A COMPARATIVE ANALYSIS OF THE ASSOCIATION OF CHRONIC INFLAMMATION VERSUS NO INFLAMMATION ON THE NUTRITIONAL STATUS OF PATIENTS ON CHRONIC MAINTENANCE HEMODIALYSIS

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ABSTRACT

Objective: *To assess the association of chronic inflammation on the nutritional status of patients on Chronic maintenance hemodialysis.*

Methodology: *This cross-sectional comparative study was performed at department of Medicine Fauji Foundation Hospital Rawalpindi. Patients having chronic renal failure who were on regular maintenance hemodialysis for more than 6 months were included in the study. Ultrasound examination was done to confirm the presence of renal parenchymal disease and shrunken kidneys. The level of C-reactive protein was measured as indicator of inflammation and serum albumin, cholesterol level, mid-arm circumference, triceps skin fold thickness, subscapular skin fold thickness and body mass index (BMI) were used as the assessment tools to evaluate the influence of inflammation on the nutritional status in patients. Patient in two groups with positive or negative CRP were compared regarding the effects of inflammation on nutritional parameters.*

Results: *Out of 30 patients, 13 (43.3%) had evidence of inflammation with positive CRP and a mean BMI of 19.2±3.3 whereas the CRP negative group had a mean BMI of 24.9±1.5. Regarding nutritional parameters, Triceps Skin Fold Thickness, Subscapular Skin Fold Thickness, mid-arm circumference and serum albumin were also statistically low in CRP positive patients although serum cholesterol levels did not differ significantly in our study. The CRP positive patients therefore were malnourished as compared to the CRP negative group.*

Conclusion: *Patients with end stage renal disease on chronic dialysis with evidence of inflammation are more at risk of malnutrition. Although there is no standardized strategy for the treatment of chronic inflammation in these patients so far but this area needs further research to improve outcome in these patients.*

Key Words: *Malnutrition, Inflammation, C-reactive protein, Malnutrition Inflammation Complex Syndrome, Chronic renal failure*

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INTRODUCTION

Inflammatory processes are common in individuals with either chronic renal failure (CRF) or with end-stage renal disease (ESRD). This is due to many underlying factors including an increased incidence of infections (most commonly dialysis-access related), uremia, raised levels of pro-inflammatory cytokines, frequent presence of widespread arteriosclerosis and many other unknown factors[1]. Although the definition of inflammation is unclear in this setting, ESRD-associated chronic inflammation as assessed by increase in C-reactive protein levels has been reported in 30 to 60 percent in a study done on

North American and European dialysis patients. So far the data reported from Asian countries show a lower prevalence[2] and the reason of this difference is unknown.

Protein-energy malnutrition (PEM) and inflammation are common and usually concurrent in patients on maintenance dialysis. Many factors leading to these conditions overlap but both these conditions are related to poor dialysis outcome. PEM in dialysis patients has been suggested to be secondary to inflammation; however, the evidence is not conclusive, and an equi-causal status or even opposite causal direction is possible[3]. Hence, malnutrition-inflammation complex syndrome (MICS) is an appropriate term.

We conducted this study on chronic hemodialysis patients to analyze the association of chronic inflammation with malnutrition in patients on chronic hemodialysis.

METHODOLOGY

This study was carried out in Nephology Ward of Department of Medicine at Fauji Foundation Hospital Rawalpindi from February to August 2011. Patients having chronic renal failure who were on regular maintenance hemodialysis for more than 6 months were included in the study. All patients who had severe co-morbid conditions leading to malnutrition and inflammation like severe chronic obstructive airway disease, pulmonary tuberculosis, rheumatoid arthritis, bronchiectasis, sepsis and patients with acute renal failure due to any cause were excluded from study. Over a period of eight months data of 30 patients was recorded according to our inclusion criteria through non-probability sampling from dialysis unit. An informed consent was taken from all patients along with approval from Ethical Review Committee of Foundation University Medical College. The indicator of inflammation C-reactive protein (CRP) was measured. The assessment tools used to evaluate the nutritional status in patients were: serum albumin and cholesterol level, mid-arm circumference, triceps skin fold thickness, subscapular skin fold thickness and body mass index (BMI). The Mid-arm circumference was measured at the level of insertion of deltoid muscle in centimeters with a measuring tape. Triceps and subscapular skin fold thickness were measured using vernier calipers. Patients were divided into two groups; those with and those without evidence of inflammation in the form of a positive or negative CRP. A CRP >6 mg/L was considered as a positive result. The two groups were compared with respect to their nutritional parameters to see if patients with evidence of ongoing inflammation were malnourished as compared to the other group. Student's t-test was used for comparison between the two groups and a p of < 0.05 was considered statistically significant. The data were stored and analyzed using SPSS 14.0.

RESULTS

Out of 30 patients included in the study there were 24 women and only 6 men with mean age of 54.79±2.3 years and with a mean time on dialysis of 8 months. Out of our patients included in the study nineteen were having hypertension and four having diabetes as underlying cause of renal failure. Thirteen patients (43.3%) had evidence of inflammation with positive CRP. The CRP positive group had a mean BMI of 19.2±3.3 whereas the CRP negative group had a mean BMI of 24.9±1.5 therefore the two groups differed significantly ($p = 0.05$). The three anthropometric measures namely Triceps Skin Fold Thickness, Subscapular Skin Fold Thickness and mid-arm circumference were also statistically different between the two groups with a p-value of 0.00. Similarly serum albumin was significantly lower in CRP positive group (29.2±3.2g/L) as compared to the patients with negative CRP (36.35±2.8 g/L)

Table 1: Various parameters of assessing malnutrition in CRP positive and negative patients

Parameters	CRP Positive Group	CRP Negative Group	P value
Body Mass Index (kg/m^2)	19.2 ±3.3	24.9 ±1.5	0.00
Triceps Skin Fold Thickness (mm)	10.5 ±3.5	18.88 ± 4.2	0.00
Subscapular Skin Fold Thickness (mm)	11.1 ± 4.3	19.05 ± 4.5	0.00
Mid-arm circumference (cm)	21.3 ± 2.6	27.35 ± 2.99	0.00
Serum Albumin (g/L)	29.2 ± 3.2	36.35 ± 2.8	0.00
Serum Cholesterol (mg/dL)	3.99 ± 0.50	4.35 ± 0.85	0.19

having a statistically significant p-value. However, serum cholesterol levels did not differ significantly (p= 0.19) between the two groups (Table 1).

DISCUSSION

According to an estimate Pakistan has 150 end stage renal failure (ESRD) patients per annum per million, so each year we have almost 16,000 new patients with ESRD[4]. The overall crude mortality rate during dialysis in South Asian (including Pakistani) patients is 120 deaths per 1000 patients per year[5]. The frequency and the severity of the association of malnutrition and inflammation during chronic renal failure have been underlined in the past decade and are being increasingly recognized in current research[6]. Possible causes of MICS include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and low nutrient intake, uremic toxins, decreased clearance of inflammatory cytokines, volume overload, and dialysis-related factors. MICS is believed to be the main cause of erythropoietin hyporesponsiveness, high rate of cardiovascular atherosclerotic disease, decreased quality of life, an increased mortality and hospitalization in dialysis patients. Because MICS leads to a low body mass index with low levels of cholesterol, creatinine, and homocysteine with a raised CRP levels, a "reverse epidemiology" of these cardiovascular risks can occur in dialysis patients[7]. Therefore theoretically obesity, hypercholesterolemia and increased blood levels of creatinine and homocysteine appear to be protective and paradoxically associated with a better outcome[8]. Successful management of MICS may ameliorate the cardiovascular epidemic and poor outcome in dialysis patients[9]. Clinical trials focusing on MICS and its possible causes and consequences are urgently required to improve poor clinical outcome in dialysis patients[10].

As Fauji Foundation Hospital is mainly serving the dependents of retired army personnel, which are mostly their wives along with only those male patients who had left army on some medical grounds are entitled in our hospital. In our study almost half of patients had evidence of inflammation with positive CRP and a significantly lower mean BMI, triceps skin fold thickness, subscapular skin fold thickness, and mid-arm circumference and low serum albumin levels as compared to CRP negative patients. Our results are in concordance with many local and international studies. In a local study by Siddiqui et al[11], out of 64 patients C-reactive protein was positive in 35.9% patients and was associated with a lower mean serum albumin (32.7 g/l vs 35.4 g/l); p=0.017. However, correlation of albumin with BMI was not significant in this study (p= 0.53. Hence, although serum albumin is a strong marker of malnutrition but needs to be associated with other physical and inflammatory parameters to correctly identify malnourished haemodialysis patients. In another study by Nihi et al[12], performed on 40 patients on hemodialysis, a positive and significant correlation was observed between BMI and CRP (R = 0.37; p = 0.02) and a negative correlation was found between serum albumin and CRP (R = -0.31; p = 0.05). However this study used the subjective global assessment (SGA) for assessment of malnutrition whereas we used anthropometric measurements.

Perunić-Peković et al[13] studied 42 hemodialysis patients and found a negative correlations between serum albumin concentration and inflammatory markers (r=-0.31; p=0.05). Anthropometric parameters in hemodialysis patients were lower when inflammatory markers were higher and correlation was significant (p=0.05). Here the mean duration on dialysis was 52.6 ± 42 months as opposed to our study population with mean dialysis duration of 8 months. Tirmenstajn et al[14] performed subjective global assessment, anthropometric and laboratory measurements to evaluate nutritional and inflammatory status in 43 hemodialysis patients. Malnutrition was present in 46.5% patients. By univariate logistic regression analysis, triceps skinfold, mid-arm muscle circumference, body fat%, lean body mass, body-mass index, total proteins, albumin and CRP were shown to be associated with malnutrition (SGA 2-4). During multivariate analysis, BMI (p=0.011) and CRP (p=0.018) remained associated with malnutrition. In multiple regression models, there was an inverse relation of serum albumin concentration with CRP (r=-0.474; p<0.001)). Faintuch et al[15] showed that malnutrition estimated by subjective global assessment (SGA) was very common (>90%) and C-reactive protein was moderately elevated in 40.9% of patients. Raised CRP was associated with malnutrition (SGA 2-4) and was also negatively associated with serum albumin as seen in our study.

Anthropometry is a simple, safe, practical, and cost-effective method, in addition to being a valid and clinically useful way of assessing the protein-energy nutritional status of patients with chronic kidney disease[16,17]. Anthropometry is useful for assessing the patient's amount of adiposity and lean mass, and comprises height, body weight, body mass index (BMI), skinfold thickness and arm circumference (AC). The lack of reference patterns considering sex, age and ethnicity jeopardizes the accuracy of the anthropometric data of dialysis patients. In addition, the interpretation of anthropometric data may be

impaired by the intra-observer variability[18]. Anthropometry identifies neither nutritional alterations in short time periods, nor the specific deficiency of a nutrient. In addition, the hydration status may significantly influence anthropometric assessment. Of the biochemical indices available, serum albumin has been the most used for assessing the nutritional status of hemodialysis patients. We also used serum albumin as a marker of malnutrition.

Biochemical indices may be difficult to interpret in the presence of concomitant liver disease, iron-deficiency anemia, and chronic inflammation. Albumin has high specificity but low sensitivity for diagnosing malnutrition, because, in addition to nutritional deficit, other causes, such as reduced synthesis due to liver disease and increased losses through gastrointestinal tract, kidneys, burns and peritonitis alter its levels. Serum albumin levels decrease in situations of hypervolemia which is very frequent among patients on dialysis[19]. Serum albumin levels significantly increase after dialysis and inversely correlate with fluid withdrawal; thus, pre-dialysis albumin levels may not be a valid indicator of the nutritional status due to the effects of inter-dialytic weight gain[20]. The chronic inflammatory state may cause a reduction in the albumin synthesis and an increase in its catabolism, with consequent hypoalbuminemia[21]. Hence, caution should be taken when serum albumin is used for diagnosing malnutrition in the presence of inflammation and hypervolemia. Some authors have identified albumin as a marker of the nutritional status associated with mortality, regardless of the presence of inflammation. Jones et al have found no correlation of albumin with other nutritional parameters assessed and according to those authors, albumin related to inflammation, but not to the nutritional status per se[22]. Despite the limitations of the method, mainly the influence of the presence of inflammation and other comorbidities, albumin level is still considered a strong indicator of nutritional status and mortality risk[23].

As in our study along with many other studies has shown a relation of inflammation with malnutrition, the term malnutrition-inflammation complex syndrome (MICS) was rightly coined. MICS is believed to be the main cause of erythropoietin hypo-responsiveness, cardiovascular atherosclerotic disease, decreased quality of life, hospitalization and increased mortality in dialysis patients[24]. Because MICS leads to a low body mass index, hypocholesterolemia, decrease in muscle mass, hypocreatininemia and hypohomocysteinemia, a "reverse epidemiology" phenomenon of cardiovascular risk factors can occur in dialysis patients. Therefore, obesity, hypercholesterolemia, and increased blood levels of creatinine and homocysteine, within certain limits, appear to be protective and paradoxically associated with a better outcome[25]. Novel strategies aimed at attenuating the adverse nutritional effects of chronic inflammatory response may improve the clinical outcome in hemodialysis patients. Combined use of anthropometric and biochemical criteria is a better method of diagnosing malnutrition in chronic hemodialysis patients.

CONCLUSION

Malnutrition is more likely associated with increased levels of inflammatory cytokines like CRP in patients with end stage renal disease. There is a complex cause and effect relationship between inflammation and nutritional status. Novel strategies aimed at attenuating the adverse nutritional effects of chronic inflammatory response may improve the clinical outcome in hemodialysis patients.

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CONTRIBUTORS

UB & GMG conceived the idea, planned the study, did the data collection and analyzed the study. Both the authors contributed significantly to the research that resulted in the submitted manuscript.