Magnesium and its relationship to C-reactive protein among hemodialysis patients

Maryam Pakfetrat1, Leila Malekmakan1, Jamshid Roozbeh1, Sezaneh Haghpanah2

1 Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; 2 Health System Research Department and Clinical Affairs, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence: Dr Leila Malekmakan, Nephro-Urology Research Center, Shiraz University of Medical Sciences, P. O. Box: 71348-14336, Shiraz, Iran
<malekl@sums.ac.ir>

Abstract. Hypomagnesaemia has been reported among patients undergoing hemodialysis (HD). Recently, a possible correlation between serum magnesium (Mg) and C-reactive protein (CRP) has been stressed. This correlation has been attributed to cytokine production and oxidative stress processes. In this study we aimed to determine the relationship between serum Mg and hs-CRP levels in patients undergoing HD. This is a cross sectional study based on data collected from 58 HD patients in the Sahraee Center of Shiraz, Iran in 2007. Data were analyzed by SPSS 15, using Mann-Whitney test, Pair t-test, and Pearson’s correlation coefficient. A p value of less than 0.05 was considered significant. The present study included 58 HD patients (33 M and 25 F). The mean age of our patients was 51 ± 17.5 years old. At the start of HD, 39% of our patients had hypomagnesaemia and 60% had high hs-CRP, and 31% had both. There was a significant negative correlation between serum Mg and serum hs-CRP (p < 0.04). Also, in those who had hypomagnesaemia, hs-CRP was higher (p < 0.02). The results of this research support our hypothesis that hypomagnesaemia in pre-dialysis patients is a risk factor for sub-clinical inflammation due to hs-CRP elevation, although further studies are clearly required.

Key words: C-reactive protein, hypomagnesaemia, hemodialysis, magnesium

HD is an established renal replacement therapy modality. Reduction of serum Mg concentration has been frequently reported as a potentially hazardous outcome of HD [1]. Hypomagnesaemia can induce inflammation and immune system alterations [2-4], and inflammation can cause morbidity and mortality in these patients [5]. However, the role of serum CRP monitoring in patients undergoing dialysis is still to be determined [6]. Recently, some studies have shown a possible correlation between Mg and CRP due to a reported relation between Mg and cellular process. Mg deficiency induces cytokine production and oxidative stress processes which then results in elevation of CRP [7, 8].

As far as we know, there are no previous data on the association between CRP and hypomagnesaemia among patients undergoing HD.

Considering the fact that HD is the most common renal replacement modality in Iran [9], this study was conducted to determine the relationship between serum Mg and hs-CRP levels among pre-HD patients in Fars, Iran.

Material and methods

Study protocol
This is a cross sectional study based on data collected by random sampling from HD patients treated at the Sahraee HD Center of Shiraz, Iran in 2007. For the study, we recruited 58 chronic HD patients without a history of endocrine tumors, diabetes mellitus, liver or heart failure, unstable coronary artery disease; any sign of infection and patients with current
or recent intake of drugs affecting Mg levels, such as diuretic, and anti-acids (4 HD patients using Aluminum-Magnesium syrup and 11 patients on daily furosemide excluded). Patient population included adults with an age range of 18-75 years.

All HD patients had been dialyzed for at least 3 months before entering the study. They were dialyzed three times a week for 4 h using Fresenius 4008B machines (Fresenius Medical Care, Bad Homburg, Germany) and a low flux synthetic, polysulfone membrane. Dialysate temperature, sodium and calcium concentration were also kept constant. In all patients, we used bicarbonate-based dialysate fluid that contains sodium 136 meq/L, potassium 2 meq/L, Mg 1 meq/L, and calcium 2.5 meq/L and those settings were the same for all patients during the HD session. Blood and dialysate flow rates were 300-350 and 500 mL/min, respectively.

Blood samples from HD patients were collected from the arterial line immediately before a mid week single dialysis session before heparin administration in a fasting state and centrifuged and frozen at -70°C before the measurements.

Biochemical determinations included: blood urea nitrogen (BUN), serum creatinine (Cr), and highly sensitive CRP (hs-CRP) before HD. Serum Mg Was measured before and at the end of the HD session. All measurements were performed at the gastrohepatology research center laboratory of Shiraz Medical University. BUN and Cr were measured using enzymatic and photometric methods, respectively. Mg was determined by atomic absorption method (Lab tech 2000, Eppendorf AG, ECOM-E 6125, Homburg, Germany) and hs-CRP was assayed by the nephelometric method (Binding site, Birmingham, England). Hypomagnesaemia was defined as Mg < 1.7 mg/dL, hypermagnesaemia as Mg > 2.3 mg/dL [10], and serum hs-CRP concentration of more than 3 mg/L was defined as elevated hs-CRP levels. This study complies with the Declaration of Helsinki and was approved by the local Ethics Committee.

All patients gave written informed consent.

Statistical analysis

Data were analyzed by Statistical Package for the Social Sciences software version 15.0 (SPSS Inc., Chicago, IL). Quantitative data are presented using the mean and standard deviation. Comparison of quantitative data was made using the Mann-Whitney test for independent samples as non parametric test. Pair t-test was done for quantitative and dependent samples (for test of Mg levels before and at the end of HD session). Correlation between quantitative data was determined by Pearson’s correlation coefficient. A p value of less than 0.05 was considered significant.

Results

The present study was done on 58 patients on chronic HD; 33 (56.89%) of them were male and 25 (43.10%) were female. The mean age of our patients was 51.14 ± 17.46 years old. The patients had been on HD for 21.02 ± 17.12 months. Demographic and biochemical data of the study group are summarized in table 1.

Overall a significant reduction of Mg levels was observed during the HD session (Pair t-test, p < 0.002). At the start of HD, 22 of our patients (39.3%) had hypomagnesaemia and 35 (60.3%) of them had high CRP. But 18 patients (31%) had both of the above. There was no significant difference between sex groups considering Mg and hs-CRP levels (Mann-Whitney test, p < 0.52 and p < 0.79, respectively).

In this study, there was a significant reverse association between Mg and hs-CRP before the HD session (r = -0.34, p < 0.04), but this association was not significant among the sex groups (p > 0.05). Also in those who had hypomagnesaemia before HD, hs-CRP level was higher (Mann-Whitney test, p < 0.01).

The risk of high hs-CRP among hypomagnesaemic patients was 4.5 times more than the patients with normal levels of Mg (Chi-square test, p = 0.02, OR = 4.50, CI = 1.26-16.11).

Discussion

The role of Mg in the inflammatory process is well-established [4]. Hypomagnesaemia increases the risk of metabolic syndrome [11, 12], type 2 diabetes [13], high blood pressure [14], and atherogenic lipid profile [14, 15]. On the other hand a reduced Mg level was reported among HD patients [1]. There was no previous report on the association between subclinical inflammation and hypomagnesaemia among HD patients. In this study nearly half of our patients had hypomagnesaemia. Also in concordance with previous studies a significant decrease in Mg concentration was seen during the HD session [1, 16].

Inflammation among HD patients can cause different complications such as a poorer response to erythropoietin, higher hospitalization rate, lower serum albumin concentration, decreased survival, and early mortality [5, 17, 18]. Some possible causes of inflammation in uremic patients include bacterial or viral infections, vascular access, heart failure, systemic or renal inflammatory diseases, factors
relating to the dialysis procedure such as the water source, type of dialysate and presence of an intravenous catheter [6, 18].

In this study, the average of serum hs-CRP was 11.9 ± 11.8, and more than half (60%) of the study group had high hs-CRP. The presence of a dialysis catheter, cardiovascular disease, male gender, higher white blood cell count, elevated phosphorus, and lower cholesterol and albumin concentrations were independent predictors of elevated CRP in the multivariate analysis [6]. Some studies reported that CRP was elevated in predialysis patients [6, 18, 19]. The CRP is the most sensitive marker of systemic inflammation [20], which can lead to the development of cardiovascular disease [21].

Our results suggest that there was a significant reverse association between Mg and hs-CRP before the HD session. In addition, HD patients with hypomagnesaemia had higher hs-CRP levels. The effects of Mg deficiency on cell function are reactions of immune cells including macrophages, polymorpho-nuclear leukocytes or mast cells [22].

The underlying mechanisms of inflammation in Mg deficiency are still unknown. It may be related to oxidative stress and endothelial dysfunction which promote the release of inflammatory cytokines [3, 8]. The inflammatory response is dependent on cytosolic calcium elevation. Since Mg acts as a calcium antagonist, the possible role of intracellular calcium in the inflammatory process resulting from Mg deficiency has been suggested [22].

Table 1. Characteristics and biochemical data of studied hemodialysis patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Standard Deviation</th>
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<tr>
<td>Age (year)</td>
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<td>Blood urea nitrogen (mg/dL)</td>
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<td>144.00</td>
<td>57.02</td>
<td>19.75</td>
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<td>1.96</td>
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<td>3.36</td>
<td>11.63</td>
<td>6.48</td>
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</table>

Magnesium-1: magnesium at the start of hemodialysis; Magnesium-2: magnesium at the end of hemodialysis; Hs-CRP: highly sensitive C-reactive protein at the start of dialysis.
The fact that CRP measurements were done in a single session and follow up measurements were not available can be considered a limiting factor in this study. Also, the presence of potentially confounding variables could not be absolutely eliminated. For practical reasons, however, we considered simple random sampling and included confounding variables in the exclusion criteria as far as possible.

In brief, as far as we know this study is the first report of association between hypomagnesaemia and elevated CRP levels in pre-dialysis patients. However larger studies, with a longitudinal follow-up of the patients with multiple samplings are needed to confirm the findings. Also, an interventional study regarding monitoring CRP levels following supplementary Mg uptake could be confirmatory.

Acknowledgments

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References