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Magnesium and infection risk after kidney transplantation: An observational cohort study

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Summary *Objectives:* Magnesium is a co-factor in natural killer and T cell reactivity and may modify the course of infections. We examined the association between baseline serum magnesium concentration and infections requiring admission the first year after kidney transplantation.
Methods: Inclusion of adults transplant recipients between January 2003 and 31 December 2013. Cox piecewise linear regression model estimating the hazard ratio for first admission for infection. Outcomes until one year post-transplantation or up to May 1, 2014.
Results: Overall, 371 of 873 persons were admitted at least once the first year after transplantation (65 events per 100 person-years). The infection-specific cumulative incidence increased with lower serum magnesium concentration ($P = 0.008$). After adjustment for confounders, a low serum magnesium was associated with an increased hazard of infection ($P < 0.0001$ in type 3 test). With 2 mg/dL as the reference value, every 0.1 mg/dL reduction in serum magnesium at baseline below 2 mg/dL (N = 165) increased the hazard ratio by 15% (HR 1.15, 95%CI 1.05 −1.27; $P = 0.002$) while every increase of 0.1 mg/dL in those with a serum magnesium

Abbreviations: CMV, cytomegalovirus; CNI, calcineurin inhibitor; DCD, donation after circulatory death; EBV, Epstein Barr virus; HLA, human leukocyte antigen; NK, natural killer; PCR, polymerase chain reaction; PRA, panel reactive bodies.

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between 2 and 3 mg/dL (N = 661) decreased the hazard ratio by 4% (HR 0.96, 95%CI 0.93—1.00; $P = 0.08$).

Conclusion: A lower baseline serum magnesium concentration is associated with an increased risk of infection after kidney transplantation.

Introduction

One third of kidney transplant recipients are hospitalized for infection during the first year after transplantation.[1] Infection is among the commonest causes of death in transplant recipients with a contemporary death rate of 0.3 per 100 patient years.[2] Aside from the hospitalization itself, diagnostic testing and antibiotics are costly.[3] The increased infection risk is largely determined by *the net state of immune suppression*, encompassing induction, maintenance and anti-rejection immunosuppressive therapy, viral co-infections, and graft dysfunction.[4] Additional risk factors include older age, female sex, diabetes and dialysis vintage before transplantation.[1]

Magnesium is a second messenger in T cell activation and contributes to natural killer (NK) and CD8 positive T cell cytotoxicity.[5,6] In people with the rare hereditary disease called XMEN, the abnormally low free intra-lymphocytic magnesium concentration is associated with the development of recurrent infections including Epstein Barr virus (EBV).[6] Hypomagnesemic rats die earlier than control rats when injected with intravenous *Escherichia coli* endotoxin. In these experiments, there was a dose response with duration of dietary magnesium restriction, while magnesium supplementation improves survival.[7]

Our objective was to examine whether a lower serum magnesium concentration at the time of transplantation is associated with an increased risk of hospitalization for severe infections the first year after transplantation. Our covariate of interest was the single baseline serum concentration of magnesium at the time of admission for transplantation. Serum magnesium concentration reflects 0.3% of the total body magnesium content considering the principal intracellular localization of magnesium, which is mainly stored in bone, muscle, and soft tissue.[8] Intracellular magnesium (10—30 mM) is largely bound to ribosomes and polynucleotides and the biologically active free fraction constitutes only 0.5—5% of the intracellular fraction depending on cell type and applied measurement technique.[8,9] Non-invasive measurement of the ionized intracellular concentration is still not optimized and remains unsuitable for daily clinical practice.[10,11] Despite limitations including the moderate correlation with intracellular concentration, determination of serum magnesium remains so far the standard evaluation in patients.[12]

Materials and methods

We used Kaplan—Meier and Cox proportional hazard analysis to examine the relation between baseline serum magnesium concentration and incident serious infections the first year after transplantation, defined as occurring during the immediate post-transplant period prior to discharge from hospital or necessitating readmission because of infection after initial discharge. Death without infection was analyzed as competing risk to infection. After transplantation, serum magnesium concentration in most kidney transplant recipients decreases rapidly and profoundly especially due to calcineurin inhibitor (CNI)-induced renal magnesium wasting.[13,14] As the intracellular magnesium concentration only decreases after long-lasting magnesium depletion,[9,15] serum magnesium concentration might not adequately reflect intracellular magnesium concentration the first weeks or months after transplantation. The intra-individual variability of serum magnesium has been reported to be below 10% in dialysis patients.[16]

In addition, we analyzed the association of serum magnesium concentration with polymerase chain reaction (PCR) positive cytomegalovirus (CMV) and BK polyoma virus infections, as indicators of the net state of immune-suppression, not necessarily leading to hospital admission.

We included all men and women aged 18 years or older, who received a single or combined graft kidney at Ghent University Hospital between January 1, 2003 and December 31, 2013 and recorded outcomes until one year after transplantation up to May 1, 2014.

People receiving a kidney graft after May 1, 2013 were administratively censored on May 1, 2014.

Procedures

We coded infection into five categories: respiratory, urinary, viral with exclusion of CMV and BK polyoma, gastrointestinal, and miscellaneous.

CMV and BK polyoma infection were analyzed separately and defined by a positive polymerase chain reaction (PCR) of serum (BK polyoma/CMV) or tissue samples (CMV), but not of urine (BK polyoma). PCR did not occur as part of a screening protocol, but was performed only for diagnostic purpose.

We measured the primary explanatory variable serum magnesium concentration at the time of transplantation using a standard colorimetric method with a normal range of 1.7—2.4 mg/dL. Assessment of baseline serum magnesium concentration preceded the initiation of immunosuppressive drugs by a few hours.

We determined the median serum magnesium concentration during the first month after transplantation mainly to determine the evolution of serum magnesium compared to the baseline concentration. We also corrected baseline serum magnesium concentration for albumin with the formula: albumin-corrected magnesium = serum magnesium (mmol/L) + 0.005 (40-albumin) whereby albumin is expressed in g/L.[17] We evaluated covariates as possible confounders for the association between magnesium and infection based on previously published research. We gathered data on covariates from a database which has

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