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An Investigation of the Relationship between Beta-2 Microglobulin (β2M) and Inflammatory Factors (Serum Levels of CRP and Albumin) and High Density Lipoproteins (HDL) in Hemodialysis Patients

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ABSTRACT

Background and Objective: Beta-2 Microglobulin (β2M) is a middle molecular weight uremic toxin. Lack of β2M removal leads to β2M accumulation and amyloidosis in hemodialysis patients. The present research aims to determine the relationship between β2M and inflammatory factors, such as C-reactive protein (CRP), albumin, and high-density lipoprotein (HDL) in hemodialysis patients.

***Methods*:** Fifty-four hemodialysis patients were selected and their pre- and post-dialysis serum levels of β2M, CRP, albumin, and HDL, were measured.

***Result*:** There was an obvious inverse relationship between β2M level and serum level of albumin, while no relationship was found between β2M and CRP or HDL.

***Conclusion*:** According to the findings of this study, it was identified that inflammatory-induced increase in β2M level in dialysis patients leads to reduced serum albumin.

Keywords: Beta-2 microglobulin, Albumin, Hemodialysis, Inflammation

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Introduction

In Recent years, the incidence rate of end-stage renal disease (ESRD) and consequently renal replacement therapy (RRT), have been growing increasingly (1-3). The prevalence of RRT in Iran is 238 cases per one million population and its treatment generally include hemodialysis (53.7%) and kidney transplant (45.5%) (4). One of the long-term complications of hemodialysis is development of amyloidosis that is caused by accumulation of beta-2 microglobulin (β2M) (5). β2M is one of the middle molecular weight uremic toxins (6). Uremic toxins are compounds that cause uremic syndrome in patients with end stage renal disease (ESRD).

These toxic compounds cause malnutrition and increase cardiovascular diseases in patients with ERSD (7). Also, according to the studies, inflammation is considered as one of the major causes of death in ESRD patients. Various epidemiological and experimental studies have

indicated that inflammatory proteins, such as C-reactive protein (CRP) along with cytokines are signs of cardiovascular abnormalities in ESRD patients (8). Decreased blood albumin level is another cause of mortality in these patients, which resulted from decreased synthesis of albumin (9). In this study, we aimed to investigate pre- and post-dialysis levels of β2M as well as relationship between this factor and a number of inflammatory factors.

Materials and methods

The present study was carried out on 54 hemodialysis patients in Research and Treatment Center of Sina Hospital affiliated to Tehran University of Medical Science from October 2005 to June 2006.

The inclusion criteria were as follows:

1. At least 6-month history of hemodialysis treatment
2. Adequate quality of hemodialysis (KT/V>1.2)
3. Having normal liver function

The exclusion criteria were as follows:

1. Systemic infections during the study period
2. Inflammatory diseases during the study period
3. Taking drugs affecting the immune system
4. Taking drugs affecting the concentrations of major lipoproteins
5. Higher level of serum parathyroid hormone compared to the level recommended by Kidney Disease Outcome Quality Initiative (KDOQI) guideline
6. Hyperphosphatemia
8. Hypercalcemia

Patients who met the inclusion criteria entered the study. A 5 ml whole blood sample was taken from each patient. Laboratory tests, including complete blood cell count (CBC), calcium, phosphorus, parathyroid hormone (PTH), ferritin, iron, total iron-binding capacity (TIBC), glucose, cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C), alanine transaminase (ALT), aspartate (AST), alkaline phosphatase and β2M, were performed on the patients' sera and the results were recorded. To measure the level of β2M, serum was separated and immediately stored at -70°C, and then serum level of β2M was assessed using ELISA method. Then, the patients were connected to hemodialysis machine and at the end of dialysis, blood samples were taken and serum levels of urea, creatinine, CRP, albumin, HDL-C, and β2M were again measured.

Also, a questionnaire was prepared for each patient and demographic information, date of start of treatment, cause of dialysis, duration of dialysis, pre- and post-dialysis serum levels of urea, creatinine, CRP, albumin, HDL-C, and β2M were recorded in the questionnaire.

Data analysis and Statistical tests

After obtaining the results, data were coded and recorded using Excel 2000 software. Then, the comparison between the two phases and evaluation of different factors influencing the response was performed by paired t- and Spearman and Pearson Correlation coefficient tests using SPSS statistical software (version 11.5). The significance level was considered to be $p<0.05$.

Results

Patients' characteristics

Fifty-four patients completed the inclusion and exclusion criteria questionnaire. Patients' characteristics, biochemical parameters, cause and duration of dialysis, age, and gender are given in Tables 1-3 and Figures 1 and 2.

Serum concentrations of biochemical and inflammatory parameters

The results of measuring the serum level of B2M by ELISA method and serum levels of urea, creatinine, albumin, and HDL by routine biochemical methods before and after dialysis are shown in Table 4.

The percentage of positive reaction (3+) for Serum CRP was 57.1% in the pre-dialysis phase and 25% in the post-dialysis phase.

Table 1
Demographics of patients under study in terms of age and the length of the dialysis

Number of patients	54
Age (year)	52.4 ± 11.20
Average dialysis time (month)	48.2 ± 18.3

Table 2
Demographics of patients under study in terms of initial cause of renal disease

Diabetes	41%
High blood pressure	43%
Other causes	16%

Table 3
Demographics of patients under study in terms of serum density of biochemical parameter

Parameter	Unit	mean± SD
PTH	pg / ml	181.12 ±67.20
Calcium	mg / dl	8.71 ±0.91
β2M	µg/dl	19.47 ±4.2
Phosphorous	mg / dl	4.12 ±1.12
ALT	U /L	21.17 ±8.15
AST	U /L	29.20 ±7.42
AIK.P	U /L	156.17 ±39.15
Urea	mg / dl	150.45 ±51.36
Ferritin	µg / dl	344.15 ±45.19
Creatinine	mg/dl	10.13 ±3.02

Evaluation of the relationship between β2M changes and other parameters

The relationship between changes in β2M concentration and the parameters, including urea, creatinine, albumin, HDL, and CRP, was assessed and it was found that there is a significant inverse relationship between changes in β2M concentration and changes in albumin concentration before and after the dialysis (Fig. 3). No significant relationship was found for other parameters.

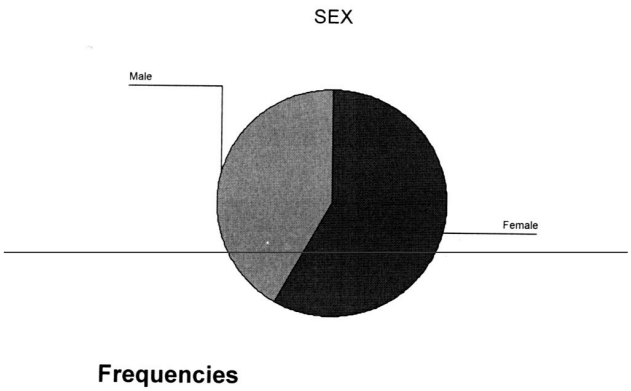

Fig. 1
Distribution of patients in terms of gender

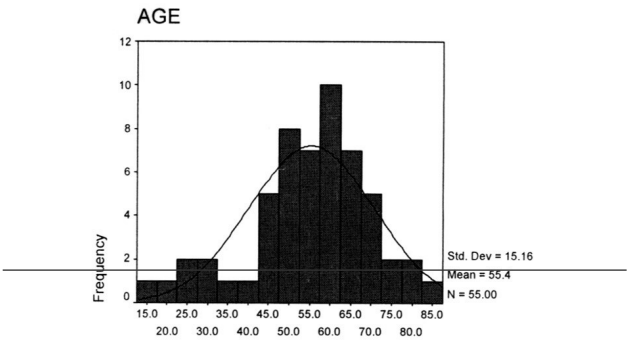

Fig. 2
Distribution of patients in terms of age

Discussion

β2M is a low molecular weight globular protein (11800 Dalton), which along with glycoproteins of the major histocompatibility complex are present on the cell membrane of

Table 4
Results obtained from β2M serum density measurement using ELISA

Analyte	Unit	Average pre dialysis density	Average post dialysis density	*P value*
B2M		19.5	14.1	0.009<
Urea		150.45	58.56	0.001<
Creatinine		10.13	4.80	0.001<
Albumin		4.23	5.34	0.054<
HDL		31.14	38.69	0.001<

all nucleated cells, such as lymphocytes. Given its small size, this protein can diffuses freely between intravascular and extravascular spaces and passes the glomerular basement membrane, and then it is reabsorbed, degraded up to 99.9%, and decomposed by proximal tubule cells. Kidney that is the main site of β2M catabolism can isolate and metabolize this protein, even in case of the absence of glomerular filtration (10). In normal conditions, the metabolism of this protein changes slightly in an Individual. The most important cause of the increase in serum β2M is renal failure, although in normal kidney function, factors, such as severe inflammation, cancer, and immunologic abnormalities can increase serum levels of β2M (11).

Due to special conditions in ESRD, chronic inflammatory conditions, increased inflammatory cytokines, and malnutrition occur in these patients, and it has been shown that changes in inflammatory cytokines, and in this context, changes in nutritional parameters are related to changes in β2M concentration. There is an inverse relationship between nutritional parameters and inflammation. Inflammation, on the one hand, increases β2M, and on the other hand, causes malnutrition and decreases nutritional parameters and serum levels of albumin and lipoproteins.

In this study on hemodialysis patients, it was revealed that there was a significant inverse relationship between changes in β2M concentration and changes in albumin concentration before and after the dialysis, while, no significant relationship was found between changes in β2M concentration and changes in HDL and CRP concentrations. Serum albumin concentration depends on factors, such as level of its synthesis, consumption in the body, and extravasation from the vascular space into the extravascular space. In the hemodialysis patients,

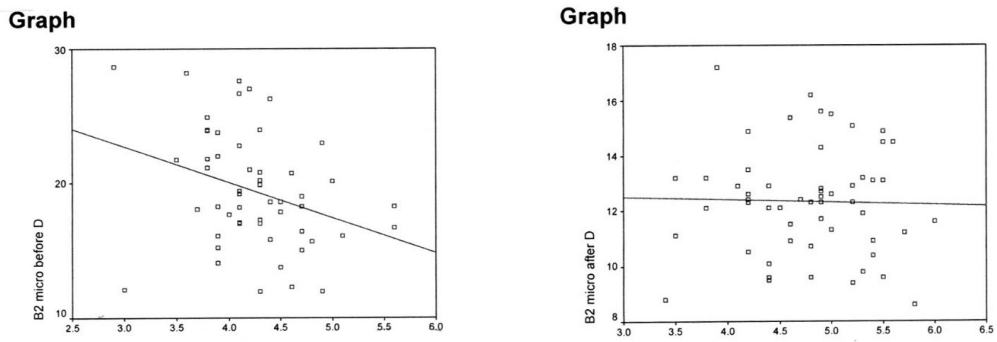

Fig. 3
The relationship between β2M and albumin before (left side diagram) and after (right side diagram) the dialysis.

decreased blood albumin

is primarily due to its decreased synthesis. The level of albumin synthesis is inversely related to acute phase protein levels. The primary cause of decreased albumin synthesis is the body's response to inflammation, however, inadequate nutrition is also important. There is no sufficient evidence on the effect of albumin extravasation into extravascular space on its decreased blood concentration.

In the present study, the mean levels of β2M, HDL, CRP, albumin, urea, and creatinine significantly decreased after dialysis. CRP decreased severely, but HDL increased significantly.

In a study by Carreno et al., it was indicated that proinflammatory cytokines, such as IL-1, TNF-α, and IL-6 play a key role in the pathogenesis of increased serum β2M in hemodialysis patients (13). It was observed that theses inflammatory cytokines, especially IL-6 play a role in regulation of β2M gene expression in human hepatoma cells, Tcells, T-lymphocytes, and monocytes (13). Therefore, it can be said that changes in proinflammatory cytokines and, in this context, changes in nutritional parameters can be associated with changes in β2M concentration. In contrast to the study by Carreno et al., in our study, no relationship was found between the changes in CRP concentration and changes in β2M concentration. This is probably due to the fact that CRP is a nonspecific inflammatory factor and unfortunately in this study, it was used qualitatively for the assessment of inflammation. To accurately determine the relationship between inflammation and β2M concentration, it was better that the concentrations of proinflammatory cytokines, especially IL-6, were measured instead of CRP.

Conflict of interest

The authors declare that there is no conflict of interests

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