TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

The effect of magnesium supplements on early post-transplantation glucose metabolism: a randomized controlled trial

Steven Van Laecke,[1] Evi Vanessa Nagler,[1] Youri Taes,[2] Wim Van Biesen,[1] Patrick Peeters[1] and Raymond Vanholder[1]

1 Renal Division, Ghent University Hospital, Ghent, Belgium
2 Endocrinology Department, Ghent University Hospital, Ghent, Belgium

Keywords
glucose, kidney transplantation, magnesium, randomized controlled trial.

Correspondence
Steven Van Laecke, Renal Division, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium.
Tel.: 003293324509;
fax: 003293323847;
e-mail: steven.vanlaecke@ugent.be

Conflict of interest
None.

Received: 14 September 2013
Revision requested: 4 November 2013
Accepted: 17 February 2014
Published online: 24 March 2014

doi:10.1111/tri.12287

Summary

Post-transplantation hypomagnesemia is common and predicts diabetes. Magnesium improves glycemic control in diabetics and insulin sensitivity in insulin resistant subjects. We aimed to assess the effectiveness of oral magnesium for improving glycemic control and insulin sensitivity at 3 months post-transplantation. We conducted a single-center, open-label, randomized parallel group study. We included adults with serum magnesium <1.7 mg/dl within 2 weeks after kidney transplantation. We randomized participants to 450 mg magnesium oxide up to three times daily or no treatment. The primary endpoint was the mean difference in fasting glycemia. Secondary endpoints were the mean difference in area under the curve (AUC) of glucose during an oral glucose tolerance test and insulin resistance measured by Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR). Analyses were on intention-to-treat basis. In patients randomized to magnesium oxide ($N = 27$) versus no treatment ($N = 27$), fasting glycemia on average was 11.5 mg/dl lower (95% CI 1.7 to 21.3; $P = 0.02$). There was no difference between the two groups neither for 2 h AUC, where the mean value was 1164 mg/dl/min (95% CI −1884 to 4284; $P = 0.45$) lower in the treatment group nor for HOMA-IR. Magnesium supplements modestly improved fasting glycemia without effect on insulin resistance. Higher baseline glycemia among patients in the control group may have driven the positive outcome (ClinicalTrials.gov number: NCT01889576).

Introduction

Hypomagnesemia occurs often after kidney transplantation, especially when patients are treated with a calcineurin inhibitor (CNI) [1–3]. It is associated with an impaired glucose metabolism and predicts the later development of diabetes, both in transplant recipients as in the general population [3–7]. Dietary induction of magnesium deficiency in both healthy volunteers and rodents reduces insulin sensitivity through impairment of the tyrosine kinase activity of the insulin receptor, and raises the fasting glycemia [8–10]. This supports a causal mechanism for the association between hypomagnesemia and diabetes. Also, in randomized controlled trials (RCT), magnesium supplements improve glycemic control and/or insulin sensitivity in diabetics, overweight insulin-resistant and healthy adults [11–14]. After transplantation, glucose metabolism is often disturbed, and this condition has been associated with increased cardiovascular morbidity and mortality [15–18]. No RCT, however, has examined the role of magnesium supplements on glucose metabolism after transplantation.

Aims

We aimed to assess whether oral magnesium supplements improve glycemic control and insulin sensitivity at 3 months after transplantation. The primary endpoint was the mean difference in fasting serum glucose concentration.

Secondary endpoints were the mean difference in area under the curve of glucose during an oral glucose tolerance test (OGTT) and insulin resistance measured by Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) index.

Materials and methods

We conducted a single-center, open-label, randomized trial with parallel groups in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and local regulatory requirements. The study was approved by the local ethics committee. The trial was registered at ClinicalTrials.gov as NCT01889576.

Participants

Patients were recruited at Ghent University Hospital in Belgium. Participants were eligible if they had at least two serial serum magnesium concentration measurements <1.7 mg/dl (0.7 mmol/l) within 2 weeks after kidney transplantation.

Study treatment

Fixed-protocol immunosuppressive therapy consisted of induction by basiliximab and maintenance treatment of tacrolimus with a target concentration 10–15 ng/ml the first month and 8–10 ng/ml afterward up to month three, mycophenolate mofetil 1 g twice daily and methylprednisolone, tapered to six mg daily at month three.

Patients could not be included in the study if they either were younger than 18 years of age, had existing diabetes mellitus, or had >10% panel-reactive antibodies. In addition, a serum C-reactive protein concentration >30 mg/l, a serum creatinine concentration >3 mg/dl, a serum calcium concentration <6.5 mg/dl a serum potassium concentration <3.5 mmol/l, or intake of digoxin or magnesium were exclusion criteria.

We randomly assigned patients to receive either oral magnesium oxide or no treatment using a computer-generated list of random numbers, with allocation concealed in sequentially numbered sealed envelopes.

In the active treatment group, patients received a starting dose of 450 mg oral magnesium oxide, which we increased during study follow-up up to a predefined maximum of three times daily, aiming for serum magnesium concentrations ≥1.9 mg/dl. In the control group, patients did not take magnesium oxide, unless the serum magnesium concentration dropped <1.2 mg/dl. In that case, we gave participants 450 mg daily to raise the serum magnesium concentration ≥1.2 mg/dl.

Study outcomes

The primary outcome was fasting serum glucose concentration at 3 months after kidney transplantation. Secondary endpoints were the 2 h area under the curve (AUC) of glycemia based on the trapezoid rule [19] and insulin resistance, assessed by the homeostasis model assessment-estimated insulin-resistance (HOMA-IR) index [20] both at 3 months after kidney transplantation.

In a *post hoc* sensitivity analysis we compared the change in fasting glycaemia between both groups to correct for differences in baseline glycemia. Also, we adjusted for tacrolimus concentrations at month three to correct for differences which might affect the primary outcome, considering the direct effects of tacrolimus on beta-cell function [21]. New-onset diabetes after transplantation (NODAT) and impaired fasting glucose were defined according to American Diabetes Association criteria [22], and their incidence in both the treatment and control group was reported next to the evolution of serum magnesium concentration in these patients.

The fractional urinary magnesium concentration was calculated both baseline and at month three by the formula: $100 \times (U_{Mg} \times P_{creatinine})/(0.7 \times U_{creatinine} \times P_{Mg})$ (%), where U_{Mg} = urinary magnesium concentration; $P_{creatinine}$ = serum creatinine; $U_{creatinine}$ = urinary creatinine and P_{Mg} = serum magnesium concentration.

Persisting hypomagnesemia was defined as the inability to increase serum magnesium concentration both through supplementation (in the intervention group) or spontaneously (in the controls). Insulin resistance was defined as a HOMA-IR ≥2.

Side effects and/or adverse events were prospectively reported. Diarrhea was defined as three or more liquid stools per day.

Statistical analysis

We estimated that with a study sample of 34 patients (17 in each group), the study would have 80% power to detect a clinically important difference in the absolute difference in fasting serum glucose concentration of approximately 10 mg/dl between the two groups, assuming a standard deviation of 10 mg/dl and a two-sided type one error rate of 5%. The expected standard deviation was determined based on glycemia measurements 3 weeks after kidney transplantation, measured by van Duijnhoven *et al.* [23], but we chose more conservative values. We have presented summaries of continuous variables as means with standard deviations for normally distributed data and medians with interquartile ranges for skewed data.

We compared continuous variables using a Student's *t*-test and a Mann–Whitney *U*-test or Spearman's correlation

coefficient, if appropriate for non-normally distributed data.

We generated the statistical analyses with SPSS software, version 21.0 of the SPSS system for Windows (SPSS Inc, Chicago, IL, USA). All statistical tests were two-tailed and a P-value <0.05 was considered to indicate statistical significance.

Results

Between January 2010 to June 2012, we randomized a total of 54 patients to treatment with magnesium oxide ($N = 27$) or no treatment ($N = 27$; Fig. 1).

Baseline characteristics of the patients allocated to the treatment or control group are described in Table 1. Both groups were rather well balanced without significant differences.

The mean dose of magnesium oxide in the treatment group was 1145 (±221) mg, while six patients in the control group were taking rescue magnesium supplements with a mean overall dose of 84 mg. Dosing of corticosteroids in both groups was not significantly different at month three ($P = 0.73$).

Primary and secondary outcome

The primary analysis was intention-to-treat and involved all participants who were randomly assigned. Apart from two patients in the control group, who opted out of the study due to the demands of the protocol, only patients with early NODAT necessitating the initiation of antidiabetic drugs ($N = 5$) had no assessment of fasting glycemia 3 months after inclusion (Fig. 1).

Fasting serum glucose concentration was 11.5 mg/dl lower for patients treated with magnesium oxide than for patients not receiving magnesium supplements (95% CI 1.7–21.3; $P = 0.02$).

Four patients (14.8%) in the treatment arm developed NODAT versus 6/27 (22.2%) in the control group, corresponding to a nonsignificant relative risk reduction of 23%; RR = 0.67 (95% CI 0.22–1.97; $P = 0.49$). In the treatment group, 8/27 (29.6%) vs. 11/25 (44%) in the control group developed impaired fasting glucose, also with a nonsignificant relative risk reduction of 23%; RR = 0.67 (95% CI 0.32–1.37; $P = 0.28$; Fig. 2).

Apart from two patients in the control group, who withdrew from the study, seven patients with early NODAT had no evaluation by OGTT or insulin measurement at month three (Fig. 1). Three patients were diagnosed as having NODAT at the time of OGTT. The 2 h-AUC of glucose was not significantly lower in the treatment group versus the control group with a mean difference of 1164 mg/dl/min (95% CI −1884 to 4284; $P = 0.45$; Table 2). There was no difference in HOMA-IR between the treated versus the control patients. Serum magnesium at month three correlated with serum insulin and HOMA ($r = -0.683$; $P < 0.001$ and $r = -0.48$; $P = 0.001$, respectively) in the

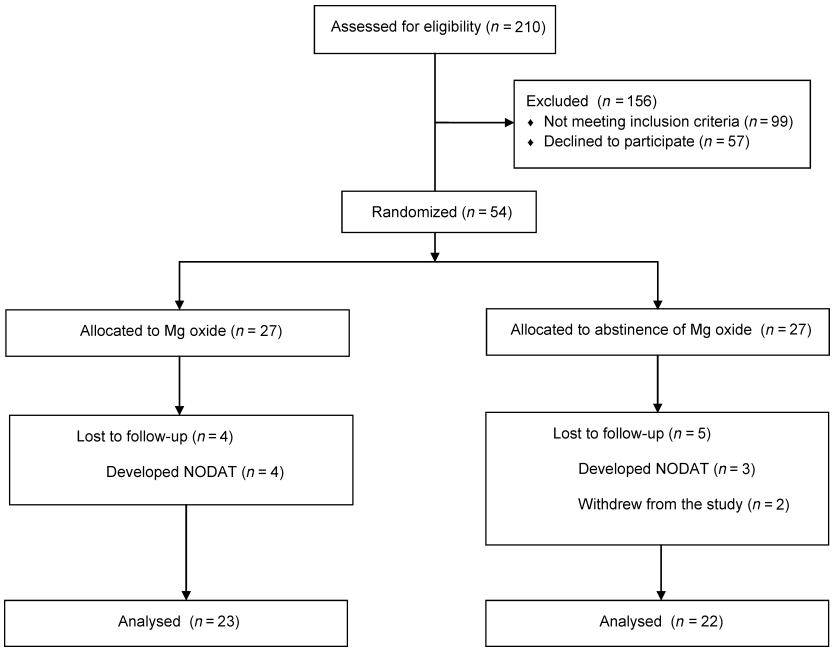

Figure 1 Flow diagram. NODAT = new-onset diabetes after transplantation.

Table 1. Baseline characteristics of treatment and control group.

Characteristic	Mg oxide (n = 27)	Controls (n = 27)	P-value
Age (years)	54.3 ± 11.9	48.5 ± 11.5	0.08
Male gender (%)	51.9	74.1	0.09
BMI (kg/m^2)	24.8 ± 3.3	25.4 ± 3.8	0.56
MAP (mmHg)	94.4 ± 14.1	101.6 ± 16.5	0.09
Donor age (years)	46.7 ± 17.7	40.8 ± 12.6	0.16
Polycystic kidney disease (%)	22.2	22.2	1.00
Proton pump inhibitors (%)	63.0	44.4	0.17
RAAS blockers (%)	33.3	18.5	0.21
Diuretics (%)	14.8	7.4	0.39
HOMA	2.3 ± 1.6	2.5 ± 1.8	0.71
Glucose (mg/dl)	91.4 ± 16.5	98.8 ± 18.4	0.13
Triglycerides (mg/dl)	150 (69)	155 (116)	0.21
Creatinine (mg/dl)	1.54 ± 0.47	1.58 ± 0.53	0.74
Adiponectin (μg/ml)	105.2 ± 66.9	127.2 ± 62.9	0.37
CRP (mg/dl)	0.5 (0.6)	0.4 (0.9)	0.74
FE_{Mg} (%)	14 (10)	11 (7)	0.89
Serum Mg^{2+} (mg/dl)	1.45 ± 0.13	1.47 ± 0.15	0.57
Erythrocyte Mg^{2+} (mg/dl)	5.68 ± 1.00	6.07 ± 0.84	0.13
Pretransplantation Mg^{2+} (mg/dl)	2.07 ± 0.31	2.11 ± 0.24	0.19
Serum K^+ (mmol/l)	4.43 ± 0.55	4.55 ± 0.58	0.43
Tacrolimus (ng/ml)	10.9 ± 2.5	9.8 ± 2.9	0.13

HOMA, homeostasis model of assessment; AUC, area under the curve; Mg^{2+}, magnesium; FE Mg^{2+}, fractional excretion of magnesium.
Mean ± SD or median (IQR) or percentages. Values are at the time of randomization except for pretransplantation Mg^{2+}.

control and to a lesser degree in the treatment group (r = −0.398; P = 0.05 and r = −0.447; P = 0.03, respectively; Fig. 3).

Post-hoc exploratory analyses

Adjustment for tacrolimus concentrations at month three did not attenuate the significance level of the difference in fasting glycemia (P < 0.01). The median tacrolimus concentration during follow-up was not different between both groups. The change in glycemia from baseline to study endpoint at month three was not significantly lower in the treatment versus the control group (P = 0.28 after adjustment for tacrolimus drug concentrations at month three). The mean rise in serum magnesium concentration at month three versus baseline was 0.11 mg/dl (95% CI −0.01 to 0.23 mg/dl; P = 0.06) higher in the treatment than the control group.

Overall, 20/54 or 37% of the study population had persisting hypomagnesemia, 7/27 (25.9%) in the treatment group and 13/27 (48.1%) in the control group (P = 0.09). These patients were more likely insulin resistant at month

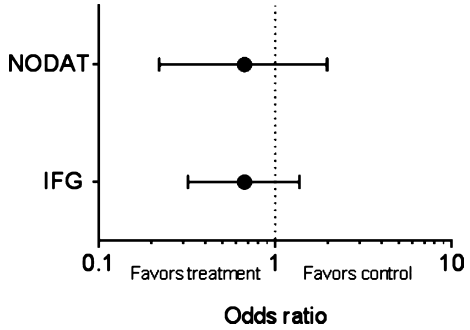

Figure 2 The effect of magnesium supplements on the relative risk of new-onset diabetes after transplantation and impaired fasting glucose the first 3 months after transplantation. IFG = impaired fasting glucose; NODAT = new-onset diabetes after transplantation. Four patients (14.8%) in the treatment arm developed NODAT versus 6/27 (22.2%) in the control group, corresponding to a relative risk reduction of 23%; RR = 0.67 (95% CI 0.22–1.97; P = 0.49). In the treatment group, 8/27 (29.6%) versus 11/25 (44%) in the control group developed impaired fasting glucose, also with a relative risk reduction of 23%; RR = 0.67 (95% CI 0.32–1.37; P = 0.28).

three (85.7% vs. 42.4%; P < 0.01) and had a baseline HOMA which was one unit higher (95% CI 0.1–2; P = 0.04) than patients without persisting hypomagnesemia. Persisting hypomagnesemia was associated with impaired glucose tolerance (Fig. 4). Fractional magnesium excretion at month three was not significantly lower in patients with persisting hypomagnesemia versus patients with increasing serum magnesium (5.8 ± 3.4 vs. 8.4 ± 4.4%; P = 0.12) but also in insulin-resistant versus insulin-sensitive patients (6.3 ± 3.5 vs. 9.2 ± 4.7%; P = 0.04).

Patients later diagnosed with NODAT or insulin resistance had early-onset and persisting hypomagnesemia and serum magnesium concentrations at month three were respectively 0.15 mg/dl (95% CI 0.02 to 0.28; P = 0.03) and 0.18 mg/dl (95% CI 0.09 to 0.028; P < 0.001) lower than patients not developing NODAT or being insulin sensitive.

Adverse events

In the treatment group, 10/27 (37.0%) of the patients reported diarrhea versus 7/27 (25.9%) in the control group (P = 0.38). Adverse events did not occur significantly more in the treatment versus the control group with respectively 22/27 and 18/27 events of which respectively nine and seven were infections and seven and six hypertension. One patient in the treatment group developed an ischemic cerebrovascular accident, but no patient discontinued the study due to adverse events.

Two patients in the control group versus none in the treatment group developed acute rejection necessitating

Table 2. Treatment effects.

	Controls (N = 27)		Mg oxide (N = 27)			
	Baseline	Month 3	Baseline	Month 3	Difference (95% CI)	P-value
Primary outcome						
Glucose (mg/dl)	98.8 ± 18.4	104.1 ± 21.9	91.4 ± 16.5	92.6 ± 9.6	11.5 (1.7 to 21.3)	0.02*
Secondary outcome						
AUC glucose (mg/dl/min)		17472 ± 5940		16308 ± 4104	1164 (−1884 to 4284)	0.45
HOMA	2.51 ± 1.84	3.49 ± 5.78	2.33 ± 1.64	3.36 ± 5.69	0.12 (−3.25 to 3.50)	0.94
Magnesium status						
Serum Mg^{2+} (mg/dl)	1.47 ± 0.15	1.49 ± 0.18	1.45 ± 0.13	1.58 ± 0.21	−0.09 (−0.19 to 0.02)	0.10
Erythrocyte Mg^{2+} (mg/dl)	6.07 ± 0.84	4.55 ± 0.88	5.68 ± 1.00	4.83 ± 0.69	−0.29 (−0.76 to 0.18)	0.23
Delta serum Mg^{2+} (mg/dl)	NA	0.02 ± 0.22	NA	0.13 ± 0.21	−0.11 (−0.23 to 0.01)	0.06
Delta Erythrocyte Mg^{2+} (mg/dl)	NA	−1.54 ± 0.96	NA	0.88 ± 1.21	−0.66 (−1.32 to 0.00)	0.05
FE Mg^{2+} (%)	14.2 ± 9.7	6.6 ± 2.9	15.2 ± 11.5	9.1 ± 5.2	−2.5 (−5.2 to 0.2)	0.07
Tacrolimus at month 3 (ng/ml)	9.8 ± 2.9	7.8 ± 3.9	10.9 ± 2.5	10.5 ± 4.3	−2.7 (−5.0 to −0.5)	0.02
Tacrolimus median follow-up (ng/ml)	NA	10.9 ± 1.3	NA	10.9 ± 1.2	0.02 (−0.67 to 0.71)	0.95

HOMA, homeostasis model of assessment; AUC, area under the curve; Mg^{2+}, magnesium; FE Mg^{2+}, fractional excretion of magnesium; NA, not applicable.

*P < 0.01 after adjustment for tacrolimus concentration at month three.

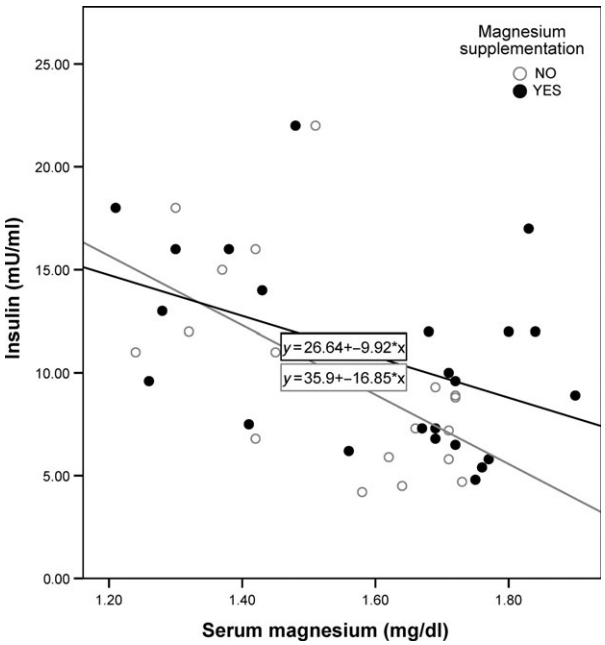

Figure 3 The relationship between serum magnesium and insulin and its interaction with magnesium supplementation. There is a good correlation between insulin and serum magnesium concentrations at month three, the study endpoint (r = −0.683; P < 0.001) in the nonsupplemented group and to a lesser degree in the supplementation group (r = −0.398; P = 0.05).

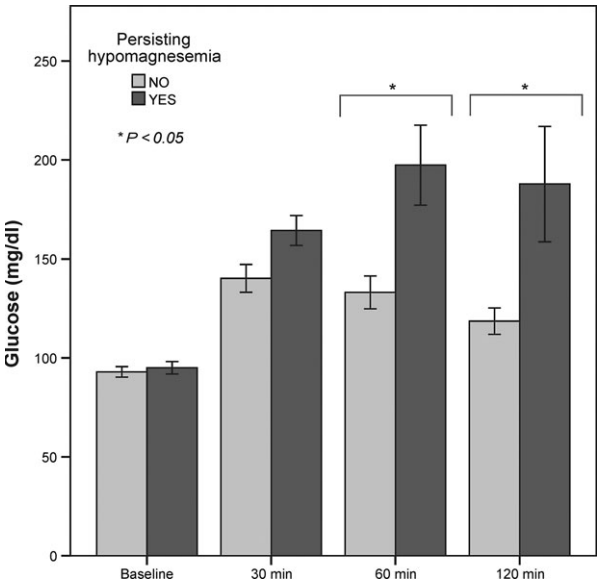

Figure 4 Impaired glucose metabolism in renal transplant recipients with persisting hypomagnesemia. Glycemia at time points 30, 60 and 120 min is depicted after oral glucose tolerance test. The area under the curve (AUC; mg/dl/min) is higher in the patients with persisting hypomagnesemia versus the patients with increasing serum magnesium (20 880 ± 4200 vs. 15 120 ± 3240; P = 0.003) pointing to decreased glucose tolerance in patients with persisting hypomagnesemia, which is defined as the absence of a rise of serum magnesium concentration after 3 months of magnesium supplementation. An oral glucose tolerance test was performed at month three, the study end point. Glycemia was higher in patients with versus without persisting hypomagnesemia at 60 and 120 min (both with a P- value of <0.01). Error bars: ±1 SEM.

boluses of corticosteroids during the first 3 months after transplantation. Both these patients had no later abnormalities in glucose metabolism including impaired fasting glucose, NODAT or impaired glucose tolerance.

Discussion

This is the first randomized controlled trial to study the effect of magnesium supplements on glucose metabolism after transplantation, whereas previously, only two small controlled trials in renal transplant recipients on cyclosporine studied the effect of magnesium oxide on blood pressure and lipid control [24,25]. High doses of magnesium oxide in our study had a beneficial but minor effect on glycemic control. Yet, the baseline serum glucose concentration in the control group was higher than in the treatment group possibly influencing outcome. We observed no significant effect of magnesium supplementation on the AUC of glucose as proxy of insulin secretion and/or insulin-mediated glucose disposal nor on insulin sensitivity.

Diabetes is associated with lower intra- and extracellular magnesium concentrations [26–29]. Proposed mechanisms to explain this consistent finding are the increased renal magnesium wasting through insulin resistance as well as osmotic diuresis and proteinuria [29,30]. Hypomagnesemia, however, also might play a causative role in the development of diabetes as its dietary induction decreases insulin sensitivity and/or insulin secretion in both human volunteers and rodents [8–10]. More recently, hypomagnesemia was also associated with decreased insulin secretion in nondiabetics [31,32]. A systematic review including 9 RCT of 370 patients with type 2 diabetes found that a median daily magnesium dose of 360 mg leads to a 10 mg/dl (95% CI 2 to 20; $P = 0.03$) greater decrease of fasting glycemia as compared with the placebo group, albeit with significant heterogeneity (P for heterogeneity = 0.02) [11]. This outcome is mostly attributed to an improvement of insulin sensitivity, which was observed as well in a RCT in obese, insulin-resistant, normomagnesemic subjects without diabetes [13]. According to a recent meta-analysis, higher magnesium intake in a population over more than 50 000 subjects of European descent was associated with lower fasting glucose and insulin concentrations [33].

Both hypomagnesemia [1–3,34] and NODAT [3,35] are common after transplantation. Insulin hyposecretion is essential in the pathophysiology of CNI-induced NODAT [35–38]. However, also insulin resistance plays a negative role [37] and especially tacrolimus acts synergistically with the reduced insulin sensitivity caused by high doses of corticosteroids the first months after transplantation [39]. Early hypomagnesemia after transplantation predicts the later development of glucose disturbances including NODAT [3–5], but could as well be the early manifestation of a disturbed glucose metabolism and insulin resistance. Considering the absence of recommendations on when or whether to supplement hypomagnesemia, we studied the potential clinical usefulness of magnesium supplements for glucose metabolism after transplantation.

Whereas the major strength of this study is its randomized nature in a single center, resulting in similar treatments besides the intervention, this study has limitations. Retrospectively, our study seems underpowered to detect significant outcome differences. The standard deviation of the mean fasting glucose concentration in the control group at month three was higher than expected from literature data [23]. Also, one in four patients in the treatment group had no rise in serum magnesium despite reasonably high doses of magnesium oxide. Despite increments of serum magnesium caused by magnesium oxide of 0.36–0.50 mg/dl in the two preliminary trials in renal transplant recipients [24,25], exceeding our increase of 0.13 mg/dl, magnesium oxide presumably is not the most suitable formulation. This is reminiscent of trials questioning its efficacy because of lower bio-availability compared with organic magnesium salts [40]. Possibly, disparities in timing of supplementation and consequent drug exposure next to use of tacrolimus versus cyclosporine can also explain the smaller effect size of our intervention compared with the previously mentioned trials. Nonadherence might have been present but is difficult to account for. Mechanistically, tacrolimus-induced dose-dependent renal magnesium wasting at the distal tubulus by decreased expression of the magnesium transporter transient receptor of potential melastatin 6 (TRPM6) [41] could explain persisting hypomagnesemia. Genetic variants of TRPM6, possibly explaining disparities in renal magnesium handling, were previously associated with a disturbed glucose metabolism in the general population [33,42]. A possible mechanism for this association is insensitivity of TRMP6 for the activating effects of insulin [43]. In our analysis, the fractional magnesium excretion at month three was *lower* in patients with persisting hypomagnesemia. These patients more often were insulin-resistant, which rather suggests the following mechanisms: noncompliant intake, decreased gastro-intestinal absorption, lower dietary intake or shifting of magnesium from the extra- to the intracellular compartment, driven by insulin which increases TRPM6 expression [43]. Altered intestinal TRPM6 expression by tacrolimus remains yet unproven [44].

Also, in the absence of observational data, we are unsure how and to what extent serum magnesium concentration in renal transplant recipients adequately reflects intracellular deficiency and is a valuable endpoint for intervention. Fasting glucose concentrations seem less sensitive to detect early NODAT and should possibly be replaced by serial OGTT, capillary blood glycemia and/or continous glucose measurement [45,46].

Our study finally fails to explain why fasting glucose after 3 months of supplementation is lower in the treatment versus the control group, while no effect on insulin sensitivity is being observed. Possibly, the observation of a strong

inverse correlation between insulin/HOMA and serum magnesium at month three can be of help (Fig. 3). As this relationship was especially present in the control group, it seems that magnesium supplementation might also increase insulin secretion after transplantation as it previously improved the ability of beta-cells to compensate for variations in insulin sensitivity in healthy individuals [31]. Obviously, as assessment of insulin secretion, which remains the predominant component of NODAT development [38] was not incorporated into the protocol, this remains speculative so far and should be explored in future trials as well. Insulin resistance and secretion are intertwined and share a complex relationship which each other.

Taken together, our data suggest that future trials evaluating a possible relationship between magnesium and glucose metabolism should be adequately powered, use more bio-available magnesium formulations, and incorporate measures of insulin secretion next to sensitive tests to detect alterations in glucose metabolism.

To conclude, our study failed to demonstrate a meaningful benefit of oral magnesium supplementation on early glucose metabolism after kidney transplantation. This partially relates to the high incidence of persisting hypomagnesemia, which appears to be associated to aberrant glucose handling.

Authorship

SVL and RVH: designed the study. SVL: collected the data. SVL, EV, WVB and RVH: analyzed the data. SVL, EV, YT, WVB, PP and RVH: wrote the manuscript.

Funding

This study was supported by Astellas Inc.

References

1. Barton CH, Vaziri ND, Martin DC, Choi S, Alikhani S. Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. *Am J Med* 1987; **83**: 693.
2. Navaneethan SD, Sankarasubbaiyan S, Gross MD, Jeevanantham V, Monk RD. Tacrolimus-associated hypomagnesemia in renal transplant recipients. *Transpl Proc* 2006; **38**: 1320.
3. Van Laecke S, Van Biesen W, Verbeke F, De Bacquer D, Peeters P, Vanholder R. Posttransplantation hypomagnesemia and its relation with immunosuppression as predictors of new-onset diabetes after transplantation. *Am J Transplant* 2009; **9**: 2140.
4. Van Laecke S, Desideri F, Geerts A, *et al.* Hypomagnesemia and the risk of new-onset diabetes after liver transplantation. *Liver Transpl* 2010; **16**: 1278.
5. Stevens RB, Lane JT, Boerner BP, *et al.* Single-dose rATG induction at renal transplantation: superior renal function and glucoregulation with less hypomagnesemia. *Clin Transplant* 2012; **26**: 123.
6. Kao WHL, Folsom AR, Nieto FJ, Mo J-P, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for Type 2 diabetes mellitus: the atherosclerosis risk in communities study. *Arch Intern Med* 1999; **159**: 2151.
7. Guerrero-Romero F, Rascón-Pacheco RA, Rodríguez-Morán M, De La Peña JE, Wacher N. Hypomagnesaemia and risk for metabolic glucose disorders: a 10-year follow-up study. *Eur J Clin Invest* 2008; **38**: 389.
8. Nadler JL, Buchanan T, Natarajan R, Antonipillai I, Bergman R, Rude R. Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. *Hypertension* 1993; **21**: 1024.
9. Chaudhary DP, Boparai RK, Bansal DD. Effect of a low magnesium diet on *in vitro* glucose uptake in sucrose fed rats. *Magnes Res* 2007; **20**: 187.
10. Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A. Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. *Diabetologia* 1995; **38**: 1262.
11. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. *Diabet Med* 2006; **23**: 1050.
12. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care* 2003; **26**: 1147.
13. Mooren FC, Kruger K, Volker K, Golf SW, Wadepuhl M, Kraus A. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects – a double-blind, placebo-controlled, randomized trial. *Diabetes Obes Metab* 2011; **13**: 281.
14. Hadjistavri LS, Sarafidis PA, Georgianos PI, *et al.* Beneficial effects of oral magnesium supplementation on insulin sensitivity and serum lipid profile. *Med Sci Monit* 2010; **16**: CR307.
15. Porrini E, Moreno JM, Osuna A, *et al.* Prediabetes in patients receiving tacrolimus in the first year after kidney transplantation: a prospective and multicenter study. *Transplantation* 2008; **85**: 1133.
16. Woodward RS, Schnitzler MA, Baty J, *et al.* Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *Am J Transplant* 2003; **3**: 590.
17. Sarno G, Muscogiuri G, De Rosa P. New-onset diabetes after kidney transplantation: prevalence, risk factors, and management. *Transplantation* 2012; **93**: 1189.
18. Cosio FG, Kudva Y, van der Velde M, *et al.* New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 2005; **67**: 2415.

19. Le Floch JP, Escuyer P, Baudin E, Baudon D, Perlemuter L. Blood glucose area under the curve. Methodological aspects. *Diabetes Care* 1990; **13**: 172.
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412.
21. Radu RG, Fujimoto S, Mukai E, *et al.* Tacrolimus suppresses glucose-induced insulin release from pancreatic islets by reducing glucokinase activity. *Am J Physiol Endocrinol Metab* 2005; **288**: E365.
22. Standards of medical care in diabetes—2012. *Diabetes Care* 2012; **35**: S11.
23. van Duijnhoven EM, Christiaans MHL, Boots JMM, Nieman FHM, Wolffenbuttel BHR, van Hooff JP. Glucose metabolism in the first 3 years after renal transplantation in patients receiving tacrolimus versus cyclosporine-based immunosuppression. *J Am Soc Nephrol* 2002; **13**: 213.
24. Gupta BK, Glicklich D, Tellis VA. Magnesium repletion therapy improved lipid metabolism in hypomagnesemic renal transplant recipients: a pilot study. *Transplantation* 1999; **67**: 1485.
25. Nguyen T, Steiner RW. A trial of oral magnesium supplementation in renal transplant recipients receiving cyclosporine. *Transpl Proc* 1998; **30**: 4317.
26. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. *Arch Biochem Biophys* 2007; **458**: 40.
27. Resnick LM, Altura BT, Gupta RK, Laragh JH, Alderman MH, Altura BM. Intracellular and extracellular magnesium depletion in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1993; **36**: 767.
28. Dewitte K, Dhondt A, Giri M, *et al.* Differences in serum ionized and total magnesium values during chronic renal failure between nondiabetic and diabetic patients. *Diabetes Care* 2004; **27**: 2503.
29. Pham P-CT, Pham P-MT, Pham SV, Miller JM, Pham P-TT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2007; **2**: 366.
30. Mandon B, Siga E, Chabardes D, Firsov D, Roinel N, De Rouffignac C. Insulin stimulates Na^+, Cl^-, Ca^{2+}, and Mg^{2+} transports in TAL of mouse nephron: cross-potentiation with AVP. *Am J Physiol Renal Physiol* 1993; **265**: F361.
31. Guerrero-Romero F, Rodríguez-Morán M. Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. *Eur J Clin Invest* 2011; **41**: 405.
32. Rodriguez-Moran M, Guerrero-Romero F. Insulin secretion is decreased in non-diabetic individuals with hypomagnesaemia. *Diabetes Metab Res Rev* 2011; **27**: 590.
33. Hruby A, Ngwa JS, Renström F, *et al.* Higher magnesium intake is associated with lower fasting glucose and insulin, with no evidence of interaction with select genetic loci, in a meta-analysis of 15 CHARGE consortium studies. *J Nutr* 2013; **143**: 345.
34. Vannini SD, Mazzola BL, Rodoni L, *et al.* Permanently reduced plasma ionized magnesium among renal transplant recipients on cyclosporine. *Transpl Int* 1999; **12**: 244.
35. Ghisdal L, Van Laecke S, Abramowicz MJ, Vanholder R, Abramowicz D. New-onset diabetes after renal transplantation: risk assessment and management. *Diabetes Care* 2012; **35**: 181.
36. Rodrigo E, Fernandez-Fresnedo G, Valero R, *et al.* New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 2006; **17**: S291.
37. Ekstrand AV, Eriksson JG, Gronhagen-Riska C, Ahonen PJ, Groop LC. Insulin resistance and insulin deficiency in the pathogenesis of posttransplantation diabetes in man. *Transplantation* 1992; **53**: 563.
38. Hecking M, Werzowa J, Haidinger M, *et al.* Novel views on new-onset diabetes after transplantation: development, prevention and treatment. *Nephrol Dial Transplant* 2013; **28**: 550.
39. Burroughs TE, Lentine KL, Takemoto SK, *et al.* Influence of early posttransplantation prednisone and calcineurin inhibitor dosages on the incidence of new-onset diabetes. *Clin J Am Soc Nephrol* 2007; **2**: 517.
40. Firoz M, Graber M. Bioavailability of US commercial magnesium preparations. *Magnes Res* 2001; **14**: 257.
41. Nijenhuis T, Hoenderop JGJ, Bindels RJM. Downregulation of Ca^{2+} and Mg^{2+} transport proteins in the kidney explains tacrolimus (FK506)-induced hypercalciuria and hypomagnesemia. *J Am Soc Nephrol* 2004; **15**: 549.
42. Song Y, Hsu Y-H, Niu T, Manson J, Buring J, Liu S. Common genetic variants of the ion channel transient receptor potential membrane melastatin 6 and 7 (TRPM6 and TRPM7), magnesium intake, and risk of type 2 diabetes in women. *BMC Med Genet* 2009; **10**: 4.
43. Nair AV, Hocher B, Verkaart S, *et al.* Loss of insulin-induced activation of TRPM6 magnesium channels results in impaired glucose tolerance during pregnancy. *Proc Natl Acad Sci U S A* 2012; **109**: 11324.
44. Gouadon E, Lecerf F, German-Fattal M. Differential effects of cyclosporin A and tacrolimus on magnesium influx in Caco2 cells. *J Pharm Pharm Sci* 2012; **15**: 389.
45. Yates CJ, Fourlanos S, Colman PG, Cohney SJ. Screening for new-onset diabetes after kidney transplantation: limitations of fasting glucose and advantages of afternoon glucose and glycated hemoglobin. *Transplantation* 2013; **96**: 726.
46. Wojtusciszyn A, Mourad G, Bringer J, Renard E. Continuous glucose monitoring after kidney transplantation in non-diabetic patients: early hyperglycaemia is frequent and may herald post-transplantation diabetes mellitus and graft failure. *Diabetes Med* 2013; **39**: 404.