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INVITED COMMENTARY

Addressing uncertainties in renal transplantation: hypomagnesemia and the case of diabetes prevention

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Magnesium (Mg) is the dominant intracellular cation along with potassium acting as a catalyst for a multitude of enzymatic reactions, especially ATP-dependent pathways involving the Mg-ATP key intermediate complex. Thus, a lack of Mg may confer detrimental effects on various intracellular metabolic pathways. Importantly, Mg deficiency has been reported to directly affect insulin sensitivity, and several observations report its association with increased rates of type 2 diabetes mellitus, whereas increased Mg intake was linked to reduced diabetes rates [1–3]. Recently, it was demonstrated that hypomagnesemia may predict diabetic nephropathy [4] and has been implicated in the development of hypertension, dyslipidemia, and sudden death by exacerbating both atrial and ventricular arrhythmias associated with hypokalemia [5]. In the context of chronic kidney disease (CKD), mounting evidence suggests a substantially increased mortality risk in hypomagnesemic patients, especially in hemodialysis patients, mainly caused by cardiovascular but also infectious complications [6].

In a recent Japanese study with >140 000 patients, a higher prevalence of diabetes was found in dialysis patients with low serum Mg [6]. However, it should also be noted that patients with serum Mg levels at the upper reference limit showed an increased all-cause mortality risk, possibly due to suppressed parathyroid hormone (PTH) secretion fostering low-turnover bone disease along with increased vessel calcification. Indeed, excluding patients with low PTH resulted in a J-shaped relationship between mortality and Mg concentration. Nevertheless, it is important to note that hypomagnesemia displayed strong associations with older age and number of severe comorbidities questioning a true causal role for Mg as independent risk factor. However, the critical role of Mg within intracellular enzyme pathways is undoubted: a conundrum of potential beneficial effects of Mg has been proposed including direct modulation of various endothelial functions such as calcium-channel blockade, stimulation of nitric oxide and prostacyclin production, further anti-inflammatory and anti-oxidative properties. Especially the reported anticalcification effects of Mg, in part mediated via interaction with the calcium-sensing receptor of the parathyroid gland, may be of great importance for patients with advanced CKD stages [7]. Finally, effects of Mg on insulin receptor signaling and on insulin secretion have been described with a profound

increase of insulin resistance detected in hypomagnesemic individuals [8].

What about Mg and renal transplant patients? A clear relationship between early post-transplant hypomagnesemia and post-transplant diabetes mellitus (PTDM), a strong risk factor for mortality and graft loss, has been observed. Hypomagnesemia is common early after transplantation, especially due to the use of calcineurin inhibitors (CNI) and tubular dysfunction [9]. Among others, Van Laecke described hypomagnesemia as independent predictor of PTDM in liver and kidney transplant recipients [10–12]. Of note, both pretransplant and *de novo* hypomagnesemia after transplantation conferred a higher PTDM risk. However, several factors in transplant patients may already confound the relationship between Mg and PTDM making causal inferences nearly impossible. For example, tubular Mg reabsorption is calcineurin-regulated [13]; therefore, hypomagnesemia may be a proxy of CNI pharmacodynamics and hence PTDM risk, and there are conflicting results regarding the role of hypomagnesemia in the development of PTDM [14].

Still, given all these strong hints on potent causal effects of Mg deficiency on PTDM development, a randomized prospective trial with early Mg supplementation was highly anticipated. In this issue of *Transplant International,* Van Laecke *et al.* [15] report on a randomized controlled trial addressing the important clinical question: Can post-transplant diabetes mellitus be prevented by administering oral magnesium supplementation?

In this open-label study, 54 patients were randomized within 2 weeks after kidney transplantation to receive either up to 1350 mg magnesium oxide daily aiming at serum Mg concentrations ≥1.9 mg/dl or no treatment. Primary study endpoint was fasting plasma glucose (FPG) 3 months after transplantation. Patients in the treatment group showed a significant increase in Mg levels after 3 months, and FPG was significantly lower in the treatment group although the effect was not large (104.1 mg/dl in the control group vs. 92.6 mg/dl in the treatment group, $P = 0.02$), and FPG levels were higher in the control group already at baseline. There were no significant differences in area under the glucose curve during an oral glucose tolerance test and in insulin resistance as expressed by HOMA-IR. Odds ratios for the relative risk for development of impaired fasting glucose or PTDM were reduced by 23%, but without statistical significance. Interestingly, 26% of patients in the treatment group showed persistent hypomagnesemia despite supplementation and these patients also displayed higher insulin resistance. There are several possible explanations for this interesting finding: Magnesium oxide may not be the ideal formulation for supplementation, and organic Mg salts may be preferable [16]; nonadherence to study medication; lower dietary intake or insulin-driven expression of the Mg transporter TRPM6 [17]. Mg may also exert its effects by improvement of beta-cell function which was not specifically determined in this study. Adverse events, most notably diarrhea, were similar in both groups, suggesting principal safety of Mg supplementation in renal transplant recipients; however, as demonstrated in the study by Sakaguchi *et al.* [6], high Mg levels may also not be without any harm at least in patients with low PTH levels. Although the effect size on FPG was relatively small leading to a nonsignificant risk reduction for development of PTDM and IFG, it might still be reasonable to advocate Mg supplementation in hypomagnesemic patients after kidney transplantation to combat cardiovascular disease especially given the safety of this intervention. Of course, a larger randomized long-term trial, ideally double-blinded and with adequate quantification of beta-cell function, would be desirable to further eliminate remaining uncertainty surrounding the question of Mg supplementation in this high-risk population.

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