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Serum C-reactive protein (CRP) in association with various nutritional parameters in maintenance hemodialysis patients

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Abstract

Malnutrition and inflammation are common in hemodialysis (HD) patients, and are usually closely associated. Serum C-reactive protein (CRP) concentrations have been found to be significantly elevated in hemodialysis patients and reflects chronic inflammation, and as an acute-phase reactant, is a sensitive and independent marker of malnutrition. To investigate the association of serum CRP level with some nutritional variables in diabetic and non diabetic end-stage renal failure patients undergoing regular hemodialysis, we designed a study on 36 maintenance hemodialysis patients (f=15, m=21), consisting of 25 non-diabetic HD patients and 11 diabetic HD patients. In this study a near significant difference of CRP between diabetic and non-diabetics of all patients with more values of CRP in diabetics and a significant difference of CRP between diabetic and non-diabetics of female HD patients with more values in diabetics were seen. A significant difference of CRP between males and females of non-diabetic population with more values of CRP in males was found too. An inverse correlation of serum CRP with serum cholesterol and triglyceride levels and a near significant positive correlations of CRP with serum ALP and with serum intact parathormone (iPTH) were found too. An inverse correlation of serum CRP with dialysis efficacy was also seen. No significant association between serum CRP and serum albumin was seen. Compatible with some studies and in contrast to some other studies, the association of serum albumin with serum CRP levels in this study was insignificant. The positive correlation of high serum iPTH with inflammation implies further need to control hyperphosphatemia and secondary hyperparathyroidism in HD patients, also inverse correlation of serum CRP with cholesterol and triglyceride further support the malnutrition-inflammation complex syndrome (MICS) which frequently seen in hemodialysis patients *(Tab. 3, Fig. 3, Ref. 42)*.

Key words: end-stage renal failure, hemodialysis, C-reactive protein (CRP), malnutrition-inflammation, lipids, malnutrition-inflammation complex syndrome (MICS), secondary hyperparathyroidism.

C-reactive protein (CRP), is an acute phase protein whose synthesis in the liver is regulated by different cytokines, particularly interleukin 6 (IL-6). Plasma levels of CRP in the absence of active disease are low, but can rise up to 1000-fold in patients with an inflammatory reaction. Besides being a marker of inflammation, CRP itself may have proinflammatory properties since it can activate the complement system (1–2). Thus elevated plasma concentrations of C-reactive protein (CRP), are a sensitive marker of underlying systemic inflammation (3–5). Serum CRP concentrations have also been found to be significantly elevated in hemodialysis patients (6–7) and reflect chronic inflammation, and as an acute-phase reactant, is a sensitive and independent marker of malnutrition (8). An elevated serum C-reactive protein has been shown to be strongly predictive of morbidity and mortality in dialysis patients, specially is a strong predictor of cardiovascular mortality in hemodialysis patients and (9–10). Uremic malnutrition is characterized by insidious loss of somatic protein stores (reflected by lean body mass or serum

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creatinine) and visceral protein concentrations (reflected by serum albumin or serum prealbumin) (11). The etiology of malnutrition in renal failure is complex and may include many factors, e.g. poor food intake because of anorexia, nausea and vomiting due to uraemic toxicity, hormonal derangements, acidosis and increased resting energy expenditure (11–12). Malnutrition and inflammation are common in hemodialysis patients, and are usually closely associated (13). Indeed the prevalence of protein-energy malnutrition in hemodialysis (HD) patients is high (23 to 73 %) in various studies (14–17). Several recent reports have focused on the association between nutritional state and clinical outcome, providing support for the hypothesis that malnutrition may cause or contribute to mortality and predict poor clinical outcome in end-stage renal disease patients (16–18). Low serum albumin as a parameter of malnutrition in HD patients is principally associated with infection/inflammation but not with malnutrition alone (19). Preliminary studies showed the association of CRP level and the serum albumin level (20). Recently in a study on a group of hemodialysis patients no correlation between baseline CRP and serum albumin was found (21). In this regard we sought to investigate the association of serum CRP level with some nutritional variables consisting of serum albumin in our diabetic and non diabetic end-stage renal failure patients undergoing regular hemodialysis.

Patients and methods

This cross-sectional study was conducted in patients with end-stage renal disease (ESRD), who were undergoing maintenance hemodialysis treatment with acetate basis dialysate and polysulfone membranes. According to the severity of secondary hyperparathyroidism, each patient being treated for secondary hyperparathyroidism was given oral active vitamin D3 (Rocaltrol), calcium carbonate, and Rena-Gel capsules at various doses. According to the severity of anemia, patients received IV iron therapy with Iron Sucrose (venofer) at various doses after each dialysis session. All patients received treatment with of 6mg folic acid daily, 500 mg L-Carnitine daily, oral Vitamin B-complex tablet daily and also 2000U IV Eprex (recombinant human erythropoietin (rHuEPO) for each patient after the dialysis session routinely. Exclusion criteria were active or chronic infection. Levels of serum predialysis creatinine(Creat), post and predialysis blood urea nitrogen(BUN), serum calcium (Ca), phosphorus (P), albumin(Alb) and also lipid profile containing serum Triglyceride (Tg), Cholestrol (Chol) and high density lipoprotein (HDL-C) as well as serum C-reactive protein (CRP) were measured using standard kits. Also intact serum PTH (iPTH) was measured by the radioimmunoassay (RIA) method using DSL-8000 of USA (normal range of values is 10–65 pg/ml). Serum 25--hydrox VitD (25-OH VitD) level (normal range of values is 25 to 125 nMol/l) was measured by enzyme-linked immunosorbent assay (ELISA) method using DRG kit from Germany. Plasma was measured by arterial blood gas. For the efficacy of hemodialysis the urea reduction rate (URR) was calculated from pre- and post-blood urea nitrogen (BUN) data (22). The Body mass index (BMI) was calculated using the standard formula (post-dialyzed weight in kilograms/height in square meters; kg/m^2) (23). Serum LDL-C was calculated using Friedewal's formula (24).Duration and dosages of hemodialysis treatment were calculated from the patients' records. The duration of each hemodialysis session was 4 hours. Statistical analysis was performed in all hemodialysis(HD), females, males, diabetics and non diabetics populations separately. For statistical analysis, the data are expressed as the mean±SD. Comparison between the groups was done using Student's t-test. Statistical correlations were assessed using partial correlation test. All statistical analyses were performed using SPSS (version 11.5.00). Statistical significance was determined at a $p<0.05$.

Results

Total number of patients was 36 (f=15, m=21), consisting of 25 (f=11, m=14) non-diabetic HD patients and 11 (f=4, m=7) diabetic HD patients. Tables 1, 2 and 3 show the patients' age expressed as mean±SD, the length of time they were on hemodialysis, the dialysis doses, and the results of laboratory tests. The mean patient's age was 46.6 (±17) years. For the whole group of patients ,no significant difference of CRP between males and females was seen, also no significant difference of CRP between diabetic and non-diabetic male HD patients was seen (p N.S.), however a near significant difference of CRP between diabetic and non-diabetics from the total number of patients was seen ($p=0.056$),also a significant difference of CRP between diabetic and non-diabetic of female HD patients was seen ($p<0.001$), moreover a significant difference of CRP between males and female of non-diabetic population was seen ($p=0.032$).In this study

Tab. 1. Mean±SD, minimum and maximum of age, duration and doses of hemodialysis and also laboratory results of all hemodialysis patients.

All patients n=36	Minimum	Maximum	Mean±SD
Age years	16	80	46.6±17
DH* months	2	156	32±3
Dialysis dose sessions	36	1584	294±3393
URR %	39	76	59±8.9
BMI kg/m^2	16	34	22±4.4
iPTH Pg/ml	16	1980	434±455
Ca mg/dl	5	10	7.7±0.94
P mg/dl	3	10	6.4±2
Alp IU/L	175	5487	628±891
HCO_3 mE/l	14	25	20±2.6
CRP mg/l	3	40	8.7±6.7
BUN mg/dl	30	180	83±33
Creat mg/dl	3	18	9.5±3.
Alb g/dl	2.4	4.8	3.8±0.5
25-OH Vit D nMol/l	1.3	105	10.5 ±18
Chol mg/dl	59	211	117±39
TG mg/dl	29	461	130±95
LDL mg/dl	12	122	61.6±22
HDL mg/dl	2	70	37±11

*Duration of hemodialysis treatment

Tab. 2. Mean±SD, minimum and maximum of age, duration and dosage hemodialysis and also laboratory results of non-diabetic hemodialysis patients.

sNon-diabetic patients n=25	Minimum	Maximum	Mean±SD
Age years	16	80	44±17
DH* months	2	156	40±40.8
Dialysis dose sessions	36	1584	370±452
URR %	60	76	61±7.5
BMI kg/m^2	16	36	21±4.6
iPTH Pg/ml	22	1980	537±483
Ca mg/dl	6	9	7.8±0.70
P mg/dl	4	10	6.6±1.8
ALP IU/L	190	5487	760±1044
HCO_3 mE/l	14	25	20±2.8
CRP mg/l	2	20	7.4±3.8
BUN mg/dl	30	180	81±32
Creat mg/dl	4	15	9.8±2.9
Alb g/dl	2.4	4.7	3.8±0.50
25-OH Vit D nMol/l	1.3	105	12.6±21
Chol mg/dl	59	171	110±33
TG mg/dl	61	461	130±85
LDL mg/dl	12	99	61±2
HDL mg/dl	25	70	38±11

*Duration of hemodialysis treatment

Tab. 3. Mean±SD, minimum and maximum of age, duration and dosage hemodialysis and also laboratory results of diabetic hemodialysis patients.

Diabetic patients n=11	Minimum	Maximum	Mean±SD
Age years	27	75	53±15.8
DH* months	6	24	14.5±6
Dialysis dose sessions	54	216	123±54
URR %	39	75	53.5±9.8
BMI kg/m^2	20	34	23±3.9
iPTH Pg/ml	16	860	202±277
Ca mg/dl	5	10	7.5±1.3
P mg/dl	3	10	6±2
ALP IU/L	175	584	327±148
HCO_3 mE/l	18	25	20±1.8
CRP mg/l	4	40	12±10
BUN mg/dl	30	140	87±3
Creat mg/dl	3	18	9±4.8
Alb g/dl	3	4.8	3.8±0.50
25-OH Vit D nMol/l	1.5	3.6	5.8±10
Chol mg/dl	60	211	133±49
TG mg/dl	29	456	130±120
LDL mg/dl	25	122	62±2
HDL mg/dl 20 46 35±9.5			

*Duration of hemodialysis treatment

the associations between serum CRP level and variables consisting of age, duration of hemodialysis, hemodialysis doses, serum lipids, parameters of bone activity, serum 25-hydroxy Vit D level, dialysis adequacy and also with plasma in all groups containing total, non-diabetic, diabetic, female and male HD patients were as follows; In all HD patients, a near significant inverse correla-

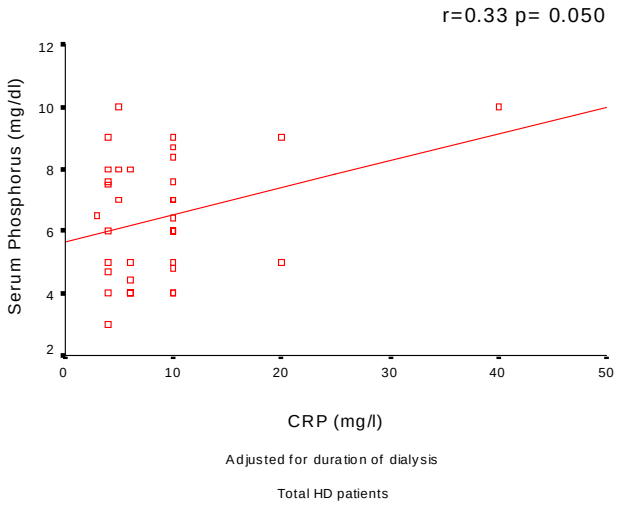

Fig. 1. Significant positive correlation of serum CRP with serum phosphorus.

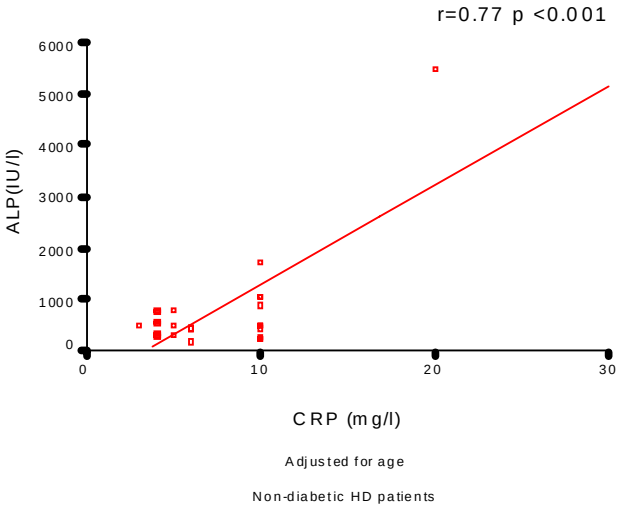

Fig. 2. Significant positive correlation of serum CRP with serum ALP.

tion of serum CRP with serum cholestrol (r=-0.29, p=0.090) and a significant positive correlation of serum CRP with serum phosphorus (r=0.33, p=0.050) (Fig. 1) were found (adjusted for duration of dialysis for two correlations). In this group also a near significant positive correlation of serum CRP with serum BUN (r=0.33, p=0.050) (adjusted for dialysis dosage) was found too. In non-diabetic HD patients a significant positive correlation of serum CRP with serum ALP (r=0.77, p<0.001) (Fig. 2) (adjusted for age) and a near significant inverse correlations of serum CRP with serum Creat (r=-0.38, p=0.065) and with dialysis efficacy as determined by URR (r=-0.37, p=0.074) were seen too (adjusted for dialysis doses for both correlations). In diabetic HD patients a significant positive correlation of serum CRP with serum iPTH (r=0.68, p=0.030) (Fig. 3) (adjusted for dialysis doses), and a near significant inverse correlation of se-

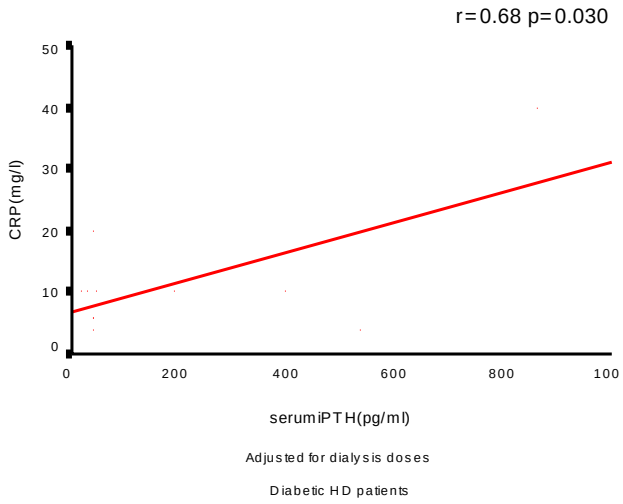

Fig. 3. Significant positive correlation of serum CRP with serum iPTH.

rum CRP with plasma HCO_3 (r=-0.52, p=0.054) (adjusted for the duration of dialysis)were found too. Moreover in this group we found a near significant positive correlation of serum CRP with age (r=0.50, p=0.065) (adjusted for the duration of dialysis). In male HD patients there was a near significant inverse correlations of serum CRP with serum Tg (*r*=-0.40, p=0.079) (adjusted for age), moreover we found that the previous near significant inverse correlation of serum CRP with cholesterol for the total number of patients was significantly negative in this population (r=-0.45, p=0.046) (adjusted for dialysis doses), in this group we also found a near significant positive correlation of serum albumin and plasma (r=0.42, p=0.065) (adjusted for dialysis duration). In this study no significant association between serum CRP and serum albumin was detecetd (p N.S.).

Discussion

In this study we found a near significant difference of CRP between diabetics and non-diabetics of the total number of patients with more values of CRP in diabetics, a significant difference of CRP between diabetic and non-diabetics of female HD patients with more values in diabetics and a significant difference of CRP between males and female of non-diabetic population with more values of CRP in males. We also found inverse correlation of serum CRP with serum cholesterol and triglyceride levels. A significant positive correlation of serum CRP with serum phosphorus and also near significant positive correlations of serum CRP with serum BUN, with serum ALP and serum iPTH, and also with age of patients were found too. Inverse correlations of serum CRP with serum Creat, and with dialysis efficacy and also with plasma were found too. No significant association between serum CRP and serum albumin was seen. It has recently been recognized that the evidence of inflammation predicts serum albumin concentration in dialysis patients (11). Uremic malnutrition and chronic inflammation often coexist in ESRD patients. A recent study by Stevinkel et al (25) demonstrated this relationship in advanced chronic kidney disease patients not yet on maintenance dialysis. Of 109 patients with advanced chronic renal failure, 44 % had moderate to severe protein-calorie malnutrition, and 32 % had signs of inflammation, as determined by elevated CRP concentrations (25). Most importantly, 53 % of the patients with malnutrition had signs of inflammation and 72 % of the patients with inflammation had signs of malnutrition. A similar association is observed in chronic hemodialysis patients. Qureshi et al have demonstrated that chronic hemodialysis patients with severe malnutrition display signs of chronic inflammation (CRP>20 mg/L) approximately four times that of well-nourished chronic hemodialysis patients (26). Recently, markers of chronic inflammation have also been associated with adverse clinical outcome in chronic renal failure patients. CRP is a significant predictor of mortality as well as morbidity in both chronic hemo- and peritoneal dialysis patients (27–29). Similarly, increased levels of proinflammatory cytokines are associated with increased risk of mortality in ESRD patients (30–31). Whereas these two unfavourable conditions independently predispose ESRD patients to increased risk of morbidity and mortality (32), when uremic malnutrition and chronic inflammation coexist, they have an exponential relationship to morbidity and mortality, i.e., a small increase in the severity of either condition leads to significant worsening of morbidity and mortality (10). In a study conducted by Fujino et al in 389 HD patients, significant negative correlations were seen between fat mass changes and CRP (12). In our study no significant correlation between serum CRP and serum albumin neither in all patients nor in subgroups were found. In accordance with our finding, Nascimento et al found that baseline C-reactive (CRP) was not correlated with serum albumin level in the group of hemodialysis (HD) patients they examined (21). Also Tsirpanlis et al in a longitudinal study in a similar patient population, reached similar finding (32). In contrast to previous studies Iseki et al in 163 dialysis patients that were divided into two groups according to their baseline CRP levels, with group one consisting of CRP<10 mg/l (n=128) and group two of CRP10 mg/l (n=35), found significant lower serum albumin in group two. Furthermore, the risk of death was significantly higher in group two. They concluded that CRP is a significant predictor of death in chronic dialysis patients, independent of serum albumin and other possible confounders (33). In contrast to the finding of this work, Panichi et al conducted a study on 102 chronic pre-dialysis patients whose mean age was 53±5.8 years with a mean creatinine clearance of 52±37 ml/min. While serum CRP was greater in patients with lower creatinine clearance, the serum albumin levels were not significantly different between the groups of patients with a creatinine clearance lower than 20 mL/min (n=32) and patients with a creatinine clearance higher than 20 mL/min (n=70) (34). In hemodialysis patients serum triglyceride and cholesterol are considered as nutritional parameters (11), their inverse correlation with CRP showed the effect of inflammatory state of uremia and its negative effects on lipids (35). To support our results, Fernandez-Reyes et al in a cross sectional study which was performed in 64 patients

(35 males, 13 % diabetics; mean age 64±12), who had beep on HD for 64±58 months showed the correlation of low serum cholesterol and high level of CRP (11). We also showed the negative correlation of dialysis adequacy with CRP, which showed that an adequate dialysis, will be accompanied with lower stimulation of proinflammatory mediators. Parathyroid hormone (PTH) promotes IL-6 secretion by osteoblasts, and may also up-regulate IL-6 production in the liver and adipose tissue; this may explain why serum IL-6 is markedly elevated in primary hyperparathyroidism, and low in hypoparathyroidism. IL-6 is the major stimulus for hepatic production of many acute phase reactants, notably fibrinogen and C-reactive protein as mentioned (36). In hemodialysis, hyperphosphatemia is accompanied by uncontrolled secondary hyperparathyroidism(SHPTH) and high serum PTH level, hence association of hyperphosphatemia and high iPTH with serum CRP in this study further support the previous confirmed data (36), which explain the need to better control SHPTH in these patients. In this regard, in vitro studies have shown that 1,25 dihydroxyvitamin D3 [1.25(OH)2D3] decreases cytokine production by monocytes and lymphocytes. In addition, intravenous or oral pulse calcitriol treatment suppresses interleukin 6 (IL6) and interleukin1beta (IL1beta) in hemodialysis patients (37).In this study we also found an inverse association of plasma with serum CRP. Metabolic acidosis has been suggested to be an important factor responsible for protein and caloric malnutrition (38–40). In contrast to the metabolic studies, many epidemiologic studies in maintenance dialysis patients have indicated a paradoxically inverse association between mildly decreased serum bicarbonate and improved markers of protein-energy nutritional state (41–42). Hence metabolic acidosis may be considered as yet another element of the reverse epidemiology in ESRD patients, to support this finding we could show the positive association of plasma with serum albumin in our male population. Taken together , we could not show the association of serum albumin with serum CRP level, we showed the positive correlation of SHPTH with inflammation that implies further need to control of hyperphosphatemia in HD patients , also inverse correlation of serum CRP with cholestrol and triglyceride further support the malnutrition-inflammation complex syndrome (MICS) which is frequently seen in HD patients.

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