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High-sensitivity C-reactive protein: Could it be used as a cardiovascular risk predictor in hemodialysis patients?

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ABSTRACT

Objective: We aimed to investigate the correlation between the chronic renal failure (CRF) and cardiovascular risk in hemodialysis (HD) patients according to the serum high-sensitive C-reactive protein (hs-CRP). **Patients and Methods:** A hundred patients were divided into two groups. In the first group, there were 50 patients (20 females, 30 males) who receive HD due to CRF. In the second group, which is arranged as a control group, there were 50 patients (22 female, 28 male) having a cardiovascular risk, but without CRF. CRP values were determined in both groups. **Results:** The average duration of dialysis patients is 38.85 ± 36.66 months. Average hs-CRP values were determined as 19.086 mg/L (1st year HD), 23.280 mg/L (2nd year HD), 19.367 mg/L (3rd year HD), 23.350 mg/L (4th year HD), 26.970 mg/L (5 and more years HD), 3.178 mg/L (non-CRF, non-revascularization), 14.386 mg/L (non-CRF, revascularization). The hs-CRP values were increasing with years of HD, except the 3rd year of HD. In the 3rd year HD patients, hs-CRP levels revealed a slight decrease. **Conclusion:** The high level of hs-CRP indicates who may be at risk for coronary incident. Elevated serum CRP levels are associated with other atherosclerotic vascular diseases in HD patients. In recent years, various studies have shown that the high levels of CRP in HD patients become a strong determinant of mortality and morbidity. High levels of hs-CRP in CRF patients should be evaluated as an indication of a rapid onset of a coronary artery disease.

KEY WORDS: Cardiovascular disease, chronic renal failure, high sensitive C-reactive protein

INTRODUCTION

Chronic renal failure (CRF) is associated with accelerated cardiovascular disease (CVD). Even in early stages of renal failure, a significant increase in cardiovascular risk has been shown. It has been investigated to establish a relationship between cardiovascular risk and prolonged CRF, by measuring increased serum high-sensitivity C-reactive protein (Hs-CRP) values.

CRP is a pentameric protein found in blood plasma. It is a member of the pentraxin family with an atomic weight of 23 kDa. It is an acute phase reactant, the levels of which rise in inflammation [1]. It was initially described in 1930 by Tillet and Francis after its identification in the serum of a patient with an acute pneumococcal pneumonia (*Streptococcus pneumonia*) [2]. It was named as CRP according to its reaction with C-polysaccharide of *Pneumococcus*. Most of the CRP in the blood circulation is released by the hepatocytes. It is the first reactive substance released from the liver during inflammation, preceding the Interleukin-1 (IL-1), IL-6, tumor necrosis factor-α, endotoxin, and other antigens [3]. However, studies are shown that it is also released in low amounts by vascular smooth muscle cells, macrophages, and also by the adipose tissue. Its normal plasma value is 1 mg/L in healthy young individuals. It increases up to 2 mg/L with aging. CRP is slightly higher in females than males. It may increase as much as 10000 fold against an inflammation. It increases soon after any inflammatory process and may reach >5 mg/L after just 6 h. CRP reaches its maximum levels in 48 h. Its half-life is 19 h. Half-life does not change among healthy and sick individuals. Therefore, if the high CRP levels do not change in a patient in the next day, it is often commented as the inflammation or any other underlying reason maintains.

In recent studies, hs-CRP is demonstrated 7-10 times higher in atherosclerotic plaques than normal vascular walls and human liver. Improvements in medical technology render the detection of lower plasma hs-CRP levels possible. Thus, hs-CRP kits have started to be used as a predictor for the risk of cardiovascular incidents [4].

CRF increases CVD risk via traditional factors like increased oxidative stress, inflammation, phosphate retention. Rapid vascular calcification, high parathyroid hormone levels, myocardial calcification, anemia, and left ventricular hypertrophy are also related to those factors. Moreover, CVD is responsible for increased mortality and morbidity in CRF patients [Table 1]. In this study, we aimed to demonstrate the relationship between CRF and cardiovascular risk with hs-CRP biomarker measurement in early phases of CRF patients. In addition, we also discussed the protection of the cardiovascular system and how would effective treatment of CRF be important for cardiovascular protection.

PATIENTS AND METHODS

In this study, 100 patients were arranged into two groups. In the first group, there were 50 patients (20 females, 30 males, mean age: 51.15 ± 13.91 years) who receive hemodialysis (HD) due to CRF. In the second group, which is arranged as a control group, there were 50 patients (22 female, 28 male, mean age: 56.12 ± 12.99 years) having a cardiovascular risk, but without CRF. 50 patients of the first group with CRF were having HD 3 times a week with a hollow fiber dialysis (PSN-140, Baxter Healthcare Corporation, AR, USA). It had a 1.4 m^2 surface areas with bicarbonate dialysis solutions with a dialysate flow rate of 500 ml/min and blood flow rate of 300 ml/min. Out of the second group of 50 patients without CRF, 25 patients were performed angioplasty (stent or balloon) or surgical revascularization. Other 25 patients were either with normal angiographical findings or needed medical treatment due to minimal coronary lesions.

The working groups were divided into seven subgroups according to the duration of the ongoing HD and the presence of coronary revascularization. The initial five subgroups were group-one patients with CRF requiring HD. Each subgroup consisted of 10 patients depending on the HD onset between 1 and 5 years. The last two subgroups were of the second group (without CRF) which was determined according to the need of revascularization (either surgery or angioplasty) or the need of medical treatment [Table 2].

Hs-CRP measurement was determined from the samples taken from the venous blood. Samples were withdrawn at the first HD day of the week following 12-h of starving in CRF patients (first 5 subgroup). Samples were withdrawn before angiography in non-CRF patients (last 2 subgroups). All blood samples were analyzed by nephelometric immunoassay method in the microbiology laboratory. Values are measured in mg/L units.

Statistical Evaluation

Data were evaluated using the statistical software package "SPSS 10.0 for Windows," "Mann–Whitney U," "Spearman's rank correlation," and "multiple linear regression analysis" tests. Data were expressed as an average ± standard deviation. Statistically, $P < 0.05$ was considered significant.

RESULTS

The average duration of dialysis patients is 38.85 ± 36.66 months. Average hs-CRP values were determined as 19.086 mg/L (1st year HD), 23.280 mg/L (2nd year HD), 19.367 mg/L (3rd year HD), 23.350 mg/L (4th year HD), 26.970 mg/L (5 and more years HD), 3.178 mg/L (non-CRF, non-revascularization), 14.386 mg/L (non-CRF, revascularization) [Table 2]. The hs-CRP values were increasing with years of HD, except the 3rd year of HD. In 3rd year HD patients, hs-CRP levels revealed a slight decrease. Patient with no CRF and no need for revascularization according to the coronary angiography showed the least increase in hs-CRP levels [Figure 1]. Highest values of hs-CRP were determined in the patients who were undergoing HD for 5 years or more [Figure 2].

DISCUSSION

Elevated serum CRP levels are associated with other atherosclerotic vascular diseases in HD patients. In recent

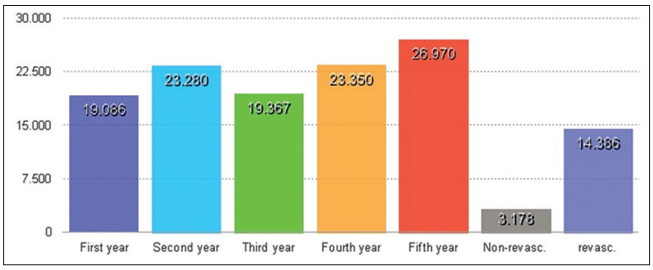

Figure 1: Graphical distribution of high-sensitive C-reactive protein values (mg/L)

Table 1: Relationship between the cardiovascular risk and the diseases in CRF

Group	CHF (%)	AMI (%)	CVA (%)	PAD (%)	Atherosclerosis (%)	Exitus (%)
All patients	10.8	1.9	8.8	16.5	0.14	6.4
non-DM and non-CRF	8.6	1.6	7.6	14.1	0.04	5.5
DM and non-CRF	18.5	3.2	13.1	25.3	0.2	8.1
non-DM and CRF	30.7	3.9	16.6	35.7	1.6	17.7
DM and CRF	52.3	6.9	22.0	49.1	3.4	19.9

CHF: Congestive heart failure, AMI: Acute myocardial infarction, CVA: Cerebrovascular accident, PAD: Peripheral arterial disease, CRF: Chronic renal failure, DM: Diabetes mellitus

Table 2: The average values of hs-CRP in patient groups

Patient groups	Average hs-CRP values
HD	
1st year	19.086
2nd year	23.280
3rd year	19.367
4th year	23.350
5th year	26.970
Non-CRF and Non-revascularization	3.178
Non-CRF and revascularization	14.386

HD: Hemodialysis, CRF: Chronic renal failure, hs-CRP: High-sensitive C-reactive protein

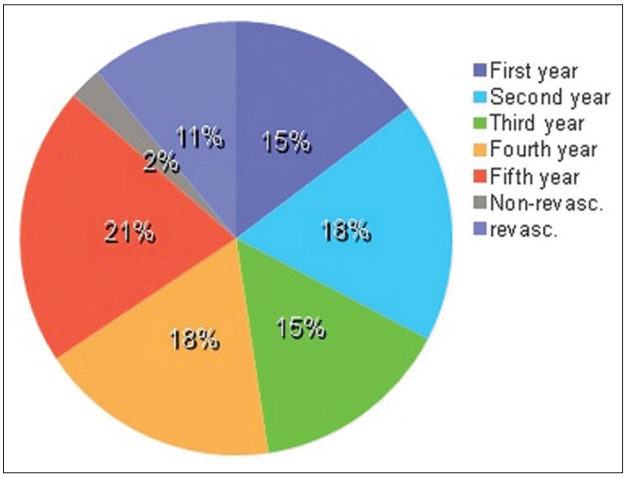

Figure 2: Overall ratios of high-sensitive C-reactive protein values

years, various studies have shown that the high levels of CRP in HD patients become a strong determinant of mortality and morbidity [5,6]. It was indicated that the mortality rate was significantly higher in patients with CRP levels above 10 mg/L, compared to those with lower than 10 mg/L, according to a 7-year follow-up [5]. Zimmermann *et al.* indicated that the patient with CRP levels of 7.5 mg/L has 2.7 times higher mortality risk compared to the patient with CRP levels <3.3 mg/L [7]. According to another article, CRP could be a long-term predictor for death in dialysis patients [6]. Moreover, Zimmerman *et al.* also showed that CRP is one the most powerful independent predictors of cardiovascular mortality in their study which was carried out for 2 years with 280 patient [7]. Other recent studies commonly revealed that the high CRP levels are a strong predictor on mortality in HD patients. CRP is a significant predictor as the other factors such as age, gender, albumin, creatinine, transferrin, and body mass index. Likewise, type of the membrane that is used during HD and administration of erythropoietin in CRF patients are among other variables increasing relative risk of mortality [6]. It was found that patients with high CRP levels, frequency of cardiac death due to heart failure, acute myocardial infarction (MI) was significantly higher compared to the patients with normal CRP levels [8,9].

Regarding the molecular mechanism, CRP-binded monocytes lead to the activation of the complement system by interacting with macrophages and neutrophils [10]. It plays a role in the regulation of immune system functions, and it increases the activation of T and B and natural killer cells. Macrophages and neutrophils of toxic oxygen radicals increase the expression of tissue factor (TF) [11]. Recent studies have shown that CRP is not only a biomarker, but also it plays a role in the development of pathogenesis of atherosclerosis and acute coronary syndrome [12]. CRP leads to endothelial dysfunction by increasing toxic oxygen radicals from the inflammatory cells and causes reduced nitric oxide production by the endothelium [13]. It increases monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, Endothelin-1, TF, intercellular adhesion molecule-1, vascular cell adhesion protein-1, and low-density lipoprotein (LDL) oxidation. Oxidized LDLs are taken by macrophages causing the formation of atherosclerotic plaque. It further facilitates the conversion of stable plaque into an unstable nature [14-16].

Depending on the above-mentioned pathophysiological mechanisms, CRP is a generally accepted risk prediction entity for CVD. Determination of risk groups according to hs-CRP serum levels is divided into three groups as low (<1 mg/L), medium (1-3 mg/L) and high (>3 mg/L) [17]. Patients who have CRP >3 mg/L (especially >10 mg/L), the cardiovascular incident risk prognostically gets higher. On the other hand, studies showed that the patients having CRP <0.5 mg/L carry almost no risk [18]. Prospective studies have indicated that cardiovascular incidents in healthy people, high baseline hs-CRP levels are shown to be a strong predictor. Furthermore, hs-CRP is considered as a significant clinical biomarker that is even stronger than LDL in prediction of vascular incidents [18].

In Reykjavik trial, Danesh *et al.* compared the hs-CRP and other inflammatory biomarkers in terms of their prognostic aspects in coronary artery disease (CAD) in a study population of 2459 patients. They found that the levels of hs-CRP are correlated with CAD moderately [19]. However, another prospective multicenter study showed the presence of increased values of hs-CRP in CAD. It was demonstrated that the increased levels of hs-CRP constitutes a severe risk factor for the development of CAD. In addition, they also found that even without other risk factors, elevated hs-CRP is an important risk factor for the development of CAD [20].

The high level of hs-CRP indicates who may be at risk for coronary incident. Compared to the healthy individual, a high level of hs-CRP encountered in a CRF patient is a strong and independent indicator for the risk of peripheral vascular disease like MI and stroke. The rate of progression to revascularization due to CAD or existing MI, stroke or peripheral arterial disease increases to 45% in patients having only the cardiovascular risk factors without a renal pathology. However, the rate inclines to 60% in the 1st year of HD in CRF patients with the same risk factors. Through the 2nd year of HD, the rate increases to 73%. At the 3rd year, it demonstrates a slight decrease to 60.09%, whereas it again increases at the 4th and the 5th year to 73% and 84%, respectively. This means, in the 1st year of HD in CRF patients, cardiovascular risk significantly increases as it does over 5 years of HD in the same group of patients.

CONCLUSION

As a conclusion, it is necessary to take precautions in order to reduce complications of HD. Especially in first 2 years, increased risk should be taken into consideration to reduce the morbidity and mortality. By applying effective HD, blood urea nitrogen, creatinine, and CRP values should be reduced more effectively in the 1st years of HD onset. In addition, vascular screening tests should be done immediately to the HD patients and appropriate treatment (statins, acetylsalicylic acid, antio™ xidants, omega 3, etc.) for vascular protection should be initiated as early and effective as it possible in the first few months. High levels of hs-CRP in CRF patients should be evaluated as an indication for a rapid onset of a CAD.

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