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Serum C-reactive protein and nutritional parameters in hemodialysis patients

Serumski C-reaktivni protein i nutritivni parametri kod bolesnika na hemodijalizi

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Abstract

Background/Aim. Inflammation is the most important factor in the genesis of vascular complication in the end-stage renal disease. The serum C-reactive protein (CRP) level is a sensitive marker of systemic inflammation as well as a predisposing factor for cardiovascular and all cause mortality in patients on hemodialysis. Albumin is the negative acute phase protein and its synthesis declines during the inflammation. The patients undergoing hemodialysis have a high prevalence of protein-energy malnutrition, due to reduced protein synthesis and increased degradation. The low serum albumin levels in these patients originate from the complex setting of conditions with systemic inflammatory response as a major cause, malnutrition and overhydratation. The aim of this study was to determine the prevalence of elevated CRP levels in the dialysis patients and to analyse its correlation with serum albumin levels and other parameters of nutritional status. **Methods.** The study included 49 patients on maintenance hemodialysis at the Department of Hemodialysis, Clinic of Nephrology, Military Medical Academy, Belgrade, Serbia. In order to analyse the parameters, the blood samples were taken during the arteriovenous fistula (AVF) puncture and before the second weekly dialyse. The following parameters were determined: serum levels of urea and creatinine before and after the dialysis procedure, CRP, hemoglobin, fasting glycemia, total cholesterol, triglycerides, albumins, iron, glycosylated hemoglobin (HbA1c), fasting insulinemia and C-peptide only before the dialysis. **Results.** Out of 49 patients on maintenance hemodialysis, 37 (75.5%) were males and 12 (24.5%) females with the average age of 56.04 ± 13.93 years. The average duration of the dialysis treatment was 7.37 ± 5 years. The high serum CRP levels (more than 3 mg/L) was found in 65.3% of patients. Singificantly more diabetic patients were observed in the group with the higher CRP levels (n = 12) compared to the group with the normal CRP levels (n = 3) ($p \leq 0.05$). A significant positive correlation was found between the CRP value and urea values after the dialysis procedure. We found negative correlation between the CRP values and serum albumin, HbA1c, total cholesterol and triglyceride levels, with no statistical significance. **Conclusion.** Our study observed a high rate of inflammation in the dialysis patients presenting as high frequency of the elevated CRP levels in the examined group. Negative correlation between CRP levels and serum albumin as well as with some other parameters of nutritional status, suggests that chronic inflammation may be the missing link that actually connect protein energy malnutrition with high morbiditiy and mortality rate in these patients.

Key words:
albumins; c-reactive protein; inflammation; nutritional status; renal dialysis.

Apstrakt

Uvod/Cilj. Inflamacija je jedan od glavnih faktora odgovornih za nastanak vaskularnih komplikacija kod bolesnika sa terminalnom bubrežnom insuficijencijom. C reaktivni protein (CRP) se smatra senzitivnim markerom sistemske inflamacije, kao i faktorom koji doprinosi povećanom riziku od opšteg i kardiovaskularnog mortaliteta. Albumin je negativni protein akutne faze zapaljenja i njegova sinteza opada sa napredovanjem sistemske inflamacije. Za bolesnike na hemodijalizi poznato je da pate od visokog stepena proteinske malnutricije usled smanjene sinteze proteina i njihove pojačane razgradnje. Nizak nivo se-

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rumskog albumina kod tih bolesnika je posledica kompleksnog stanja koje podrazumeva sistemsku inflamaciju, malnutriciju i prekomernu hidrataciju. Cilj naše studije bio je da se ispita učestalost povišenog serumskog CRP-a u našoj populaciji dijaliznih bolesnika i da se utvrdi stepen njegove korelacije sa serumskim albuminom i drugim parametrima nutritivnog statusa. **Metode.** Ispitivanjem je obuhvaćeno 49 bolesnika na hroničnom programu hemodijalize u Centru za hemodijalizu Klinike za nefrologiju Vojnomedicinske akademije u Beogradu. Uzorci krvi za analizu uzimani su tokom punkcije arteriovenske fistule, a pre druge nedeljne hemodijalize. Određivanu su sledeći parametri: serumski nivo uree i kreatinina pre i posle procedure, CRP, hemoglobin, glikemija, ukupni holesterol, trigliceridi, glikozilirani hemoglobin (HbA1c), insulinemija i C-peptid pre hemodijalize. **Rezultati.** Od ukupno 49 dijaliznih bolesnika, bilo je 37 (75,5%) muškaraca i 12 (24,5%) žena, prosečne starosti 56,04 ± 13,93 godine. Dužina lečenja hemodijalizom je prosečno iznosila 7,37 ± 5 godina. Povišene vrednosti serumskog CRP-a (više od 3 mg/L) imalo je 65,3% bolesnika. U grupi bolesnika sa povišenim nivoom CRP-a u serumu, bilo je značajno više dijabetičara (n=12) u odnosu na grupu sa normalnim nivoom CRP-a u serumu (n = 3) ($p \leq 0,05$). Uočili smo postojanje značajne pozitivne korelacije između serumskog CRP-a i serumske uree nakon dijaliznog procesa. U ispitivanoj grupi postojala je negativna korelacija između serumskog CRP-a i serumskog albumina, HbA1c, ukupnog holesterola i triglicerida. Ta korelacija nije bila statistički značajna. **Zaključak.** Naša studija je potvrdila visok stepen sistemske inflamacije kod dijaliznih bolesnika izražene kroz visoku učestalost povišenih vrednosti serumskog CRP-a. Negativna korelacija između nivoa serumskog CRP-a i serumskog albumina kao i drugih nutritivnih parametara, sugeriše da hronična inflamacija može biti ključna karika koja povezuje proteinsku malnutriciju sa visokim morbiditetom i mortalitetom ovih bolesnika.

Ključne reči:
albumini; c-reaktivni protein; zapaljenje; nutritivni status; hemodijaliza.

Introduction

The patients undergoing hemodyalisis have a high prevalence of protein-energy malnutrition and inflammation, which is considered as the most important factor that generate several complications in uremic state. For a long time, C-reactive protein (CRP) has been presented as a marker of inflammation and advanced atherosclerosis. Some studies have shown that CRP may be a direct marker of vascular disease [1]. Serum levels of CRP are one to five times more prevalent in the dialysis patients than in the general population. On the other hand, it was observed that the level of inflammation shown by CRP, is the strongest predictor of serum albumin level [2]. Increased oxidative stress in malnutrition, combined with a chronic inflammation can lead to an increased risk of atherosclerotic lesions. Synthesis of albumin and other nutritional markers, such as prealbumin or transferrin, decreases with the duration of the inflammation as well as their serum levels. This shows that the higher values of the parameters of inflammation are associated with a poor nutritional outcome in the uremic patients. Accordingly, a new clinical significance of CRP is that it represents the index that reflects the general health situation of patients on dialysis [3].

Among protein malnutrition, uremic anorexia and chronic inflammation, there is an overlap which means that the conditions leading to malnutrition can actually cause the inflammation. Besides, a strong correlation between these occurances can explain the high cardiovascular (CVS) morbidity and mortality rate in these patients, despite improvemenet in dialysis technologies [4].

The aim of this study was to determine the prevalence of elevated CRP levels in the dialysis patients and to analyse its correlation with the serum albumin levels and other parameters of nutritional status.

Methods

The study included 49 patients on maintenance hemodialysis at the Department of Hemodialysis, Clinic of Nephrology, Military Medical Academy, Belgrade, Serbia. All patients were dialysed three times per week for 4 hours, using an arteriovenous fistula (AVF) as permanent vascular access. All participants signed the written informed consent to participate in this clinical research. In order to analyse the parameters, blood samples were taken during the AVF puncture and before the second weekly dialyse. The following parameters were determined: blood urea nitrogen (BUN) and creatinine before and after the dialysis procedure, CRP, hemoglobin, glycemia, cholesterol, triglycerides, albumins, iron, glycosylated hemoglobin (HbA1c), insulinemia and C-peptide only before the dialysis. The concentrations of biochemical blood parameters were obtained spectrophotometrically using the Simens Dimension Rxl Max analyzer. The value of CRP was calculated by the enhanced turbidimetric-immunoassay (PETIA) using the Simens Dimension Rxl Max analyzer, while C-peptide and insulin were determined by the CMIA (Chemiluminescent Microparticle Immunoassay) method using the Beckman Unicel DXI 800 machine.

The Kt/V value was calculated using the following formula by Daugirdas and Blake [5]:

$$Kt/V = -\ln(R-0.008xt) + (4-3.5 \times R) \times UF/W$$

R-Ratio = Post BUN/Pre BUN; t = time; UF/W = Ultrafiltrate Volume/Weight

K – urea clearance; t – dialysis time; V – urea volume distribution.

Statistical analysis

Complete statistical analysis of data was done by the statistical software package, SPSS Statistics 18. Most of the variables were presented as frequency of certain categories, while a statistical significance of differences was tested with the χ^2 test. In case of continuous data, the variables were presented as the mean value ± standard deviation (SD), median, minimal and maximal values. The Kolmogorov-Smirnov test was used for the evaluation of distribu-

tion of data. The Pearsons correlation analyses was used to establish the relation of parameters. All the analyses were estimated at $p < 0.05$ level of statistical significance.

Results

Out of 49 patients on maintenance hemodialysis, 37 (75.5%) were males and 12 (24.5%) females, with the average age of 56.04 ± 13.93 years. The average duration of the dialysis treatment was 7.37 ± 5 years. The baseline characteristics of our patients are shown in Table 1.

Table 1

Baseline clinical characteristics and C-reactive protein (CRP) values in 49 dialysis patients

Patients characteristics	Values
Sex, men/women, n (%)	37/12 (75.5/24.5)
Age (years), mean ± SD	56.04 ± 13.9
HD duration (years), mean ± SD	7.37 ± 5
DP/non DP, n (%)	15/24 (30.6/69.4)
CRP ≤ 3 mg/L, n (%)	17/32 (34.7/65.3)

HD – hemodialysis; DP – diabetic patients; non DP – nondiabetic patients; SD – standard deviation.

Of the total number of patients, 15 (30.6%) had diabetes mellitus, 4 patients had type 1 and 11 type 2 diabetes. Among all patients with diabetes, diabetic nephropathy was the initiator for a chronic renal failure stage 5 and for the beginning of dialysis treatment. The patients were divided into two groups according to the CRP values. The first group consisted of 17 (34.7%) patients with the normal CRP values (CRP ≤ 3 mg/L), while the second group consisted of 32 (65.3%) subjects with the increased CRP values (CRP> 3 mg/L). Singificantly more diabetic patients were observed in the group with the higher CRP levels (n = 12) compared to the group with the normal CRP levels (n = 3) ($p \leq 0.05$). The mean serum albumin level in the patients with high CRP (> 3 mg/L) was only numerically lower than in the patients with the low CRP values (37.06 ± 3.57 *vs* 37.65 ± 2.57 mg/L; $p \geq 0.05$). The correlation of CRP values with gender, age, smoking status, length of dialysis, diabetes mellitus and Kt/V are shown in Table 2.

During the comparison of the analyzed blood biochemical parameters, a significant positive correlation was found between the serum CRP value and urea values after the dialysis procedure (Figure 1). We found negative correlation between CRP values and serum albumin, HbA1c, total cholesterol and triglyceride levels. These correlations did not reach statistical significance (Table 3).

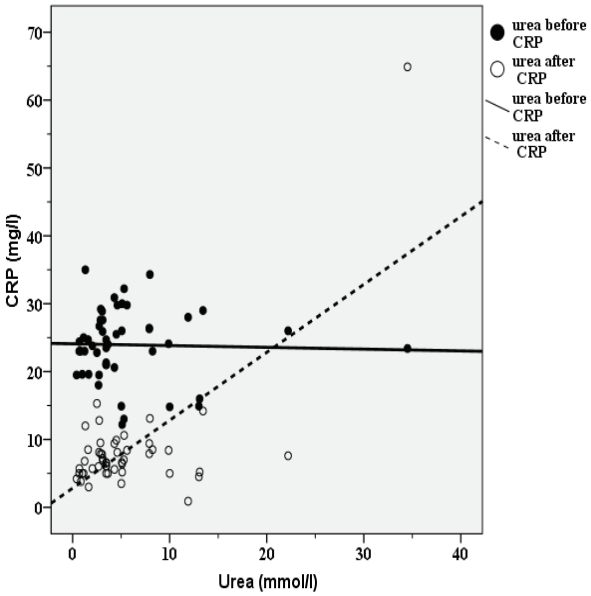

Fig. 1 – A significant positive correlation between the serum C-reactive protein (CRP) values and urea values after the dialysis procedure.

Table 2

Correlation between C-reactive protein (CRP) values and the different clinical characteristics of dialysis patients

Groups	Age	Gender	Smoke	HD durat.	DM	Kt/V
CRP (≤ 3 mg/L) (n = 17)						
r	-0.194	-0.577	0.223	0.104	0.064	-0.235
p	0.455	0.015	0.389	0.691	0.808	0.363
CRP (> 3 mg/L) (n = 32)						
r	0.202	0.232	-0.125	0.097	0.118	-0.209
p	0.268	0.200	0.497	0.597	0.521	0.251

HD – hemodialysis; DM – diabetes mellitus.

Table 3

Correlation between serum C-reactive protein (CRP) values with the differnet biochemical parameters of dialysis patients

Groups	BG	HbA1C	Insul.	CP	Urea		Creatinine		Alb	TChol	Tg
					before	after	before	after			
CRP (≤ 3 mg/L)											
r	0.278	0.035	-0.349	0.261	0.133	0.560	0.406	0.610	-0.312	-0.480	-0.451
p	0.281	0.893	0.170	0.312	0.610	0.019	0.106	0.009	0.223	0.051	0.069
CRP (> 3 mg/L)											
r	-0.009	-0.091	-0.087	0.244	-0.059	0.742	-0.255	0.058	-0.271	0.082	-0.122
p	0.959	0.619	0.640	0.195	0.749	0.001	0.158	0.754	0.134	0.654	0.506

BG – blood glucose; HbA1c – glycosilated hemoglobin; Insul – insulinemia; CP – C-peptide; Alb – albumin; TChol – total cholesterol; Tg – triglyceride.

Discussion

Inflammation is the most important factor in the genesis of vascular complication in the end stage renal disease (ESRD). The inflammation is potentially caused by decreased elimination of cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF) and IL-6, or by accumulation of advanced glycation end products (AGEs). Metabolic acidosis is another potential factor that originated from a significant number of endocrine, musculosceletal and other metabolic abnormalities, leading to the enhanced inflammation. Oxidative stress and acompanied infection from several sites including graft or fistula, infections from bioincompatible dialysis membrane; periodontal infections or endotoxine exposure could be another cause that provoke an inflammatory reaction [6].

The serum CRP level is a sensitive marker of systemic inflammation as well as a predisposing factor of cardiovascular and atherosclerotic diasease [7]. CRP levels are 8-fold higher in the hemodialaysis patients than in the healthy controls, being a powerful predictor of all-cause and CVS death, even after a follow- up period of 4 years [8]. CRP is present in almost all atherosclerotic plaques, binds to modified low density lipoproteins (LDL) and activates the complement pathway. It was shown that human CRP can contribute to ishemic tissue damage of heart and brain in experimental rat models [6]. Many studies showed that the elevated CRP levels predict all cause and cardiovascular mortality in the patients on hemodyalisis. The 5-year survival rate and the risk of death was significantly poorer in Japanese population of chronic dialysis patients with the higher CRP levels [9]. In the study of Krane et al. [10], the CVS outcome in the dilaysis patients was influenced by CRP levels more than by LDL cholesterol levels.

The frequency of elevated serum CRP varies among different studies, from 20% do 65% of dialysis and predialysis patients [9–13]. In our study group, 65.3% of uremic patients had the serum levels of CRP higher than 3 mg/L. Abraham et al. [13] found the elevated CRP levels in 67% of dilaysis patients, while Iseki et al. [9] found the elevated CRP levels in only 21.5% of dialysis patients. These variations among studies may be caused by different biochemical techinques used to measure CRP levels. Observed differences could be also explained by the absence of consensus in related literature, regarding the optimal cutoff value of serum CRP levels to define the presence of inflammation in ESRD.

In addition, the level of the serum CRP increases with declining the serum albumin concentrations. Albumin is the negative acute phase protein and its synthesis declined during the inflammmation. The patients undergoing hemodyalisis have a high prevalence of protein-energy malnutrition due to the reduced protein synthesis and inreased degradation. The patients with end-stage of renal disease (ESRD) develop the low serum albumin levels due to the complex setting of conditions with the systemic inflammatory response as a major cause; malnutrition and overhydratation could also play an important role. It has been obeserved that the serum CRP levels are in correlation with anorexia [4]. In our study group, the serum albumin levels among dialysis patients with the low serum CRP values were higher than in those with the higher CRP levels. We found negative corellation between the serum CRP levels and the serum albumin, cholesterol and triglyceride levels; still, those differences and correlations did not reach statistical significance. Abraham et al. [13] found a significant negative correlation the between serum albumin and CRP levels among the dialysis population. The same results were obsereved in the diabetic patients with ESRD undergoing hemodyalisis [14]. A serum albumin level is one of the most important markers of malnutrition in the patients with ESRD, even when only slightly less than 4.0 g/dL. When the inflammatory process increases, there is a decrease in the serum albumin due its loss into extravascular space because of increased vascular permeability, or by increased consumption by cells locally, while decreased synthesis is a result of a direct cytokine inhibition [15]. High levels of CRP and low albumin levels often occur simultaneosly in the hemodialysis patients and are reffered together as a malnutrition-inflammation-atherosclerosis syndrome to emphasize its improtant interreaction leading to the advanced atherosclerotic cardiovascular disease (CVD) in these population [15]. A chronic inflammation may be the missing link that actually ties protein energy malnutrition to morbiditiy and mortality in these patients. It is interesting that some markers that predict a low risk of CVS events in the general population, such as decerased body mass index (BMI) or lower cholesterol levels, become a strong risk factor for the CVS death in the dialysis patients. The fenomenon of risk factor paradox is caused by the conditions that potentially attenuates the magnitude of protein energy malnutrition, or inflammation [4].

In accordance with this, some studies provided the evidence that the dialysis patients who had gained weight moderately and a larger BMI are more likely to survive [16, 17] Galland et al. [18] showed that more frequent dialysis process increased significantly the body weight and serum albumin of the patients. Rashidi et al. [4] found that increase in dialysis frequency decreased the systemic inflammation and improved the nutritional status if the hemodialysis patients with no influence on the triglyceride, total cholesterol, LDL and HDL cholesterol levels, energy protein and fat intake. In our examination, we observed a significant correlation between CRP values and serum urea levels before and after the hemodialysis procedure. The value of urea after hemodialysis depended on the efficacy of the dialysis procedure itself and the residual renal function. Positive correlation CRP and urea values after dialysis could be explained by the state of the chronic catabolic condition of dialysis patients, or the uremic inflammation [19].

The presence of inflammation seems to be influenced by genetics and/or different cultural habits, since it is a common phenomenon in the European and North American ESRD patients, with lower prevalence in the Asian patients. The same goes to frequency of diabetes mellitus. The frequency od diabetic nephropathy among the ESRD patients population varies from 12% do 50% [4, 11, 20, 21]. The impact of diabetic nephropathy in ESRD in our study was 30.6%. There was no corellation between CRP levels and frequency of diabetes mellitus among our patients. Nevertheless, in the group with the higher CRP values, we observed significantly

more diabetics than in the group with the normal CRP serum levels. In the longitudinal study which included over 2,500 Japanese type 2 diabetic patients, CRP was indipendently associated with future risk for developing nephropathy, but not with the risk of progressing of diabetic nephropathy [22]. In the study of Nath et al. [14] , CRP serum levels were significantly higher and positively correlated with albumin levels in the group od 80 patients with diabetic nephropathy compared to the controls. Diabetes mellitus is a proinflammatory state *per se* that is accompanied with accelerated CVS events and by up to 10-fold elevated CRP levels [8] . Tubular and glomerular CRP staining increases with declining renal function and increasing severity of hystological lesions in the diabetic patients with nephropathy. Still it is independent of proteinuria and it is possibly locally produced [23]. So, an absence of significant corellation between CRP serum levels and diabetic states in our study group as well as with other parameters of metabolic control was somewhat unexpected. The explanation could be found in a small sample size of our examined group.

Conclusion

Our study observed a high rate of inflammation in the dialysis patients presenting as the high frequency ~~of~~ elevated CRP levels in the examined population. Negative correlation between the CRP levels and serum albumin and cholesterole levels, suggests that a chronic inflammation may be the missing link that actually connect protein energy malnutrition with a high morbiditiy and mortality rate in these patients. Interventions that improve nutritional status and reduce a chronic inflammation along with routine measurement of the serum CRP levels may improve the survival rate of dialysis patients.

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