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Serum Magnesium Level and Cardiovascular Disease in Dialysis Patients

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Magnesium is the second major intracellular divalent cation which is involved in maintaining normal cellular function.[1] Approximately, 50% of the total body magnesium is found in the bone. The other half is present predominantly inside cells and only 1% is in blood. The serum concentration of magnesium is closely monitored within normal range (1.5 mEq/L to 2.3 mEq/L or 1.8 mg/dL to 2.8 mg/dL).[1] In chronic kidney disease (CKD) patients, fractional excretion of magnesium increases with diminution of glomerular filtration rate in order to maintain serum magnesium within normal ranges; however, when glomerular filtration rate goes down to 30 mL/min, hypermagnesaemia occurs.[1,2] Although, the severity of hypermagnesaemia is variable, hypermagnesaemia is generally mild and asymptomatic. In CKD stage 5 dialysis patients, dialysis solution magnesium concentration and oral magnesium intake are the main factors controlling serum magnesium levels.[2,3] In fact, there is a wide variability in magnesium balance in dialysis patients and it is not surprising that magnesium balance to be normal or even low in dialysis patients, because of low dietary intake or impaired intestinal absorption.[3,4]

Cardiovascular disease (CVD) is the most important cause of morbidity and mortality in both CKD and dialysis patients.[3-5] Recently, there is increasing evidence suggesting an association between low serum magnesium levels and CVD in CKD as well as in general population.[3-5] It seems that magnesium depletion may be the missing link between cardiovascular risk factors and atherosclerosis. Vascular calcification is an important factor for increased morbidity and mortality in CKD and dialysis patients.[4-6] Although, the mechanism of vascular calcification is multifactorial, it is now evident that magnesium depletion is involved in the pathogenesis of vascular calcification.[6-8] On the other hand, low serum magnesium level is associated with the other CVD risk factors including hypertension, dyslipidemia, coronary vasospasm, atherosclerosis, and ischemic heart disease. Moreover, at least in animal model, the association between hypomagnesemia and the presence of pro-inflammatory state has been shown.[7] This pro-inflammatory state can disrupt the arterial endothelium and promote thrombosis and atheroma formation, hypertension, arteriosclerosis, and vascular calcification.[7,8]

There are unanswered questions about magnesium balance and its effects in both CKD and dialysis patients. Further studies, especially randomized trials, are required to confirm the

potential benefits of magnesium in these patients. According to recent studies, magnesium not only has an effect on the bone, serum phosphate, and parathyroid hormone levels, but also is regarded as a cardiovascular risk factor in CKD and dialysis patients.[3-5,8-10] Magnesium affects calcium uptake and distribution in the vascular smooth cells and also has direct effects on the vascular tone and can reduce peripheral resistance.[4,5,9] Magnesium depletion can be associated with cardiovascular disturbances such as ventricular arrhythmias, prolonged QT interval, and torsades de pointes.[3,11] Magnesium not only affects the vascular system, but also reduces triglycerides and low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol levels.[7,12,13] There are studies which have shown that magnesium supplementation improves flow-mediated vasodilation in stable coronary artery disease patients, which confirms magnesium effect on regulation of vascular tone.[3,4,12]

The pathogenesis of CVD in CKD and dialysis patients is complex and involves traditional and nontraditional risk factors. Among the nontraditional risk factors, uremia, anemia, hyperparathyroidism, hyperhomocysteinemia, increased oxidative stress, high state of inflammation, and low serum magnesium are the most important ones.[3-5,13,14] In dialysis patients, a higher incidence of CVD is present in patients with magnesium depletion. Although the exact cause of this observation is not understood, vascular calcification seems to have an important role.[6,9,14] In fact, most studies evaluating the effects of magnesium levels in dialysis patients were concerned about influence of magnesium on vascular reactivity and vascular calcification. Generally, there are studies that reported a direct effect of low serum magnesium in the development of CVD in the general population. Also, there are several studies which have shown the relationship between serum magnesium level and vascular calcification and CVD in dialysis patients. One study has shown that serum magnesium level was higher in patients with slow progression of vascular calcification compared to patients with rapid progression.[15] Also, there are studies which have reported the inverse relationship between magnesium level and carotid intima-media thickness. A study from Japan which evaluated the association between serum magnesium levels and vascular calcification in hemodialysis patients showed that serum magnesium levels were significantly lower in patients with calcification compared to patients without calcification. In addition, serum magnesium level was reported to be a significant independent factor for vascular calcification in hemodialysis patients.[16] The authors concluded that higher serum magnesium levels could have a protective role against the arterial calcification. Tzanakis and colleagues showed a strong inverse relationship between serum and intracellular magnesium and carotid intima-media thickness.[17] Each 0.5 mmol/L increase in serum magnesium was associated with a 0.35-mm reduction in carotid intima-media thickness. The same authors in a prospective study evaluated the mitral annular calcification by the M mode and 2-dimensional echocardiography in hemodialysis patients. Using multiple regression analysis, they showed that serum magnesium level with overall accuracy of 86% could predict the occurrence of mitral annular calcification.[18] In a large study performed in the United States included approximately 27 500 hemodialysis patients to assess the effects of serum magnesium levels on mortality.[19] The authors revealed lower mortality risk associated with higher magnesium levels. A serum magnesium level greater than 1.15 mmol/L was associated with reduced risk of mortality in dialysis patients.

In this issue of the *Iranian Journal of Kidney Disease*, Khatami and coworkers[20] studied the association between serum magnesium level and some CVD risk factors in 103 hemodialysis patients. The mean serum magnesium level was 2.8 ± 0.55 mg/dL. Among the patients, 41 (39.8%), 61 (59.2%), and 1 patient had normal (1.8 mg /dL to 2.6 mg/dL), high (< 2.6 mg/dL), and low (< 1.8 mg/dL) serum magnesium levels, respectively. Serum magnesium had a significantly positive correlation with serum albumin and phosphorus levels. They could not find a significant correlation between serum magnesium levels and serum calcium, parathyroid hormone and atherogenic lipids. Interestingly, the majority of patients had normal and high serum magnesium and just 1 patient had a low serum magnesium level, which could be one of the reasons that explain no correlation between serum magnesium and atherogenic lipids and blood pressure in this study. The small number of the patients is the main limitation of the study.

In conclusion, there are clinical studies which have shown that lower serum magnesium levels are associated with a higher rate of vascular calcification and CVD mortality in ESRD patients; however, there are only 2 human interventional studies which suggest that magnesium supplementation in CKD patients retards the arterial calcification and reduces carotid intima-media thickness.[21,22] The urge for the randomized controlled trials to show the protective role of magnesium in the cardiovascular system in CKD and dialysis patients is still present.

CONFLICT OF INTEREST

None declared.

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