

Significance of Albumin and C-Reactive Protein Variations in 300 End Stage Renal Disease Patients in Tehran University of Medical Sciences Hospitals During Year 2010

Nasrin Dashti¹, Nahid Einollahi¹, Fariba Nabatchian¹, Mostafa Moradi Sarabi², and Mitra Zarebavani¹

¹ Department of Clinical Laboratory Sciences, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran

² Departments of Medical Biochemistry, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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Abstract- Protein- energy malnutrition, wasting and inflammation are frequent complication among patients with end-stage renal disease (ESRD). Malnutrition is associated with cardiac co-morbidity, inflammation and poor survival in ESRD patients. Serum albumin is a well-known marker of nutrition in ESRD patients. Serum albumin is still the most commonly used nutritional marker in ESRD patients. C-reactive protein (CRP), the major acute phase response (APR) protein is elevated in these patients. High CRP levels are linked to the degree of atherosclerosis in coronary, peripheral, and extracranial brain arteries. The aim of the present study was to investigate nutritional factor (albumin) and CRP levels in ESRD patients. In this cross-sectional study a total of 300 patients who had ESRD and had been on hemodialysis treatment for at least 6 months were selected. The laboratory tests consisted of measurement of CRP and albumin using high sensitive ELISA kits. The study patients included 157 males (52.3%) and 143 females (47.7%) with average age of 41.5±14.3 years. Mean CRP level was 7.96 mg/ dl (±1.52), mean serum albumin was 4.07 g/dl (±0.19). Of 300 patients, 21 died (7%). These were patients with serum albumin <4 g/dl and CRP>9.5 mg/dl. This study showed that low albumin and high CRP levels are the main predictors for death. There was a significant difference between CRP and albumin levels in ESRD patients ($P<0.0001$). Measuring CRP as a marker of inflammation can be helpful in managing these patients.

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Introduction

Over the last two decades the increase in the number of dialysis patients has been seen globally although to varying degrees. Certain trends in end stage renal disease (ESRD) epidemiology have been observed. The annual increase in number of patients undergoing hemodialysis has been around 8% (1). The National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) practice guidelines, was first established in 1997 to create standards for dialysis care (1).

Protein-energy malnutrition and wasting are frequent complication among patients with ESRD (2-4). Moreover, considerable evidence has accumulated over several years that malnutrition is associated with cardiac co-morbidity, inflammation and poor survival in ESRD patients.

Malnutrition of visceral proteins often occurs in many chronic illnesses such as chronic renal failure, protracted infections and cancer (5-7).

Clinical assessment of malnutrition is most commonly done by biochemical indicators of nutrition (8). Serum albumin is a well-known marker of nutrition in ESRD patients. There is a linear increase in death rate with declining serum albumin levels in the dialysis patients (9). Low serum albumin levels may reflect poor nutrition. Presence of an inflammatory reaction, old age and degree of hydration could also cause hypoalbuminemia (10-12). Although several approaches have been used to assess nutrition, serum albumin is probably still the most commonly used nutritional marker in ESRD patients (5). Several studies have shown that inflammation is another cause of problems attributed to malnutrition (13).

Corresponding Author: Nahid Einollahi

Department of Medical Laboratory Sciences, School of Allied Health Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 64053277, Fax:+98 21 88953077, E-mail: naeinollahi@yahoo.co.uk

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Although the circulating levels of cytokines are high in patients with ESRD (14), the sources of inflammation in these patients are not clear. Of the variety of circulating inflammatory markers, C-reactive protein (CRP), the major acute phase response (APR) protein is elevated in hemodialysis patients. Recent epidemiological data have shown an association between CRP and cardiovascular disease and its complication in general population (15). High CRP levels are linked with the degree of atherosclerosis in coronary, peripheral, and extracranial brain arteries. Furthermore CRP is used as a marker of infection or ongoing inflammatory disease in ESRD patients (16). CRP is also considered as a biomarker of chronic, systemic inflammation as well as a predictor or atherosclerosis (17).

The severity of inflammation could be estimated by the levels of circulating CRP (18). CRP and albumin are predictors of all cause and cardiovascular mortality in chronic kidney disease (19).

The inflammatory association between outcome processes in ESRD led us to measure the CRP concentration and obtain other common laboratory measures in large sample of hemodialysis patients. The serum concentration of CRP reflects the activity of cytokine-mediated acute phase processes and is roughly proportional to the extent of tissue injury. Also there is convincing evidence for the involvement of interleukin 1alpha (IL-1 α) during glomerular injury (20).

The aim of the present study was to investigate nutritional factor and CRP levels in ESRD patients.

Materials and Methods

In this cross-sectional study a total of 300 patients who had ESRD and had been on regular dialysis treatment for at least 6 months were enrolled.

Exclusion criteria were age >70 years and unwillingness to participate in this study. Also clinically unstable patients and those with tumors, diabetes mellitus, inflammatory diseases (such as diabetic ulcers of chronic pulmonary disease, systemic lupus erythematosus, rheumatoid arthritis, tuberculosis infection) or those treated with immunosuppressive drugs were excluded. No patients showed signs of inflammation or infection during the study period.

Body temperature was measured before each dialysis session and was never elevated. Informed written consent was obtained from all enrolled patients prior to the study. The required information regarding each

patient was gathered through predesigned questionnaires including the patient's medical history, clinical examinations and laboratory findings. All ESRD patients were treated three times weekly with standard bicarbonate dialysis with semi-synthetic dialysis membranes.

The laboratory tests consisted of measurement of CRP and albumin using high sensitive ELISA kits. The creatinine was measured using Zist Chimi kits (Tehran, Iran).

Statistical analysis was performed using SPSS software version 12.0, Wilcoxon test was performed for analysis of all the data.

Results

All results are reported as mean \pm SD (normally distributed data), and categorical data are presented as percentages. The study patients included 157 males (52.3%) and 143 females (47.7%) with average age of 41.5 \pm 14.3 years. Mean CRP level was 7.96 mg/dl (\pm 1.52) and mean serum albumin was 4.07 g/dl (\pm 0.19) where their distributions has been shown in Figures 1 and 2 respectively. Of 300 patients, 21 died (7%). These were patients with serum albumin <4 g/dl and CRP>9.5 mg/dl.

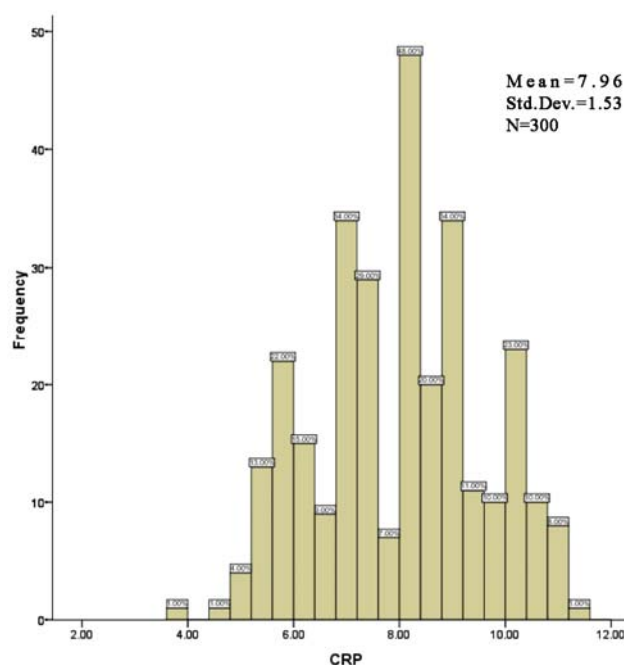


Figure 1. Distribution of CRP levels in ESRD patients. Mean CRP level was 7.96 mg/dl (\pm 1.52).

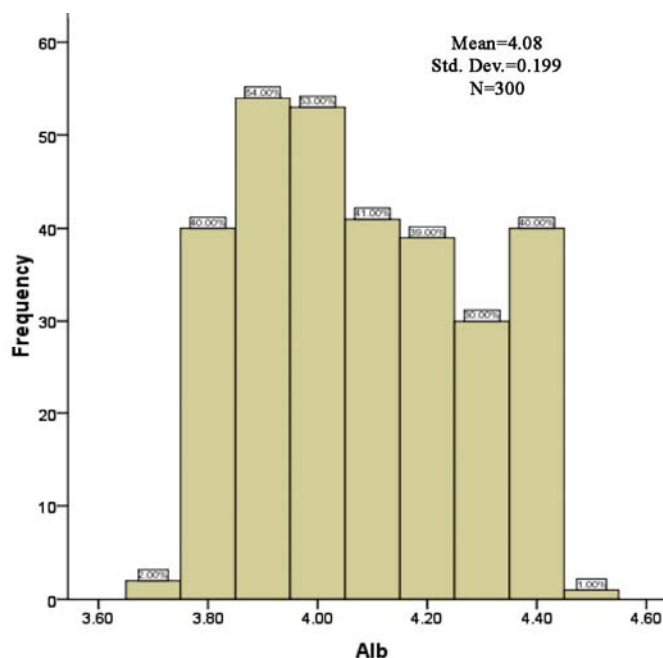


Figure 2. Distribution of albumin levels in ESRD patients. Mean serum albumin was 4.07 g/dl (± 0.19)

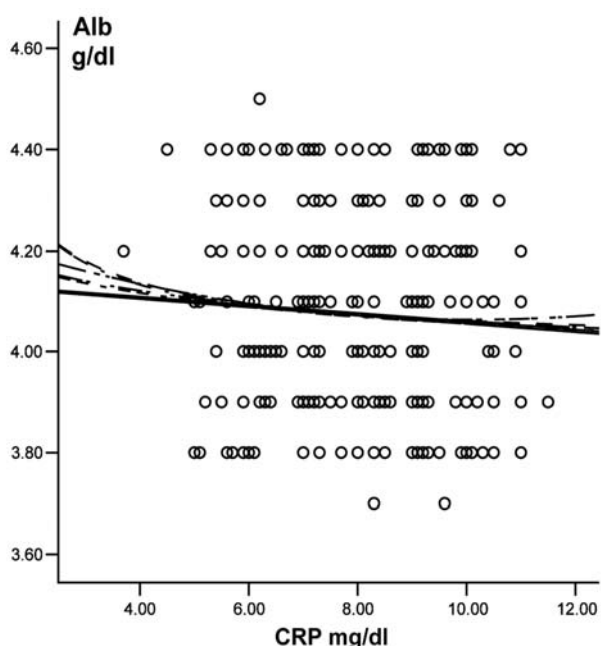


Figure 3. Relationship between average CRP and serum albumin levels in ESRD patients ($P < 0.000$).

There was a significant correlation between serum albumin and CRP levels ($P < 0.0001$) in ESRD patient, as CRP levels increase there is a decrease in serum albumin. Relationship between average CRP and serum albumin levels in ESRD patients has been shown in Figure 3.

Discussion

It is very difficult to associate complicated data elements to meaningful pathobiological results. One of the most important aspects of patient care is the odds of survival on hemodialysis. Because it is impossible to internally or externally monitor the processes of clinical care in a direct manner, clinicians must rely upon laboratory findings.

Albumin is a negative acute-phase reactive protein and its synthesis is actively suppressed as a part of response to inflammation (21). Most of the patients on dialysis have albumin values that fall within the normal range. Many have albumin levels that fall below normal. Patients with normal renal function might lose albumin in the urine. Their body response by increasing the rate of albumin synthesis, although this response is inadequate to normalize serum albumin concentration (9).

Hypoalbuminemia is a well-known marker for morbidity and mortality in ESRD population. Lowrie and Lew documented a linear increase in death rate with declining serum albumin levels at the initiation of dialysis as well as during the course of maintenance dialysis (22).

Serum albumin level is a marker for nutrition, inflammation plasma volume. Serum albumin is frequently considered a nutritional marker and has been shown to predict outcome in ESRD patients (23).

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There is increasing evidence that it may be more related chronic inflammation than to nutritional status. The reported association between hypoalbuminemia and mortality may be due to inflammation rather than to poor nutritional intake (24). Hypoalbuminemia is frequently associated with cardiac co-morbidity. Thus hypoalbuminemia is not simply a marker of malnutrition but also reflects inflammation and co-morbidity, therefore its regular assessment is very important in ESRD patients (5). CRP protein stimulates tissue factor production and neutrophil aggregation. The tendency to coagulation could indicate a direct contribution of CRP to mortality.

Greater CRP levels indicate patients at risk of progression of cardiovascular disease (18). In our study, we observed that a large proportion of patients had elevated serum CRP levels ($\geq 10\text{mg/L}$). The presence of elevated CRP in a significant number of ESRD patients confirms the existence of chronically activated APR. Recent data from ESRD patients also showed elevated CRP levels have significant association with hypoalbuminemia, malnutrition, increased morbidity and mortality in ESRD patients (15). Bergstrom *et al.*, were first to show that elevated CRP was a strong predictor of mortality. Owen and Lowrie showed the association between CRP and nutritional measures (15). Three recent studies showed CRP was a significant and independent predictor of death in chronic hemodialysis patients (25).

Noh *et al.* observed that two-year patient survival was significantly lower in the elevated CRP group than in the normal CRP group (15). Also several studies in patients with ESRD have shown CRP levels are linked with cardiovascular disease. CRP levels were found to be associated with various classic markers of cardiovascular disease in ESRD population (26,27). Strong association exist among laboratory findings for malnutrition and acute phase processes and pathobiology implied by these laboratory abnormalities influences mortal risk in patients primarily through depletion of vital body proteins. Deplete stores of vital proteins may result in part from down regulation of protein synthetic processes and up-regulation of catabolic processes. The finding that hypoalbuminemia is the main prognostic factor for death was largely reported and it was suggested that chronic inflammation may be the missing link or factor that causally ties hypoalbuminemia to morbidity and mortality. However, data consistent with the possibility that malnutrition may affect survival independently exist (28). Markedly elevated other circulating cytokine levels are found in

ESRD patients, which may be due to impaired removal of cytokines, and increased synthesis due to various infectious processes, co-morbid conditions such as coronary heart disease and chronic heart failure (29).

Inflammation can be assessed by means of inflammatory biomarkers; such as interleukins and CRP, and associations between levels of these biomarkers and CVD and mortality have been well documented in the renal literature. IL-6 and CRP also are associated with protein energy malnutrition because inflammation affect nutritional status through inhibition of protein synthesis and induction of catabolism (30).

Other markers such as ghrelin are also involved in the pathogenesis of protein-energy wasting, inflammation, and cardiovascular complications in ESRD. Plasma ghrelin may prove to be a powerful biomarker of mortality in ESRD but should be considered in the context of assay specificity, other weight-regulating hormones, nutritional status, systemic inflammation, and cardiovascular risk factors (31).

Although the precise mechanisms, that are responsible for inflammation in ESRD patients is unclear, low grade infection, repeated exposure to dialysis filters, and auto-oxidation products are considered as likely inciting factors in these patients (32).

This study showed that low albumin and high CRP levels are the main predictors for death. We conclude that acute phase response occurs in the majority of ESRD patients. We believe that measuring CRP as a marker of inflammation can be helpful in managing these patients. Our findings have important implications for clinical practice. More important, ESRD patients with low albumin and/or high CRP levels should receive close follow up and all sources of malnutrition and inflammation should be controlled.

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