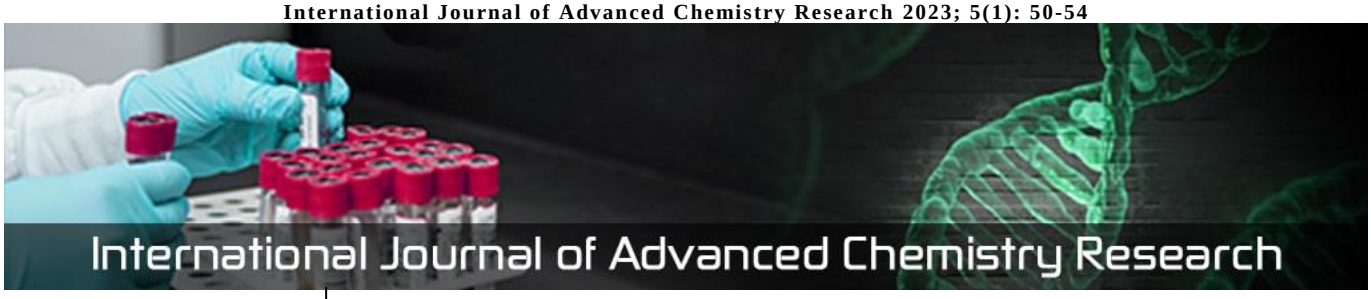

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Evaluation of Apolipoprotein A-1 and some biochemical parameters in the blood of patients with chronic kidney disease

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Abstract
Aim: This study was designed to determine the level of serum Apolipoprotein A-I (ApoA-I), Cystatin C, and homocysteine among three groups - CKD patients without the end-stage renal disease (ESRD), patients with ESRD on hemodialysis and healthy controls.
Materials and Methods: A retrospective, hospital-based study was carried out from 100 patients' records from each group, and serum Cystatin-C, homocysteine, apo-A1values were noted.
Results: The duration of dialysis treatment was 31 [+ or -] 35 months. Paired t-test analyses showed a significant increase in mean urea and creatinine, uric acid, and Cystatin C among CKD patients which then declined significantly after hemodialysis. Serum Apo-A1 and homocysteine levels were significantly higher in both hemodialysis and pre-dialysis groups compared to control subjects.
Conclusion: HD increases apoA1 and Cystatin C whereas decreases HCM and uric acid as both are antagonists that might play a vital role in the pathogenesis of related disorders in CKD Patients.

Keywords: Chronic kidney disease, hyperuricemia, hemodialysis

Introduction
Chronic kidney disease (CKD), also called chronic kidney failure, is on the rise, and it has become one of the most common complications worldwide. Is the progressive and irreversible loss of normal functioning of kidneys [1]. There are five stages of CRF based on the glomerular filtration rate (GFR), from very mild in stage 1 to complete kidney failure in stage 5. Patients suffering from stage 5(ESRD) [2-4], are characterized by the progressive accumulation of uremic toxins (UTs). Hemodialysis (HD), which is the most common form of treatment for ESRD, is the standard approach to removing uremic toxins (UTs) from the body. Creatinine and urea levels are important indices of hemodialysis effectiveness, but the utility of those markers to estimate the removal of UTs, especially protein-binding UTs is limited [5, 6]. CRF is associated with increased levels of some biochemical parameters and decreased others.
High-density lipoprotein (HDL) represents a main factor in reverse cholesterol transport and offers protective effects against atherosclerosis. HDL is made up of apolipoproteins and the major components of HDL are apolipoprotein (apo) A-I and apoA-II. Apolipoprotein A1 (ApoA1) is the major protein component of high-density lipoprotein (HDL) It has a molecular weight of 28. 1 kDa and is encoded by the Apo A-1 gene and plays an important role in transporting excess cholesterol from peripheral cells to the liver. Besides the atheroprotective effect, ApoA1 also has anti-inflammatory and antioxidant effects. Apolipoprotein A-I (ApoA-I) is secreted predominantly by the liver and intestine as lipid-free ApoA-I and constitutes approximately 70% of HDL protein, being required for normal HDL biosynthesis. ApoA-I levels are strongly associated with those of HDL-C. ApoA-I binds to circulating phospholipids and forms pre-β HDL (lipid-poor nascent discoid HDL particles) it plays an important role in transporting excess cholesterol from peripheral cells to the liver. Besides the atheroprotective effect, ApoA1 also has anti-inflammatory and antioxidant effects [7-9].
Cystatin C is a non-glycosylated, 13.3-kDa member of the endogenous cysteine proteinase inhibitor family that is produced at a constant rate by nucleated cells.

After glomerular filtration, it is fully catabolized in the proximal renal tubule and is not passed back into the blood. It might be a promising alternative to serum creatinine in the estimation of GFR. Cystatin C may have a slightly more favorable kinetic profile than serum creatinine [10-12].

Homocysteine is a non-proteinogenic thiol-containing amino acid endogenously liberated as a by-product of methionine transmethylation reactions [13]. Hcy can be either degraded through the transsulfuration pathway or remethylated to methionine. In the transsulfuration pathway, homocysteine combines with serine to form cystathionine; then, cystathionine is hydrolyzed into cysteine and alpha-ketobutyrate [14]. In plasma, 99% of the Hcy is bound to proteins, including cysteine, and cysteinyl glycine via disulfide linkages, while only 1% is found in a free reduced form [15].

The objective of this study was to determine the level of serum ApoA-I, Cystatin C, and homocysteine among three Groups-CKD patients without ESRD, patients with ESRD on hemodialysis and healthy controls.

Patients and Methods

Fifty-six patients with chronic renal failure undergoing maintenance hemodialysis treatment for 4h, 3 times/week as a patient group (25 male and 31 female; mean age 48,78±12,64 years) and 56 healthy subjects as a control group (34 male and 22 female; mean age 46,92±10,99 years)were evaluated. None of the patients had received any medication. After a 12-hour overnight fast usually within 24 hours after arrival at the Emergency Department venous blood samples were taken and sera were isolated. One serum sample was frozen and stored at -70 °C until further analysis of ApoA-I, Cystatin C, and homocysteine.

The study was a retrospective study carried out by analyzing patient records in the Department of Biochemistry at a Tikrit teaching Hospital in Tikrit City. The study was approved by the institutional research committee and ethics committee. Serum The Cystatin-C, homocysteine, apoA1 was measured by enzyme-linked immunosorbent assay (ELISA) method using DRG kits (DRG Diagnostics, Berlin, Germany).

Results

The mean + SD of serum Apo A-1 levels in the normal individuals were observed to be 126.98±5.32 (mg/dL), against 155.43±11.23, and 182.25±6.41 (mg/dL), in the Pre, and post-dialysis patients respectively. On the other hand, the mean ± SD serum HCM levels were 26.17±1.72 (µmol/lit) in the healthy individuals and against 26.43±2.7, and 23.17±2.50 (µmol/lit) in the Pre, and post-dialysis patients respectively.

There was a significant increase in serum cystatin C levels in CKD patients (0.67±0.11 mg/L) as compared to healthy controls. (6.40±0.71 mg/L) (p<0.001) which further increased significantly after hemodialysis (7.60±0.72) (p<0.001). The mean serum uric acid concentration in patients with CKD (7.62±0.62 mg/dl) was significantly higher than that of the control group (4.70±0.48 mg/dl) after HD the level of UA decreased (4.07±0.86 mg/dl) when compared with pre- HD.

Table 1: Levels of Apo-A1, homocysteine, and Cystatin-C in CRF patients before and after HD and in apparently healthy controls.

Study group	Apo-A1 (mg/dL)	HCM (µmol/lit)	Cystatin C (mg/L)
Control	126.98±5.32c	26.17±1.72a	0.67±0.11c
Pre-HD	155.43±11.23b	26.43±2.71a	6.40±0.71b
Post-HD	182.25±6.41a	23.17±2.50b	7.60±0.72a
P-value	2.8383	0.8212	0.2054

Table 2: Levels of Uric acid, BU, and Cr in CRF patients before and after HD and in apparently healthy controls.

Study group	Uric acid (mg/dl)	BU (mmol / L)	Cr (mmol/L)
Control	4.70±0.48b	4.48±0.7	0.082±0.08
Pre-HD	7.62±0.62a	31.02±2.27	0.89±0.081
Post-HD	4.07±0.86c	20.4±1.67	065±0.10
P-value	0.2637	0.669	0.0380

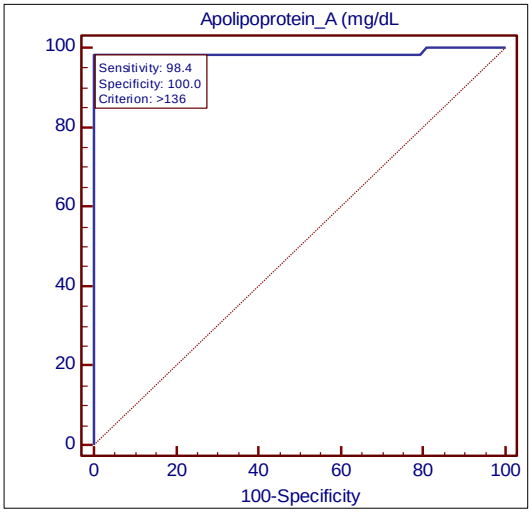

Fig 1: ROC curve for Apo-Ain pre- hemodialysis

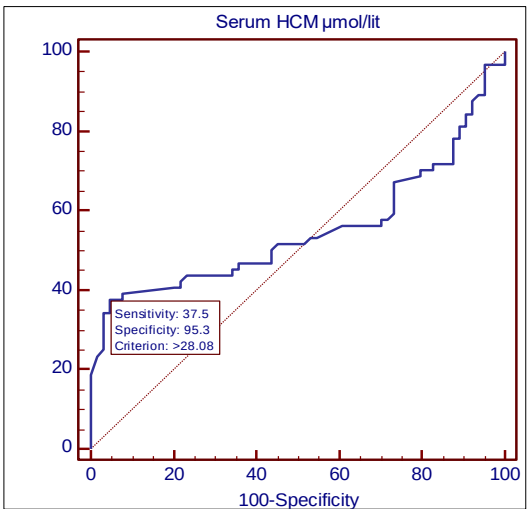

Fig 2: ROC curve for HCM in pre- hemodialysis

Diagnostic accuracy

The diagnostic accuracy of Serum apolipoprotein, HCM, in terms of sensitivity and specificity, is presented by receiver operating characteristic (ROC) curve analysis.

When it comes to that of apolipoprotein A, the area under the curve was 0.983 (95% CI: 0.935 to 0.998), and the cut of point > 136 for Apo-A to point at a possible diagnosis of CRF (sensitivity 98.4 and specificity 100.00).

For HCM, the area under the curve was 00.509 while ≤ 28.08 was the cutoff level for HCM (sensitivity: 37.5; specificity: 95.3).

Post dialysis

The ROC curves for the variables that remained significantly related after HD, apolipoprotein, and HCM, were shown in Figs.

For parathyroid hormone, the area under the curve was 1.000 ((95% CI: 0.964 to 1.000) while ≥ 22.87 was the cutoff level for post-HD (sensitivity: 100.0; specificity: 100.0). The area under the ROC curve of Apo-A was 1.000 (95% CI: 0.964 to 1.000) (sensitivity 100.00 and specificity 100.00), and the cut of point >136. For HCM, the area under the curve was 0.924 while ≤24.6 was the cutoff level for HCM (sensitivity: 85.9; specificity: 84.4).

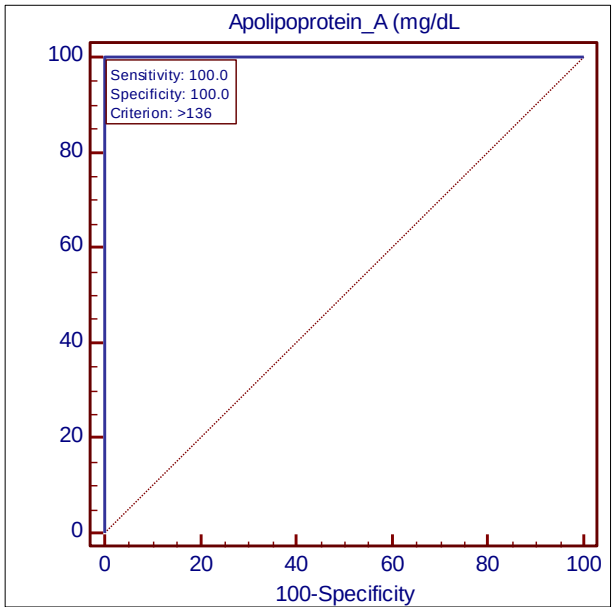

Fig 3: ROC curve for Apo-A in post-hemodialysis

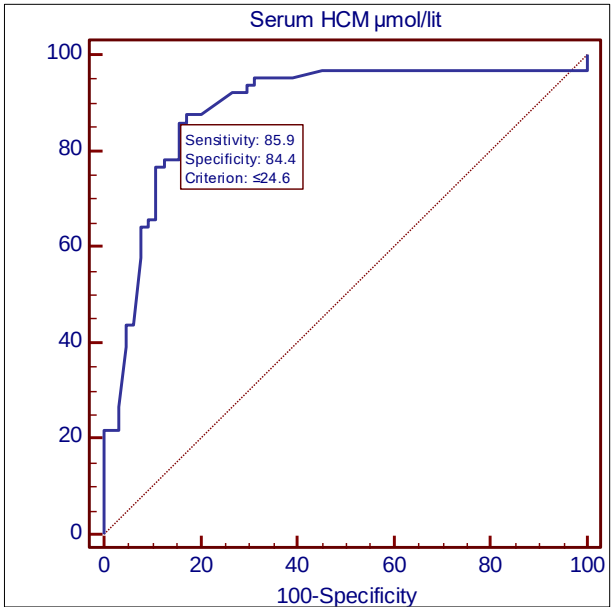

Fig 4: ROC curve for HCM in post-hemodialysis

Discussion

The dyslipidemia of renal disease has characteristic metabolic abnormalities. It usually involves all lipoprotein classes and shows considerable variations depending on the stage of CKD. It develops during the asymptomatic stages of renal insufficiency and becomes more pronounced as renal failure advances. Dyslipidemia is associated with a reduction of the glomerular filtration rate (GFR). The most characteristic feature of CRF -associated dyslipidemia is the accumulation of apolipoproteinA1 [16, 17]. In this study, there was a significant elevation of serum Apo A1 levels in CKD patients when compared to healthy controls (p<0.001), which further increased significantly after hemodialysis (p<0.001). Our results agree with [18]. The increase of apolipoprotein A1 in patients with renal failure has been attributed to reduced renal clearance and/or homocysteine-releasing Apo-A from Lp (a) and has been suggested to be one of the reasons contributing to the incidence of vascular diseases [19-20].

Normally lipoprotein (a) is fragmented and excreted by the kidneys. During hemodialysis rate of ApoA-I production did not change because of their large molecular size, but could be removed by hepatic scavenger receptors of lipoprotein (a) that cleave the apolipoprotein (a) during hemofiltration. Serum cystatin C reflected predominantly renal not dialytic clearance in chronic renal failure patients on peritoneal dialysis. Following dialysis elevated Cystatin C levels could be attributed to several factors such as the nature of the dialyzing membrane and the composition of the dialyzing fluid. When dialysis is carried out using a low flux membrane, the pore size is smaller than 1.5 nm which does not permit the removal of proteins such as cystatin C. The present study reports significantly higher serum Cystatin C levels in CKD patients as compared to healthy controls (p<0.001) which further increased significantly after hemodialysis (p<0.001). These findings are by [21, 22]. The major route of Hcy clearance from plasma is the kidney, which is filtered by the glomerulus; however, it is almost completely (over 98%) reabsorbed by tubular cells in the kidneys. The mechanisms responsible for the elevated homocysteine levels in patients with CRF in post-HD measures may be due to (i)homocysteine disposal in the kidneys themselves is disturbed and (ii) extra renal homocysteine metabolism is impaired [23, 24]. Uric acid is the end product of purine metabolism and is eliminated by renal (60%-70%) and intestinal (30%-40%) excretion [25]. In this study, there was a significant elevation of serum UA levels in CKD patients when compared to healthy controls which then declined significantly after hemodialysis. Serum uric acid was a double-edged sword. On the one hand, it constitutes the most crucial natural antioxidant, providing up to 60% of the body's free radical scavenging capacity. But on the other hand, long-term high uric acid exposure can induce gout and renal damage. In preclinical studies, SUA has been proven to elicit nitric oxide pathway alteration, activate the renin-angiotensin system and induce pro-inflammatory cytokines [26]. Underlying mechanisms by which sUA is the final product of purine degradation with

xanthine oxidase, an enzyme implicated as a mechanistic participant in oxidative stress, and contributes to endothelial dysfunction and increased oxidative stress within the glomerulus and the tubulointerstitium with associated increased remodeling fibrosis of the kidney and to be pro-atherosclerotic and pro-inflammatory [27]. In patients treated with hemodialysis, SUA is efficiently removed from the blood, given its clearance pattern and sieving coefficient (1.01) similar to that of urea; thus, during 1 hemodialysis session on average 1 g uric acid is eliminated [28]. The findings showed that among the analyzed ApoA-I, Cystatin C, and Hcy was different in patients with HD when compared to controls might play a vital role in the pathogenesis of related disorders in CKD Patients. Further studies involving larger patient populations and healthy controls should be done to clarify the pathogenic significance of ApoA-I, Cystatin C, and Hcy in CKD complications. Creatinine is a breakdown metabolite of creatine phosphate in muscle. It is eliminated by kidneys, mostly via glomerular filtration and partly via secretion at the proximal tubule. Therefore, creatinine clearance could be used to estimate the glomerular filtration rate (eGFR) by measuring serum creatinine (SCr), urine creatinine, and volume [29-30]. Urea and creatinine, being small molecules, are removed mainly due to the counter-current flow of the blood. During HD, excess urea and creatinine from the patient's blood are removed to avoid accumulation. It is observed that leafy green vegetables and meat might lead to an increase in the burden on the kidney and cause an increase in serum urea and creatinine level [31, 32].

Conclusion

HD increases apoA1 and Cystatin C whereas decreases HCM and uric acid as both are antagonists that might play a vital role in the pathogenesis of related disorders in CKD Patients.

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