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Association between CA-125, ESR, and high-sensitive C-reactive protein and cardiac function in hemodialysis patients

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ABSTRACT

Introduction: Inflammation plays an important role in the pathogenesis of cardiovascular diseases in patients receiving hemodialysis.

Objectives: To compare serum levels of quantitative as high-sensitive C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and cancer antigen 125 (CA-125) among three groups including hemodialysis with heart failure (HF), hemodialysis without HF and healthy controls.

Patients and Methods: Seventy patients with chronic kidney disease (CKD) receiving hemodialysis were included. Thirty-five healthy subjects were in the control group. Inflammatory markers were measured. All subjects underwent 2D transthoracic echocardiography. HF was defined as LVEF (left ventricular ejection fraction) <50%.

Results: ESR and hs-CRP levels, but not CA-125, were significantly higher in hemodialysis group versus control group. Median (IQR) ESR was significantly higher in hemodialysis group with systolic HF ([16.50 [17]) and without systolic HF (15.50 [21]) compared to control group (8 [7]); $P<0.001$. Likewise, median (IQR) hs-CRP was higher in hemodialysis with HF (9 [3]) and without HF (9 [5]) than in control group (4[2]); $P<0.001$. The Mann-Whitney U tests did not show any statistically significant difference within hemodialysis group between those with and without HF regarding ESR ($P=0.81$) or hs-CRP ($P=0.76$). However, median (IQR) CA-125 value was significantly higher in hemodialysis with systolic HF group (23.20 [25.04]) compared to hemodialysis without systolic HF (11.40 [8.91]); $P=0.003$.

Conclusion: ESR and hs-CRP levels are increased among ESRD patients on hemodialysis regardless of the presentence of HF. However, CA-125 was the only marker which showed a significant increase in the presence of HF. CA-125 needs further studies to determine its role in follow-up and prognosis of CKD patients with systolic HF.

Implication for health policy/practice/research/medical education:
Hemodialysis patients are at greater risk of developing cardiovascular diseases. Inflammation has a major role in this condition. Inflammatory markers erythrocyte sedimentation rate (ESR) and high-sensitive C-reactive protein (hs-CRP) rise significantly in hemodialysis patients. This finding is regardless of the presence or absence of systolic heart failure (HF). On the other hand, cancer antigen 125 (CA-125) is a marker that is higher when systolic HF is present in hemodialysis patients.

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Introduction

Important bidirectional interactions exist between cardiac and renal diseases. It is now clear that patients with chronic kidney disease (CKD) have the higher rate of heart failure (HF) and coronary artery disease (CAD). It is estimated that 40%-45% of all deaths in CKD patients are attributed to cardiac causes (1). The incidence of cardiovascular diseases may be as high as 40 folds in CKD patients receiving hemodialysis when compared to healthy controls (2).

In addition to conventional cardiovascular diseases risk factors such as hypertension, diabetes, and dyslipidemia

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other factors have an important role in the pathogenesis of HF and CAD in hemodialysis patients. Of these non-traditional risk factors, inflammation has been the focus of recent research studies (3,4). The effects of inflammation and oxidative stress on the occurrence of cardiovascular diseases in patients receiving renal replacement therapies have been noted (2).

In view of the mentioned role of systemic inflammation, several studies have been done to elucidate the utility of various inflammatory biomarkers in the diagnosis of cardiovascular diseases as well as in predicting the outcome of such conditions in hemodialysis patients (5). These markers include C-reactive protein (CRP) (4,6-9), homocysteine (2), cancer antigen 125 (CA-125) (10), albumin, interleukin-6 (11), erythrocyte sedimentation rate (ESR) (12), and many other biomarkers. As observed, among these biomarkers, CRP is the most frequently studied. However, some biomarkers have not been evaluated thoroughly. For example, CA-125 is a tumor marker which is usually used in the follow-up of patients with ovarian cancer (13). Some reports suggest that this marker was significantly associated with functional class as well as outcome in HF patients with a sensitivity value of 85% in diagnosing New York Heart Association (NYHA) Functional Classification III/IV (14).

Objectives

Here, we decided to measure three inflammatory markers including quantitative CRP, ESR, and CA-125 in hemodialysis patients and to investigate the possible association between these markers and cardiac function assessed by echocardiography.

Patients and Methods

Study population and research design

In this cross-sectional study, the study population consisted of patients with CKD who were receiving hemodialysis at our university hospital. Inclusion criteria consisted of receiving hemodialysis for the last 6 months. Exclusion criteria were congenital cardiac valvular diseases, congenital cardiomyopathy, recent (within three months) myocardial infarction, evidence of any active infections (like periodontitis or pancreatitis), endometriosis, pelvic inflammatory disease (PID), uterine leiomyoma, malignancy, and chronic hepatic diseases. These factors were evaluated by history taking from the patients, and if necessary abdominal and pelvic ultrasound was done to exclude gynecologic conditions for women. The controls were recruited from patients who presented to outpatient clinics for getting routine check-ups.

Sample size

The sampling method was a census. During the study period, 70 patients were present to the hemodialysis center of our hospital. All of them were included in the study. Thirty-five subjects were included in the control group.

Variables

The variables gathered included demographic data, hematologic indices, biochemistry profile, echocardiography indices, and inflammatory markers including hs-CRP (normal range was <5.3 mg/L), ESR (normal range was <17 mm/h), and CA-125 (normal range was <35 IU/mL). 2D-Echocardiography indices included LVEF (left ventricular ejection fraction; values <50% were abnormal), LVESD (left ventricular end-systolic diameter; normal range = 20 to 40 mm), LVEDD (left ventricular end-diastolic diameter; normal range = 36 to mm), PAP (pulmonary artery pressure; normal range;15 to 30 mm Hg), RV (right ventricular) size (normal range;10 to 26 mm), RV TAPSE (normal range;15 to 20), and LAD (left atrial diameter; normal range = 24 to 40 mm). Systolic HF was defined as LVEF of lower than 50%.

Data collection

The demographic data gathered at the first presentation included age, gender, height, and weight. Body mass index (BMI) was calculated. Venous blood sample was obtained from the brachial vein and sent to the laboratory in order to measure the inflammatory markers. In addition, routine lab tests were assayed. 2D transthoracic echocardiography was done for all patients and controls. HF was defined as LVEF of lower than 50%.

Ethical considerations

The research followed the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Birjand University of Medical Sciences, Birjand, Iran. The study objectives were explained to the patients prior to participation and if agreed, written informed consent was obtained from them (Ethical code# ir.bums.1394.44).

Statistical analysis

The collected data were entered into the SPSS software for Windows (version 22.0). Descriptive indices such as frequency, percentage, mean and its standard deviation (±SD), and median (interquartile range, IQR) were used to express data. For comparison of qualitative variables between the two studied groups (hemodialysis versus control). Chi-squared or Fischer's exact test was applied. The Kolmogorov-Smirnov test was performed to determine normal distribution of quantitative variables within the sample. Age and BMI had a normal distribution. In order to compare the quantitative variables with normal distribution between the two groups, Student's t-test was used. ESR, CRP, and CA-125 values had a non-normal distribution. The Mann-Whitney U test was applied to compare these variables between the two groups. A Kruskal-Wallis test was used to test for differences among the three studied because ESR, hs-CRP, and CA-125 had non-normal distributions. For pairwise comparisons within the groups, the Mann-Whitney U test was applied. The significance level was set at 0.05.

Results

There were 70 patients in hemodialysis group and 35 in control group. There were 38 males in hemodialysis group (54.3%) and 16 males (54.7%) in control group (P= 0.41). Mean (±SD) age in hemodialysis group (53.01± 15.81 years) was higher than in control group (43.43± 13.81 years, P= 0.003). The two groups were comparable regarding mean (±SD) BMI values (23.66 ± 3.76 kg/m^2 in hemodialysis group and 23.99 ± 3.99 kg/m^2 in control group, P=0.68).

Median (IQR) ESR and CRP values were significantly higher in hemodialysis group than in control group. But, no significant difference was observed between the two groups regarding CA-125 level (Table 1).

In hemodialysis group, 18 patients (25.7%) had systolic HF. The findings of echocardiography showed that 27 cases (38.6%) had abnormal PAP, 51 cases (72.9%) had diastolic dysfunction, eight cases (11.4%) had abnormal LVEDD, 15 cases (21.4%) had abnormal LVESD, 58 cases (82.9%) had abnormal RV size, 41 cases (58.6%) had abnormal RV TAPSE (Tricuspid Annular Plane Systolic Excursion), and six cases (8.6%) had abnormal LAD. Table 2 compares echocardiography indices between hemodialysis and control groups.

Based on the presence of systolic HF, the hemodialysis group was divided into two groups. There were 18 patients who were receiving hemodialysis and had HF with a mean (±SD) LVEF value of 40.41% (±11.35). Fifty-two hemodialysis patients did not have HF with a mean (±SD) LVEF value of 59.61% (±1.59). There were nine males (50%) in hemodialysis with HF group compared to 29 males (55.8%) in hemodialysis without HF group (P= 0.78). Mean (±SD) age in hemodialysis group with HF (48.06 ± 15.89 years) was comparable to the other group (54.73 ± 15.57 years; P= 0.12). The two groups were also comparable regarding BMI value (22.38 ± 3.03 in HF group versus 24.10 ± 3.91 in the other group; P= 0.09). Table 3 shows median (IQR) values of ESR, hs-CRP, and CA-125 and their comparisons amongst the three groups. The Kruskal-Wallis test for comparison of three study groups indicates that there were statistically significant differences in the distribution of ESR, hs-CRP, and CA-125 between the groups.

Median (IQR) values for ESR and hs-CRP were significantly higher in both hemodialysis groups with and without systolic HF compared to control group. The Mann-Whitney U tests did not show any statistically significant difference within hemodialysis group between those with and without HF regarding ESR (P= 0.81) or hs-CRP (P= 0.76). However, median (IQR) CA-125 value was significantly higher in hemodialysis with systolic HF group compared to hemodialysis without systolic HF (P= 0.003; Figure 1).

Table 1. Comparison of ESR, hs-CRP, and CA-125 between hemodialysis and healthy control groups

	Hemodialysis (n= 70)	Control (n= 35)	*P* value[a]
ESR, mm/h	23.01 (±18.17) 15.50 (19)	8.17 (±4.09) 8 (7)	<0.001
hs-CRP, mg/L	12.63 (±12.50) 9 (4)	3.26 (±1.50) 4 (2)	<0.001
CA-125, IU/mL	18.50 (±19.06) 13.42 (13.33)	12.68 (±6.66) 11.90 (8.47)	0.33

Abbreviations: ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; CA-125, cancer antigen 125.
Data are presented as mean (±SD) in the first row and median (IQR) in the second row.
[a] Mann-Whitney U test.

Discussion

Based on the current findings, ESR and hs-CRP values were higher in hemodialysis patients than in healthy subjects. This has been reported previously in several studies (4,5). ESR is elevated usually higher than 25 mm/h in almost all ESRD patients (11). These alterations have been recognized for long time and are due to a chronic inflammatory process which plays a major role in hemodialysis patients. Several factors namely elevated circulating pro-inflammatory cytokines, chronic infections, malnutrition, poor oral health and fistula infections, are sources for chronic inflammation in hemodialysis patients (4). The main phenomenon seen in ESRD patients on hemodialysis is acute phase response that accompanies inflammation. This acute response may become chronic and therefore reflected by increased levels

Table 2. Comparison of echocardiography indices between hemodialysis (70 subjects) and normal individuals (35 subjects)

	Hemodialysis	Control	Mean difference	*P* value[a]
LVEF, %	54.67 (±10.24)	59.71 (±1.17)	- 5.03	<0.001
PAP, mm Hg	35.31 (±10.81)	25.02 (±5.23)	10.28	<0.001
RV size, mm	31.92 (±5.48)	24.65 (±3.92)	7.27	<0.001
RV TAPSE	24.55 (±5.45)	19.48 (±2.81)	5.07	<0.001
LVESD, mm	37.81 (±8.66)	35.2 (±4.59)	2.61	0.04
LVEDD, mm	46.31 (±7.27)	41.37 (±3.82)	4.94	<0.001
LAD, mm	33.32 (5.24)	31.97 (4.93)	1.35	0.2

Abbreviations: LVEF = left-ventricular ejection fraction; PAP = pulmonary artery pressure; RV = right ventricle; LVESD = left-ventricular end-systolic diameter; LVEDD = left ventricular end-diastolic diameter; TAPSE = tricuspid annular plane systolic excursion.
[a] Independent samples *t* test; data are expressed as mean (standard deviation).

Table 3. Comparison of ESR, hs-CRP, and CA-125 between hemodialysis patients with and without HF and control group

	Hemodialysis with heart failure	Hemodialysis without heart failure	Control	*P* value[a]
ESR, mm/h	16.50 (17)	15.50 (21)	8 (7)	<0.001
hs-CRP, mg/L	9 (3)	9 (5)	4 (2)	<0.001
CA-125, IU/mL	23.20 (25.04)	11.40 (8.91)	11.90 (8.47)	0.005

Abbreviations: ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; CA-125, cancer antigen 125.

of inflammatory markers such as CRP and ESR (15). On the other hand, CA-125 did not show a significant difference between hemodialysis and healthy subjects. This tumor marker has been studied in previous reports and most reports agree that alterations in CA-125 among hemodialysis patients should be interpreted cautiously (13). This is due to the fact that renal function can change CA-125 level. Even significant renal failure may not change CA-125 levels (14). In addition, it has been reported that hemodialysis may not necessarily affect CA-125 level (16). However, the role of CA-125 in hemodialysis patients has been recently become prominent due to findings that relate the elevated level of this marker to left ventricular function. The results of this study showed that CA-125 may be a useful biomarker to be addressed in CKD patients on hemodialysis with systolic HF. In a previous study (10) including 110 maintenance hemodialysis patients and 47 healthy controls, mean CA-125 levels in hemodialysis group (38.7 U/mL) was significantly higher in comparison to healthy subjects (9.2 U/mL; $P = 0.003$). This contradicts our findings as we did not find significant difference regarding CA-125 between hemodialysis and healthy subjects. The authors (10), then divided the hemodialysis group (based on CA-125 level of 26.6 U/mL) into two groups. Those with CA-125 levels of more than 26.6 U/mL had significantly higher LVESD and LVEDD and lower LVEF (32% vs. 59%). Similar to our study, mean CA-125 level in hemodialysis group with systolic HF (74.4 U/mL) was significantly higher than hemodialysis group without HF (13.1 U/mL) and control group (9.2 U/mL). The authors concluded that CA-125 level is significantly associated with LV cardiac failure in hemodialysis patients. Several studies have implicated the role of CA-125 level in congestive heart failure (CHF) (17) as well as non-ischemic dilated cardiomyopathy (18). In a study on 77 male patients with CHF, it was shown that CA-125 levels were associated with CHF severity (determined by NYHA classification) and fluid overload defined by pulmonary congestion and ankle edema (19).

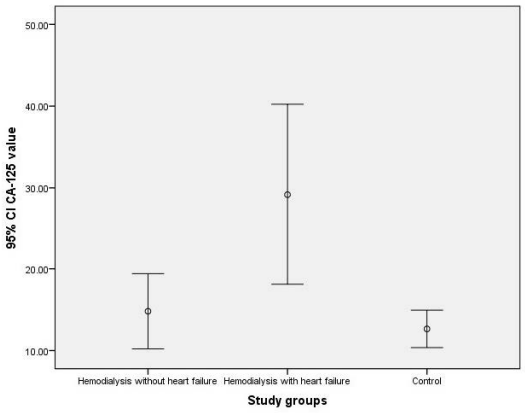

Figure 1. CA-125 level in the three studied groups (hemodialysis with and without systolic heart failure and healthy control group).

We did not find any difference within hemodialysis group regarding CRP and ESR levels. However, there are reports that inflammatory markers such as CRP can adversely affect LV function among hemodialysis patients. Increased CRP level may be able to characterize the severity of LV dysfunction (20). This finding is attributed to the documented effect of inflammatory markers and atherosclerosis in CKD patients (21,22). Additionally, the role of pro-inflammatory markers in particular TNF-alpha and LV hypertrophy in hemodialysis patients has been addressed previously (23). However, there is controversy in the literature regarding the definite role of inflammatory markers for predicting LV dysfunction in hemodialysis patients. For instance, a previous study using logistic regression reported that although N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and cardiac troponin T were able to exclude the possibility of LV hypertrophy, hs-CRP did not have such ability (7). Likewise, using ROC curve, it was shown that NT-pro-BNP and LV hypertrophy were correlated closely (24). In contrast, applying multivariate analysis, hs-CRP as well as systolic blood pressure were found as significant and independent predictors for LV mass index among 104 hemodialysis patients (9).

Conclusion

CA-125 level could be a useful marker to recognize hemodialysis patients with systolic HF. Further longitudinal studies are required to determine the prognostic value of this marker. However, hs-CRP and ESR, though increased in hemodialysis patients compared to healthy subjects, did not reach significant difference within hemodialysis group based on the presence of systolic dysfunction.

Limitations of the study

There were some limitations in this study. Firstly, the sample size was low. Second, we were not able to follow the patients to determine the prognostic value of the measured inflammatory markers in predicting cardiac function.

Authors' contribution

ZS; the concept, design, data analysis, and manuscript preparation and final revision. ZS, NA, and ZT; performing experiments and data collection and writing proposal. ZS and ZT; statistical analysis, manuscript editing, and manuscript review. ZS, data collection and providing first draft and submission.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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