Derangement in Serum Inflammatory Biomarkers Among Patients with End Stage Renal Disease

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Abstract

Background: End stage renal disease is an important public health problem. Renal replacement therapy, dialysis and transplantation are used to provide relief from the symptoms of end stage renal disease whilst also preserving the life of the patients though they are not curative. Haemodialysis is the widely used method although it produces a negative impact on quality of life of the patients. Hypoalbumianemia has been reported to be frequently present in haemodialysis patients and correlates strongly with mortality and morbidity. **Objective:** To determine the frequency of deranged inflammatory biomarkers in patients with end stage renal disease on hemodialysis, in Nishtar Hospital Multan. **Material and methods:** One hundred thirty-one cases with ESRD were selected from Hemodialysis Department, Nishtar Hospital Multan and 3ml of venous blood sample was taken before starting a session of hemodialysis and sent to central laboratory of Nishtar Hospital Multan. Serum Albumin was obtained by an automatic analyzer, and serum CRP by slide test, free of cost, to measure deranged inflammatory biomarkers. Data was analyzed by using SPSS version 20. **Results:** Of these 131 study cases, 85 (64.9%) were male patients while 46 (35.1%) were female patients. Mean age of our study cases was 42.37 ± 5.98 years. Of these 131 patients with ESRD on hemodialysis 33 (25.2%) were diabetic, 65 (49.6%) were hypertensives and 13 (9.9%) were obese. Mean duration on hemodialysis was 19.51 ± 7.59 months, 80 (61.1%) had to undergo hemodialysis twice a week and 51 (38.9%) had to undergo three times a week. Mean serum albumin level was noted to be 3.37 ± 0.59 g/dl. Mean serum C-reactive protein level was noted to be 20.73 ± 15.84 mg/l. Frequency of deranged inflammatory biomarkers in our study was noted to be in 109 (83.2%) of the study cases. **Conclusion:** Very high frequency of derangement in inflammatory biomarkers have been noted in our study. This derangement in these inflammatory biomarkers was significantly associated with female gender, increasing age, increased duration on hemodialysis and increased frequency of hemodialysis. The early diagnosis of these derangements followed by preventive measures can help decrease disease morbidity and mortality among targeted population.

Keywords: Inflammatory biomarkers, deranged, end-stage renal disease, hemodialysis.

Introduction:

End stage renal disease (ESRD), a consequence of chronic kidney disease (CKD), includes patients treated either by dialysis or transplantation, irrespective of the level of glomerular filtration rate (GFR)[1]. The number of patients with CKD and thus ESRD are increasing day by day and the problem is worldwide[1]. In Pakistan almost 15-20% of persons above 40 years of age are suffering from CKD[2]. Patients with chronic kidney disease (CKD) have an increased prevalence of inflammation as measured by any of a number of biomarkers[3]. These biomarkers are proteins whose plasma concentrations increases or decreases in response to inflammation. The causes of inflammation are multifactorial and include underlying disease, comorbidity, oxidative stress, infections, obesity, and genetic or immunologic factors[3]. The hemodialysis related factors depend on membrane biocompatibility and dialysate quality[3].In one study, between 30 and 50% of prevalent patients who were on hemodialysis (HD) had elevated serum levels of inflammatory biomarkers[3]. These markers can be used for the prediction of future cardiovascular events [4]. Cardiac diseases are one of the main causes of mortality and morbidity in ESRD patients[1]. Different studies showed that cumulative risk of cardiac disease is approximately 20%, in patients with renal disease, which is almost equivalent to the risk seen in patients who are suffering from previous cardiovascular disease[1]. Chronic inflammation is a risk factor for cardiovascular disease among HD patients and contributes to the excess cardiovascular morbidity and mortality[5]. Among several novel risk factors, inflammation has attracted considerable interest in the last 10 years[6]. Serum Albumin and C reactive protein are two important inflammatory biomarkers. HEMO study found that both CRP and albumin were independent

predictors of all-cause mortality in HD patients[7]. Serum Albumin concentration decreases in dialysis patients primarily as a consequence of increased inflammation with a subsequent decline in the rate of albumin synthesis[8]. Hypoalbuminemia is a strong and independent predictor of mortality[9]. Serum albumin, predicts mortality in HD patients, particularly when <3.8 g/dL[10]. A similar study conducted in Pakistan showed that 90.6% of 64 hemodialysis patients had serum albumin <4g/dL[11].C reactive protein was >10 mg/L in 39.5% patients[11].

C reactive protein is a protein produced in the liver. CRP level is an independent predictor for all-cause mortality in HD patients [12]. In one study, after exclusion of those with a clinically apparent infection, 29.3% of HD patients had increased CRP levels[13]. CRP is a prominent product of the inflammatory response syndrome and a marker of overall and cardiovascular death in the general population as well as in HD patients. A successful treatment of the underlying inflammatory conditions will improve long-term survival[7]. By emphasizing on screening of inflammatory biomarkers in ESRD, causes of inflammation in patients with these biomarkers, can be determined through clinical investigation and can be eliminated or corrected. A successful treatment of the inflammatory conditions and thus modification of risk factors of cardiovascular outcome, will reduce mortality among patients on HD[14, 15].

Materials and Methods:
One hundred thirty-one cases with ESRD were selected from Hemodialysis Department, Nishtar Hospital Multan. Patients with acute renal failure having S. Creatinine levels more than 1.2 mg/dL, for less than 3 months, patients with any pre existing acute infection having Neutrophils > 75%, patients with pre-existing malignant tumors and patients with history of any surgical procedure in last 10 days were excluded. After detailed history, examination and record review, anthropometric measures like weight and height were measured by a standardized weight scale and a standardized height measuring tape respectively. Deranged Inflammatory Biomarkers was defined as Presence of any one of following was labelled as a deranged inflammatory biomarker.

Serum Albumin < 4 g/dL, Serum C reactive protein > 10 mg/L.End Stage Renal Disease was defined as Patients with GFR < 15 ml/min and on hemodialysis for the last 3 months or greater than that. GFR estimated by Cockroft-Gault Formula i.e for male: (140-Age)×Weight(Kg) / 72×S.Creatinine (mg/dL) for female: (140-Age)×Weight(Kg)×0.85 / 72×S.Creatinine (mg/dL).   3ml of venous blood sample was taken before starting a session of hemodialysis and sent to central laboratory of Nishtar Hospital Multan. Serum Albumin was obtained by an automatic analyzer, and serum CRP by slide test, free of cost, to measure deranged inflammatory biomarkers. Data was analyzed by using SPSS version 20. Descriptive statistics was applied to calculate mean and standard deviation of age, S. Albumin and serum CRP of participants. Frequencies and percentages were calculated for qualitative variables like gender, age groups, Diabetes Mellitus (Yes/No), Hypertension (Yes/No), deranged inflammatory biomarkers (Yes/No) in hemodialysis patients.

Results:
Our study included a total of 131 patients with end stage renal disease (ESRD) meeting inclusion and exclusion criteria of this study. Of these 131 study cases, 85 (64.9%) were male patients while 46 (35.1%) were female patients. Mean age of our study cases was 42.37 ± 5.98 years ranging from 29 years to 50 years and 105 (80.2%) were having their ages ranging from 36 – 50 years of age. Of these 131 patients with ESRD on hemodialysis 33 (25.2%) were diabetic, 65 (49.6%) were hypertensives and 13 (9.9%) were obese. Mean duration on hemodialysis was 19.51 ± 7.59 months ranging from 10 months to 36 months while 79 (60.3%) were having duration up to 18 months, while 80 (61.1%) had to undergo hemodialysis twice a week and 51 (38.9%) had to undergo three times a week. Mean serum albumin level was noted to be 3.37 ± 0.59 g/dl ranging from 2.5 g/dl to 4.5 g/dl. Mean serum C-reactive protein level was noted to be 20.73 ± 15.84 mg/l (with minimum level of serum C-reactive protein was 6 while maximum level was 48 mg/l). Frequency of deranged inflammatory biomarkers in our study was noted to be in 109 (83.2%) of the study cases. This derangement of inflammatory biomarkers was stratified with regards to gender, age, diabetes, hypertension, obesity, duration on hemodialysis and frequency of hemodialysis and p values were found to be p=0.000, p=0.075, p=0.430, p=0.124 , p=0.168, p=0.000 and p=0.000, respectively.

Table No. 1   Stratification of deranged inflammatory biomarkers with regards to gender.

Gender	Deranged inflammatory biomarkers		P – value
	Yes (n=109)	No (n=22)	
Male (n=85)	63	22	0.000
Female (n=46)	46	00	
Total	131		

Table No. 2   Stratification of deranged inflammatory biomarkers with regards to age.

Age groups	Deranged inflammatory biomarkers		P – value
	Yes (n=109)	No (n=22)	
20 – 35 Years (n=26)	25	01	
36 – 50 Years (n=105)	84	21	0.075
Total	131		

Table No. 3   Stratification of deranged inflammatory biomarkers with regards to diabetes. (n=131)

Diabetes	Deranged inflammatory biomarkers		P – value
	Yes (n=109)	No (n=22)	
Yes (n=33)	26	07	
Yes (n=98)	83	15	0.430
Total	131		

Table No. 4   Stratification of deranged inflammatory biomarkers with regards to hypertension.

Hypertension	Deranged inflammatory biomarkers		P – value
	Yes (n=109)	No (n=22)	
Yes (n=65)	51	14	
Yes (n=66)	58	08	0.168
Total	131		

Table No. 5   Stratification of deranged inflammatory biomarkers with regards to duration on hemodialysis.

Duration	Deranged inflammatory biomarkers		P – value
	Yes (n=109)	No (n=22)	
Equal/Less than 18 months (n=79)	57	22	
More than 18 months (n=52)	52	00	0.000
Total	131		

Table No. 6   **Stratification of deranged inflammatory biomarkers with regards to frequency of hemodialysis.**

Frequency	Deranged inflammatory biomarkers		P – value
	Yes (n=109)	No (n=22)	
Twice a week (n=80)	59	21	0.000
Thrice a week (n=51)	50	01	
Total	131		

Discussion:

Our study included a total of 131 patients with end stage renal disease (ESRD) meeting inclusion and exclusion criteria of this study. End stage renal disease has been documented to be more prevalent in male patients, similarly of these 131 study cases, 85 (64.9%) were male patients while 46 (35.1%) were female patients. Siddiqui et al [11] reported 67 % male gender predominance which is in consistent with that of our study results. A study conducted by Iftikhar et al [16] from Lahore has reported 58 % male gender predominance, which is in compliance with that of our study findings. A study from Saudi Arabia [17] has also reported male gender predominance in 61 % male patients, which is similar to that of our study results. Machingura et al [18] from Zimbabwe has reported male gender predominance in 70 % patients with ESRD on hemodialysis, these findings are close to that of our study results. Menon et al [19] also reported 58 % male gender predominance which is close to our study results.

Mean age of our study cases was 42.37 ± 5.98 years (with minimum age was 29 years while maximum age was 50 years). Our study results have further indicated that majority of our study cases i.e. 105 (80.2%) were having their ages ranging from 36 – 50 years of age. Siddiqui et al from Rawalpindi [11] has reported 44.5 ± 14.3 years mean age of ESRD patients on hemodialysis. A study conducted in Lahore by Anees et al [20] has reported 46.10 ± 16.29 years mean age of patients on hemodilaysis, these findings are close to that of our study results. Machingura et al [18] reported 46.7 ± 13.5 years mean age of these patients of ESRD on hemodialysis, these findings are close to that of our study results. Of these 131 patients with ESRD on hemodialysis 33 (25.2%) were diabetic, 65 (49.6%) were hypertensives and 13 (9.9%) were obese. Anees et al [20] reported similar findings. Mean duration on hemodialysis was 19.51 ± 7.59 months (with minimum duration on hemodialysis was 10 months while maximum duration was 36 months). Our study results have reported that majority of our study cases i.e. 79 (60.3%) were having duration up to 18 months. Anees et al [20] reported mean duration on hemodialysis to be 24.87 ± 22.1 months which is similar to that of our findings.

While 80 (61.1%) had to undergo hemodialysis twice a week and 51 (38.9%) had to undergo three times a week. Anees et al also reported majority of the patients 40 (74.1%) were on twice weekly dialysis. These findings of Anees et al [20] are similar to that of our study results. Mean serum albumin level was noted to be 3.37 ± 0.59 g/dl (with minimum serum albumin level was 2.5 and maximum serum albumin level was 4.5 g/dl). Machingura et al [18] reported mean serum albumin level to be 3.36 ± 0.61 g/dl which is similar to that of study results. Menon et al [19] reported 4.0 ± 0.4 g/dl mean serum albumin level which is close to our study results. Siddiqi et al [11] reported 3.4 ± 0.4 mean value of serum albumin level which is close to that of our study results. Mean serum C-reactive protein level was noted to be 20.73 ± 15.84 mg/l (with minimum level of serum C-reactive protein was 6 while maximum level was 48 mg/l). Menon et al [19] reported 1 – 73 mg/liter range of CRP in these patients.

Frequency of deranged inflammatory biomarkers in our study was noted to be in 109 (83.2%) of the study cases. Machingura et al [18] from Zimbabwe has reported 70.4 % derangement in inflammatory biomarkers (hypoalbuminemia), which is close to our study results. Siddiqui et al [11] from Rawalpindi reported 90.6 % frequency of derangement in inflammatory biomarkers, which is close to our study results. Menon et al [19] also reported similar results and documented these inflammatory biomarkers were independently associated with mortality in these patients with ESRD.

Conclusion:

Very high frequency of derangement in inflammatory biomarkers have been noted in our study. This derangement in these inflammatory biomarkers was significantly associated with female gender, increasing age, increased duration on hemodialysis and increased frequency of hemodialysis. The early diagnosis of these

derangements followed by preventive measures can help decrease disease morbidity and mortality among targeted population.

References

1.   Wanner C, Tonelli M. KDIGO clinical practice guideline for lipid management in CKD: Summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85(6):1303-9.

2.   Jafar TH. The growing burden of chronic kidney disease in Pakistan. N Engl J Med 2006;354(10):995-7.

3.   Jofré R, Rodriguez-Benitez P, López-Gómez JM, Pérez-Garcia R. Inflammatory syndrome in patients on hemodialysis. J Am Soc Nephrol 2006;17(12 Suppl 3):S274-80.

4.   Heidari B. C-reactive protein and other markers of inflammation in hemodialysis patients. Caspian J Intern Med 2013;4(1):611–6.

5.   Nadeem M, Stephen L, Schubert C, Davids MR. Association between periodontitis and systemic inflammation in patients with end-stage renal disease. SADJ 2009;64(10):470-3.

6.   Tanaka A, Sakakibara M, Asada H, Tanaka T, Ishii H, Murohara T. Practical approach to evaluate asymptomatic coronary artery disease in end-stage renal disease patients at the initiation of dialysis. Ther Apher Dial 2014;18(2):167-73.

7.   Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999;55(2):648-58.

8.   Kaysen GA, Dubin JA ,Müller HG,Rosales L, Levin NW, Mitch WE. HEMO study group NIDDK: Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. Kidney Int 2004;65(4):1408-15.

9.   de Castro LL, de Carvalho e Martins Mdo C, Garcez AM, Pacheco JF, Cunha FV, Moita Neto JM, *et al.* Hypoalbuminemia and oxidative stress in patients on renal hemodialysis program. Nutr Hosp 2014;30(4):952-9.

10.   Sridhar NR, Josyula S. Hypoalbuminemia in hemodialyzed end stage renal disease patients: Risk factors and relationships--a 2 year single center study. BMC Nephrol 2013;14:242.

11.   Siddiqui UA, Halim A, Hussain T. Nutritional profile and inflammatory status of stable chronic hemodialysis patients at nephrology department, Military hospital Rawalpindi. J Ayub Med Coll Abottabad 2007;19(4):29-31.

12.   Ishii J, Takahashi H, Kitagawa F, Kuno A, Okuyama R, Kawai H, *et al*. Multimarker approach to risk stratification for long-term mortality in patients on chronic hemodialysis. Circ J 2015;79(3):656-63.

13.   Kubrusly M, Oliveira CM, Santos DC, Mota RS, Pereira ML. A comparative analysis of pre- and post-dialysis albumin as indicators of nutritional and morbi-mortality risks in haemodialysis patients. J Bras Nefrol 2012;34(1):27-35.

14.   Kim Y, Molnar MZ, Rattanasompattikul M, Hatamizadch P, Benner D, Kappler JP, Kavesdy CP, Kalantar-Zadch K. Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis. Int Urol Nephrol. 2013;45(1):215–227.

15.   Heidari B[1]. C-reactive protein and other markers of inflammation in hemodialysis patients. Caspian J Intern Med. 2013 Winter;4(1):611-6.

16.   Iftikhar U, Anees M, Nadeem M, Aman S, Kazmi AH. Frequency of cutaneous manifestations in patients of end stage renal disease on haemodialysis. Ann King Edward Med Uni 2015;21(2):61-6.

17.   Gazzaz ZJ, Dhafar KO, Tashkandi MA, Farooq MU. Clinical profile of haemodialysis patients with diabetic nephropathy leading to end stage renal disease. Pak J Med Sci 2010;26(1):82-7.

18.   Machingura PI[1], Mahiya NM[1], Chikwasha V[2]. Hypoalbuminaemia in haemodialysis patients at Parirenyatwa group of hospitals and Chitungwiza central hospital. Pan Afr Med J. 2015 Jun 1;21:79. doi: 10.11604/pamj.2015.21.79.4171. eCollection 2015.

19.   Menon V[1], Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, et al. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int. 2005 Aug;68(2):766-72.

20.   Anees M, Asim Mumtaz, Sumaira Frooqi, Ibrahim M, Farooq Hameed. Serum trace elements (aluminium, copper, zinc) in hemodialysis patients. Biomedica 2011;27(2):106-10.