizei AM, Alatab S, Miri R, Yaseri M. Differences in cardiovascular disease risk factors associated with maximum and mean carotid intima-media thickness among hemodialysis patients. *Iran J Kidney Dis* 2012; **6**:203–208.

35 Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, *et al.* Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2012; **291**:451–459.

36 Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr., *et al.* LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2007; **192**:211–217.

37 Rao AR, Bitla E, Reddy P, Sivakumar V, Srinivasa R. Lipid abnormalities, lipoprotein (a) and apoprotein pattern in non-dialyzed patients with chronic kidney disease. *Indian J Clin Biochem* 2010; **25**:47–50.

38 Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value ofcommonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990; **15**:458–482.

39 Stenvinkel P, Heimbürger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T. Strong associations between malnutrition, inflammation and atherosclerosis in chronic renal failure. *Kidney Int* 1999; **55**:1899–1911.

40 Kaysen GA. Biological basis of hypoalbuminemia in ESRD. *Kidney Int* 1998; **9**:2368–2376.

41 Bergström J, Heimbürger O, Lindholm B, Qureshi AR. Elevated serum C-reactive protein is a strong predictor of increased mortality and low serum albumin in hemodialysis (HD) patients. *J Am Soc Nephrol* 1995; **6**:57.

42 Owen WF Jr., Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 1993; **329**:1001–1006.

43 Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005; **81**:543–554.

44 Joki N, Hase H, Tanaka Y, Takahashi Y, Saijyo T, Ishikawa H, *et al.* Relationship between serum albumin level before initiating haemodialysis and angiographic severity of coronary atherosclerosis in end-stage renal disease. *Nephrol Dial Transplant* 2006; **21**:1633–1639.

45 Nand N, Aggarwal HK, Yadav RK, Gupta A, Sharma M. Role of high-sensitivity C-reactive protein as a marker of inflammation in pre-dialysis patients of chronic renal failure. *JIACM* 2009; **10**:18–22.

46 Barany P. Inflammation, serum C-reactive protein and erythropoietin resistance. *Nephrol Dial Transplant* 2001; **16**:224–227.

47 Francisco ALM, Braun J, Burnier M, Portolés J, Gorriz JL. *Intra-patient (Pt) haemoglobin (Hb) variability and erythropoiesis stimulating agent (ESA) type: is there a difference? Presented at American Society of Nephrology Annual Congress 2006,San Diego, CA, USA*; 14–19 November 2006.

48 Eschbach JW, Downing MR, Egrie JC, Browne JK, Adamson JW. multicenter clinical trial with recombinanthuman erythropoietin. *Contrib Nephrol* 2001; **76**:160–165.

49 Macdougall IC. Role of uremic toxins in exacerbating anemia in renal failure. *Kidney Int* 2001; **59**(Suppl 78):S67–S72.

50 Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, *et al.* Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999; **34**:125–134.

51 Fishbane S, Schiller B, Locatelli F, Covic AC, Provenzano R, Wiecek A, *et al.* Peginesatide in patients with anemia undergoing hemodialysis. *N Engl J Med* 2013; **368**:307–319.