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Clinical Pathology

Acute Phase Reactants in End Stage Renal Disease, Early Diagnosis and Six Months After Dialysis

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ABSTRACT

Background: The definition and classification of chronic kidney disease (CKD) have evolved over time, but current international guidelines define this condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m², or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause.
Aim of work: This study was planned to investigate the association between the inflammatory biomarkers including [C reactive protein (CRP) and tumor necrosis factor alpha (TNFα)] and end stage renal disease (ESRD).
Patient and Methods: 60 subjects were enrolled in this study.They were divided into 30 control and 30 patients on hemodialysis. Serum TNFα and CRP of ESRD patients early diagnosed and 6 months after dialysis were measured compared to the control.
Results: There was highly statistical significant difference between control and ESRD patients in TNFα and CRP early diagnosis and 6 months after dialysis. Regarding difference between early diagnosis and also 6 months after dialysis in ESRD group there was statistical significant difference in both.There was also no statistical significant difference linear relationship between serum CRP level early diagnosed and 6 months after dialysis with other studied parameters in patients groups.
Conclusion: TNFα and CRP has increased in ESRD patients early diagnosed and markedly increased 6 months after dialysis compared to control. TNFα and CRP were both associated with the prevalence of ESRD.There was statistically significant linear relationship between serum TNFα level early diagnosed and the age in patients groups.

Keywords: *End stage renal disease;Tumor necrosis factor α- C reactive protein.*

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INTRODUCTION

The development of CKD and its progression to this terminal disease remains a major source of reduced quality of life and significant premature mortality. It is a very debilitating disease. It needs imperative medical care involve monitoring for signs of disease progression as well as early referral to specialists for dialysis or possible renal transplant. Kidney Disease Improving Global Outcomes (KDIGO) guidelines define CKD using markers of kidney damage, specifically markers of proteinuria and glomerular filtration rate [1, 2].

Kidney failure, also known as end stage renal disease, is a medical situation in which the kidneys no longer function. Symptoms include swelling of leg , feeling tired, vomiting, loss of appetite, confusion, heart disease, increased blood pressure and anemia[3]. In developing countries such as Egypt end stage renal disease (ESRD) has increased. It was considered that the leading cause of ESRD is diabetes mellitus and hypertension [4].

In North African countries the average incidence of ESRD is estimated as 182 patients per million populations (pmp), that is, about 31,000 new cases every year, including 1,700 transplants[5].The risk of kidney disease can be determined by genetic and phenotypic factors of the patient [6]. Kidney failure causes a syndrome called uremia**.** The clinical manifestations are systemic (fatigue, hypothermia, diabetes and inflammation), gastrointestinal (decreased appetite, nausea and vomiting), neurological (impaired cognition, mental fatigue, peripheral neuropathy, decreased taste and smell, restless leg, pruiritis and convulsions), hematological and immunological (anemia, platelets dysfunction and impaired antibody response), cardiovascular (increased blood pressure, left ventricular hypertrophy and pericarditis)[7].

Diagnosis is commonly made after screening tests (urinary dipstick or blood lab tests), or when symptoms become severe. eGFR is considered the best available indicator of overall kidney function, which is measured either via exogenous markers or by using equations[1].

TNFα plays a crucial role in the pathogenesis of immune disorders and tumor development and is one of the most important proinflammatory cytokines [8]. It plays vital role in the progression of ESRD[9]. In blood of ESRD patients higher levels of TNFα indicate rapid renal disease loss of peritoneal membrane functions. It stimulates the secretion of chemokines which induce the recruitment of polymorphonuclear neutrophils to the injury site [10].

C reactive protein (CRP) is an acute inflammatory protein that rises up to 1,000-fold at sites of infection or inflammation[11].It is a vital marker for the inflammation identification. Higher levels of CRP and soluble tumor necrosis factor receptors were associated with loss of kidney function [12]. Abnormalities of immune functions are caused by impaired excretory function of kidneys and the accumulation of uremic toxins in chronic renal failure patients. These abnormal immune functions strictly associate with abnormalities of immune cell reactivity and altered expression of cell surface receptors. Therefore, increased proinflammatory cytokines play an important role in inflammation and renal pathology [13].

This study was planned to investigate the association between the inflammatory biomarkers including [C reactive protein (CRP) and tumor necrosis factor alpha (TNFα)] and end stage renal disease (ESRD).

PATIENT AND MATERIALS

This case-control study was conducted on 60 subjects of both sexes from Al-Azhar University Hospitals. They were selected from the outpatient clinic and inpatients of internal medicine departments hemodialysis units and the laboratory part of this study was done in Al-Azhar University Hospitals.These cases will be diagnosed by history talking, clinical examination and routine investigation: kidney function tests (serum urea, creatnine levels and eGFR). Patients with acute kidney injury and current clinical trial participation that may have an impact on end stage renal disease were excluded. Additional exclusion criteria were patients who had a history of chronic dialysis more than 6 months or receiving chemotherapy or immunotherapy.

They divided into the following groups: Group 1 (patients group): including 30 patients with end stage renal disease early diagnosed (at the beginning of hemodialysis).Group 2 (patientsgroup): including the same patients of the first group 6 months after hemodialysis.Group 3 (controlgroup): including apparently healthy individuals (age and sex matched).

Measurement:Venous blood sample was collected from each subject using a sterile plastic syringe. The blood was allowed to clot then centrifuged to separate the serum. The serum was used for the measurement of liver enzymes (ALT&AST), albumin, urea,creatinine byjaffe method and eGFRwas estimated from serum creatnine level, sex, age and race using the CKD-Epi equation. The serum of control normal group is preserved in -80C for testing TNFαand CRP. Another venous blood sample was collected from each subject of ESRD patients early diagnosed group (group 1) using a sterile plastic syringe. The blood was allowed to clot then centrifuged to separate the serum. The serum was stored in epindorph tubes in a deep freeze at – 80 C till tested for TNFα and CRP. Six months after hemodialysis another venous blood sample was collected from each subject of ESRD patients of the previous group. The blood was separated and stored as the previous procedure till tested for TNFα and CRP. Estimation of TNFα by the quantitative sandwich enzyme immunoassay technique (USA& Canada R&D Systems, Inc. 614 McKinley Place NE, Minneapolis, MN 55413, USA)[14].Estimation of CRP levels was done using spectrum diagnostic. www.Spectrum-diagnostic.com. Email:info@Spectrum-diagnostic.com.CRP values are determined photometrically by Calculation (A2-A1) sample/ (A2-A1) calibrator x caliberator concentration= mg/L CRP. Linearityisup to 150mg/L.Values < 6 mg/L are within the normal range[15].

Ethical Approval: This study was approved by the Ethics Committee of the Al-Azhar University, Faculty of Medicine, Egypt and written consent was obtained from all the participants.

Statistical analysis**:** Mean values of the study were calculated and considered for comparisons.Two independent sample t test and mann-whitney U test were used to compare means between patients and control. Paired Wilcoxon testwas used to compare mean values obtained early diagnosed and 6 months afterdialysis. Pearson correlation coefficient was used to measure of the linear correlation between two variables.P value of <0.05 indicates significant results.The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 25.0.

RESULTS

Demographic data		Control group N=30		ESRD group N=30		T test	P value
Age	Mean± SD	53.7 ± 5.2		53.6 ±7.4		0.059	0.4
	Median (Range)	53 (46– 65)		51 (40-68)			
Gender		No.	%	No.	%		
Male		17	56.6 %	19	63.3 %		
Female		13	43.4 %	11	36.7 %		
Resid-ence	Urban	14	46.6 %	12	40%		
	Rural	16	53.3 %	18	60%		

Table 1: The demographic data of normal (control) compared to ESRD patients group.

SD: Standard deviation t≠:Independent t test Significant (P<0.05)

Thirty ESRD patients with mean dialysis vintage 6 months andthirty healthy age and sex matched subjects were enrolled in this study (Table 1).

Laboratory investigation	Control group Mean ± SD N=30	ESRD group Mean ± SD N=30	T test	P value
AST (u/l)	28.7 ± 5.3	25.9±5.3	2.004	0.02
ALT (u/l)	29.7 ± 4.4	26.6 ±5.0	2.4	0.007
Albumin (g/dl)	4.4±0.25	4.2±0.24	2.8	0.003
Serumcreatinine (mg/dl)	0.7±0.1	11.6±1.1	-49.3	<.00001
Urea (mg/dl)	24.9±4.5	158.7±22.1	-32.4	<.00001
eGFR (ml/min)	94.6±8.2	13.9±3.49	49.2	<.00001

SD:Standard deviation t≠:Independent t test
Significant (P<0.05)
Highly significant (P<0.01)

Table 2: The laboratory investigations of normal control group compared to ESRD patients.

Serum samples were measured for different parameters and analyzed. The laboratory investigations show statistically significant difference (p-value < 0.05) between control and patients as regard AST, ALT, Albumin. Also, there was highly statistical significant difference (p-value < 0.001)between control and patients as regard serum creatinine, urea and eGFR (Table 2).

	Normal control (n=30)	ESRD patients early diagnosis (n=30)	ESRD patients after dialysis (n=30)	P1	P2	P3
TNFα						
Mean ±SD	4.53±2.22	27.72±11.03	30.75±11.27	<0.001	<0.001	0.01
Median	3.21	28.90	32.60			
Range	1.31-9.76	6.87-48.29	8.28-60.37			
CRP						
Mean ±SD	2.73±1.57	14.25±3.34	16.78±6	<0.001	<0.001	0.02
Median	2.36	14.27	15.49			
Range	0.95-7.56	5.57-19.95	7.3-34.29			

SD: standard deviation **: Highly significant (p<0.01) P1: Normal versus before dialysis (MW test). P2: Normal versus after dialysis (MW test). P3: Before dialysis versus after dialysis (Paired Wilixocon).

Table 3: Comparison between the mean value of serum TNFα factor and CRP levels of control (normal) group and end stage renal disease patients early diagnosis and after 6 months of dialysis.

According to serum levels of inflammatory markers, there was highly statistical significant difference between normal group and ESRD patient group in both TNFα and CRP early diagnosed and 6 months after dialysis. Regarding difference between early diagnosed and 6 months after dialysis in ESRD group only there was statistical significant difference in both CRP and TNFα (Table 3).

Parameter	TNFα before dialysis		TNFα after dialysis		CRP before dialysis		CRP after dialysis	
	R	Pvalue	R	Pvalue	R	Pvalue	R	Pvalue
Age	0.444	0 .0139	0.292	0.117	-0.234	0.213	-0.105	0.599
Albumin	0.073	0.697	0.164	0.386	-0.293	0.120	-0.276	0.139
Creatinine	-0.035	0.874	0.181	0.336	0.143	0.450	0.272	0.145
AST	0.08	0.674	0.13	0.493	-0.062	0.744	-0.094	0.636
ALT	-0.148	0.460	-0.135	0.476	0.067	0.724	0.114	0.545
Urea	0.090	0.632	0.188	0.318	0.209	0.265	0.098	0.605
eGFR	-0.082	0.674	0.149	0.429	-0.058	0.793	0.043	0.821

Table 4: Correlation study between serum levels of TNFα and CRP in ESRD patients early diagnosis and 6 months after dialysis with the other studied parameters in all patients using Pearson correlation coefficient test.

There was statistically significant linear relationship (p-value < 0.05) between serum TNFα level early diagnosed and the age in patients groups.The direction of relationship is positive (serum TNFα level early diagnosed and the age is positively correlated) (r = 0.44) and the magnitude of association is approximately moderate(0.3> r < 0.5) in patients group. However, there was statistically non significant correlation (p-value > 0.05) between serum TNFα level early diagnosed and 6 months after dialysis with the other studied parameters in patients groups. There was also no statistical significant difference linear relationship (p-value >0.05) between serum CRP level early diagnosed and 6 months after dialysis with the other studied parameters in patients groups (Table 4)

DISCUSSION

Circulating Tumor necrosis factor α (TNFα) and CRP are proinflammatory chemokines that are linked to the pathophysiology of renal disease. Measurement of these inflammatory mediators are very important in ESRD patients because these mediators progress the renal injury to its end-stage[16].

kidney function is predicted by TNFα and CRP as higher levels of them were associated with loss of kidney function [(12)].Our study is concerned with estimation of TNFα and CRP in patients with end stage renal disease early diagnosed and 6 months after dialysis to evaluate the association between these inflammatory biomarkers and end stage renal disease (ESRD).

In this study, comparison between the estimated TNFα in ESRD patient earlydiagnosed and the normal (control) was done. It was found that the

mean value of serum TNFα levels of normal people is (4.53 ± 2.22) whereas, the mean value of serum TNFα levels of ESRD patients early diagnosed is (27.72 ± 11.03) (table 3). There was highly statistical significant difference between both. An explanation for these results may be due to the detection of albuminuria that increases cytokines and TNFα levels. In addition, cytokines clearance may be decreased in ESRD patients [(17)].Our results were confirmed by **El Haddad et al.** [18]who revealed that the TNFα gene quantification was higher between ESRD patients than the healthy people. Our findings are consistent with **Gupta et al.** [19]who concluded that TNF α plasma levels was higher in patients with decreased eGFR and also agree with **Lee et al.** [20]who confirmed that the prevalence and severity of CKD is significantly associated with TNF α.

As regard the estimated TNFα in ESRD patients 6 months after dialysis, the mean value of serum TNFα levels of normal people is (4.53 ± 2.22) whereas, the mean value of serum TNFα levels of ESRD patients 6 months after dialysis is (30.75 ± 11.27) (Table.3) . There was highly statistical significant difference between both. These results agree with **Meuwese et al.** [21]who stated that during 3-months follow-up period a persistent elevation of TNFα in dialysis patients was associated with a poor prognosis. Our findings were also supported by **Babaei et al.** [22]who stated that TNF-α plasma levels were significantly increased in ESRD patients on regular hemodialysis group compared to control group. Our results were also confirmed by**Colombo et al.** [23]who stated that only HD session have different impacts on the different types of biomarkers. The explanation for these results may be due to the presence of Tamm-Horsfall glycoprotein in the regulation of TNFα activity in addition to its short half-life and the local tissue degradation which may lead to inhibition of cytokines especially TNFα. This reveals the importance of the kidney in TNF regulation[24].

Concerning, the level of CRP in ESRD patients early diagnosed. The mean value of serum CRP levels of normal people is (2.73 ± 1.57) whereas, the mean value of serum CRP levels of ESRD patients early diagnosed is (14.25 ± 3.34) (Table 3). There was highly statistical significant difference in serum CRP levels between normal group and ESRD patients group early diagnosed. These results agree with **Haubitz et al.** [25]who showed that hemodialysis (HD) patients have the highest values of CRP levels versus peritoneal dialysis (PD) or patients receiving conservative treatment .This were also confirmed by**Levey et al.** [26]who approved that CRP is a well-known risk factor in ESRD patients. our result are also in agreement with **Racki et al.** [27]who said that CRP serum level above 6.2 mg/L is a important predictor of mortality in ESRD patients and with **Pallos et al.** [28]who approved that the HD group showed increased levels of CRP versus to the control**. Taylor and Taylor**[29]support our results as they emphasized that at the beginning of hemodialysis increased the levels of CRP is important predictor for the future risk of long-term mortality.CRP is not just a marker of inflammation or infection but also a significant regulator of inflammatory processes. CRP mediated the inflammation and host responses to infection by the complement pathway, apoptosis, phagocytosis, NO release and cytokine. at sites of inflammation IL-6 and TNF-α production are induced by CRP [(11)]In contrast, our results disagree with **Lee et al.** [20]who stated that the prevalence and severity of ESRD are not correlated to CRP. The difference between these results and ours may be due to established risk factors, history of CVD and use of antihypertensive, antidiabetic and lipid-lowering agents as well as aspirin.

Concerning the estimated CRP in ESRD patient 6 months after dialysis, the mean value of serum C reactive protein levels of normal people is (2.73 ± 1.57) whereas, the mean value of serum C reactive protein levels of end stage renal disease patients 6 months after dialysis is (16.78 ± 6)(table. 3) . There was highly statistical significant difference in serum CRP levels between normal group and ESRD patient group 6 months after dialysis. These results agree with **Haubitz et al.** [25]who proved that at 6, 12, and 18 weeks after the beginning of chronic HD therapy in ESRD patients CRP level was increased compared to its level before beginning HD. However, **Meuwese et al.** [21]stated that at 3-months follow-up period a poor prognosis were connected to an elevation of CRP in hemodialysis patients. Our findings of an increased CRP levels among ESRD patient 6 months after hemodialysis emphasized with **Nascimento et al.** [30]who said that in hemodialysis patients there were a constant elevation of CRP levels.

Regarding the difference between the estimated TNFα and CRP in ESRD patient early diagnosed and 6 months after dialysis, there was significant difference between these groups (Table 3)**. Tripepi et al.** [31]**and Wetmore et al.** [32]stated that there is strong connection between the measurement of TNFα and CRP and this can be explained by the alteration in the profile of cytokines which is noticed in HD patients by **Cohen et al.** [33].**Babaei et al.** [22]also proved that on regular hemodialysis ESRD patients have increased serum levels of TNFα and CRP.

It was approved that on maintenance hemodialysis there was a positive significant association between TNFα and CRP in ESRD patients [34].

Our findings are in agreement with **Rysz et al.** [35]who stated that in ESRD patients the concentrations of CRP and TNFα were increased within minutes in HD session compared to healthy controls. This can be explained by **Herbelin etal.** [36]who stated that the stimulated monocytes induce TNFα production which plays a critical role in inflammatory and immune reactions. Another explanation was done by **Girndt et al.** [37]who approved that the activation of macrophages and neutrophils increases inflammatory mediators in HD. Our findings are consistent with **Heidari**[38]who emphasized that the serum level of CRP and TNFα were increased in ESRD patients on regular hemodialysis due to inflammatory reaction against factors originating from graft, fistula, dialysis membrane and infection sites**. Colin-Benoit et al.** [39]also supported our results as they reveal that maintenance HD will create a variety of endotoxins

from the dialysate which run into the circulation magnifying the inflammatory response which lead to CRP and TNFα production.

CONCLUSION

From this study we conclude that: TNFα and CRP has increased in ESRD patients early diagnosis and markedly increased 6 months after dialysis compared to control (normal) group. TNFα and CRP were both associated with the prevalence of ESRD and 6 months of hemodialysis. There was statistically significant linear relationship (p-value < 0.05) between serum TNFα level early diagnosis and the age in patients groups.

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