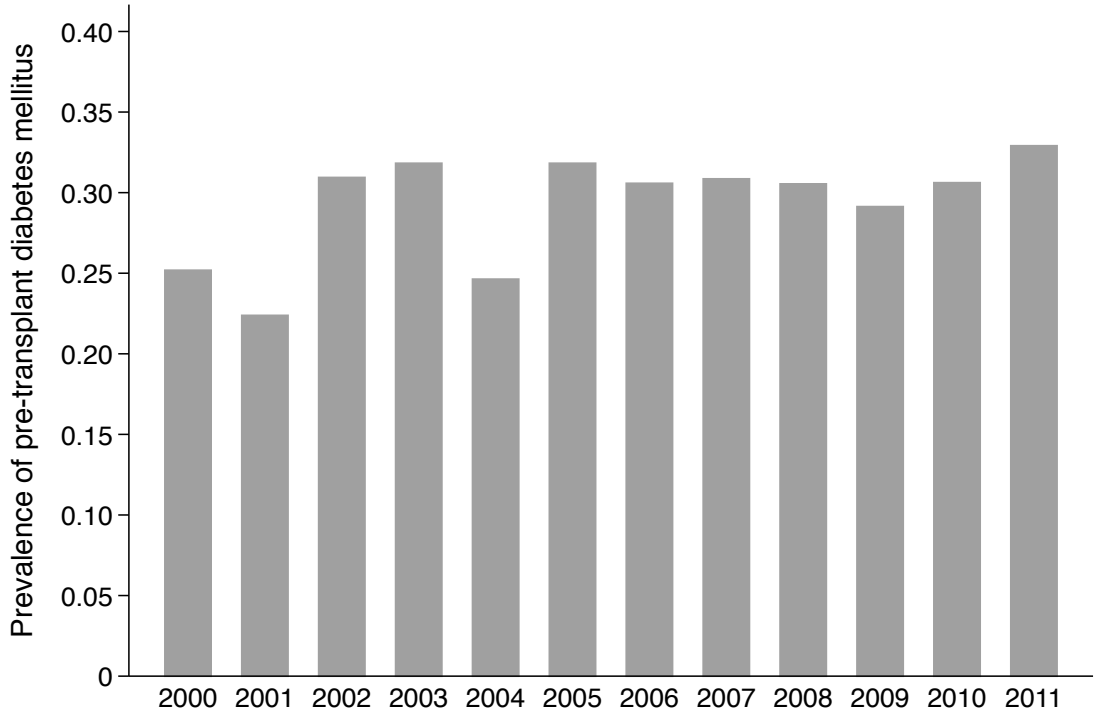
SUPPLEMENTAL APPENDIX

HYPOMAGNESEMIA AND THE RISK OF NEW-ONSET DIABETES MELLITUS AFTER KIDNEY TRANSPLANTATION (JASN-2015-04-0391)

SA-1. Prevalence of Pre-Transplant Diabetes Mellitus as a Function of Transplant Year



SA-2. Subgroup Analyses by Recipient Age, Sex, Race, Body Mass Index, and Calcineurin Inhibitor Type

Variables		Hypomagnesemia at one-month post-transplant (Yes vs. No)		Time-varying hypomagnesemia (Yes vs. No)		Rolling average hypomagnesemia (Yes vs. No)	
		HR (95% C.I.)	*P* value for interaction	HR (95% C.I.)	*P* value for interaction	HR (95% C.I.)	*P* value for interaction
Recipient age (years)	< 48	1.14 (0.59, 2.19)	0.47	1.56 (0.87, 2.77)	0.64	1.51 (0.83, 2.73)	0.49
	≥ 48	1.53 (0.94, 2.50)		1.83 (1.26, 2.67)		1.93 (1.29, 2.91)	
Recipient sex	Male	1.55 (0.92, 2.62)	0.54	1.90 (1.27, 2.83)	0.61	2.31 (1.48, 3.59)	0.09
	Female	1.22 (0.68, 2.18)		1.61 (0.96, 2.68)		1.28 (0.77, 2.15)	
Recipient race	White	1.29 (0.77, 2.16)	0.92	1.48 (1.00, 2.19)	0.25	1.53 (1.01, 2.32)	0.26
	Black	1.38 (0.49, 3.92)		3.18 (1.04, 9.72)		3.92 (1.13, 13.64)	
	Other	1.54 (0.73, 3.23)		2.31 (1.24, 4.30)		2.15 (1.12, 4.13)	
Recipient BMI	< 25	1.23 (0.69, 2.19)	0.53	2.13 (1.25, 3.63)	0.35	2.43 (1.38, 4.30)	0.17
	≥ 25	1.55 (0.90, 2.68)		1.61 (1.07, 2.42)		1.54 (1.00, 2.35)	
CNI type	Tac	1.85 (1.19, 2.88)	0.75	1.60 (0.93, 2.75)	0.41	2.44 (1.46, 4.08)	0.09
	CsA	1.71 (1.07, 2.74)		1.17 (0.65, 2.13)		1.38 (0.85, 2.23)	

SA-3. Cox Proportional Hazards Models for the Risk of New-Onset Diabetes Mellitus After Kidney Transplantation with Sequential Incorporation of Recipient, Donor, and Transplant Covariates

Exposure variables		Models	Origin: one-month post-transplant			
			Baseline magnesium		Time-varying magnesium	
			HR (95% C.I.)	*P* value	HR (95% C.I.)	*P* value
Continuous magnesium	Magnesium (per 0.1 mmol/L decrease)	1	1.26 (1.08, 1.47)	0.003	1.31 (1.13, 1.51)	< 0.001
		2	1.25 (1.07, 1.45)	0.005	1.31 (1.14, 1.51)	< 0.001
		3	1.23 (1.05, 1.44)	0.01	1.30 (1.13, 1.50)	< 0.001
		4	1.24 (1.05, 1.46)	0.01	1.32 (1.14, 1.52)	< 0.001
		5	1.24 (1.05, 1.46)	0.01	1.32 (1.14, 1.52)	< 0.001
	Average magnesium in the first month post-translant	1	1.29 (1.09, 1.52)	0.003	-	-
		2	1.23 (1.04, 1.45)	0.02	-	-
		3	1.20 (1.02, 1.43)	0.03	-	-
		4	1.21 (1.02, 1.45)	0.03	-	-
		5	1.21 (1.02, 1.45)	0.03	-	-
	Rolling average magnesium in the previous 3 months	1	-	-	1.35 (1.14, 1.58)	< 0.001
		2	-	-	1.33 (1.14, 1.56)	< 0.001
		3	-	-	1.32 (1.12, 1.55)	0.001
		4	-	-	1.34 (1.13, 1.57)	0.001
		5	-	-	1.34 (1.13, 1.57)	0.001
Dichotomous magnesium	Hypomagnesemia (Yes vs. No)	1	1.64 (1.12, 2.40)	0.01	1.66 (1.22, 2.26)	0.001
		2	1.63 (1.11, 2.40)	0.01	1.76 (1.28, 2.41)	< 0.001
		3	1.58 (1.07, 2.33)	0.02	1.72 (1.25, 2.37)	0.001
		4	1.58 (1.07, 2.34)	0.02	1.78 (1.29, 2.45)	< 0.001
		5	1.58 (1.07, 2.34)	0.02	1.78 (1.29, 2.45)	< 0.001
	Average magnesium in the first month post-translant	1	1.51 (1.03, 2.22)	0.03	-	-
		2	1.47 (1.00, 2.16)	0.05	-	-
		3	1.41 (0.96, 2.08)	0.08	-	-
		4	1.40 (0.94, 2.07)	0.10	-	-
		5	1.40 (0.94, 2.07)	0.10	-	-
	Rolling average magnesium in the previous 3 months	1	-	-	1.76 (1.26, 2.45)	0.001
		2	-	-	1.83 (1.30, 2.56)	< 0.001
		3	-	-	1.78 (1.27, 2.50)	0.001
		4	-	-	1.83 (1.30, 2.57)	0.001
		5	-	-	1.82 (1.29, 2.57)	0.001

Unit conversion for serum magnesium: 1 mmol/L = 2.43 mg/dL.

Model 1: Post-transplant serum magnesium (or hypomagnesemia)

Model 2: Model 1 + recipient age, recipient sex, recipient race, recipient body mass index, peak PRA, time on dialysis before transplant, recipient eGFR, pre-transplant hypomagnesemia, and cause of end-stage renal disease

Model 3: Model 2 + donor age, donor sex, donor type, donor body mass index, delayed graft function, and donor history of hypertension

Model 4: Model 3 + CNI type at one month, re-graft, and transplant era

Model 5: Model 4 without peak PRA

SA-4. Cox Proportional Hazards Models for the Risk of New-Onset Diabetes Mellitus After Kidney Transplantation Excluding Subjects with Any Hyperglycemia Within the First Month After Kidney Transplantation

Exposure variables		Origin: at one month post-transplant			
		Baseline magnesium		Time-varying magnesium	
		HR (95% C.I.)	P Value	HR (95% C.I.)	P Value
Continuous magnesium	Magnesium (per 0.1 mmol/L decrease)	1.23 (1.04, 1.45)	0.01	1.30 (1.13, 1.51)	< 0.001
	Average magnesium in the first month post-translant	1.20 (1.01, 1.44)	0.04	-	-
	Rolling average of magnesium in the previous 3 months	-	-	1.33 (1.12, 1.57)	< 0.001
Binary magnesium	Hypomg (Yes vs. No)	1.54 (1.04, 2.28)	0.03	1.76 (1.27, 2.45)	< 0.001
	Average magnesium in the first month post-translant	1.38 (0.93, 2.05)	0.11	-	-
	Rolling average of magnesium in the previous 3 months	-	-	1.89 (1.33, 2.68)	< 0.001

Unit conversion: 1 mmol/L = 2.43 mg/dL.

Models were adjusted for recipient age, sex, race, body mass index, peak PRA, time on dialysis, eGFR, pre-transplant hypomagnesemia, cause of end-stage renal disease, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, regraft, type of CNI at baseline, and transplant era.

SA-5. Cox Proportional Hazards Models for the Risk of New-Onset Diabetes Mellitus After Transplantation (NODAT) Using (A) Glucose Readings Alone or (B) Diabetes Treatment to Diagnose NODAT

(A)

Exposure variables		Origin: one-month post-transplant			
		Baseline magnesium		Time-varying magnesium	
		HR (95% C.I.)	*P* value	HR (95% C.I.)	*P* value
Continuous magnesium	Magnesium (per 0.1 mmol/L decrease)	1.26 (1.04, 1.52)	0.02	1.30 (1.10, 1.54)	0.002
	Average magnesium in the first month post-translant	1.22 (1.00, 1.50)	0.05	-	-
	Rolling average magnesium in the previous 3 months	-	-	1.38 (1.15, 1.67)	0.001
	Hypomg (Yes vs. No)	1.68 (1.04, 2.71)	0.03	1.99 (1.36, 2.90)	< 0.001
Binary magnesium	Average magnesium in the first month post-translant	1.33 (0.84, 2.12)	0.23	-	-
	Rolling average magnesium in the previous 3 months	-	-	2.15 (1.43, 3.24)	< 0.001

Unit conversion for serum magnesium: 1 mmol/L = 2.43 mg/dL.

Models were adjusted for recipient age, sex, race, body mass index, peak PRA, time on dialysis, eGFR, pre-transplant hypomagnesemia, cause of end-stage renal disease, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, regraft, type of CNI at baseline, and transplant era.

(B)

Exposure variables		Origin: one-month post-transplant			
		Baseline magnesium		Time-varying magnesium	
		HR (95% C.I.)	*P* value	HR (95% C.I.)	*P* value
Continuous magnesium	Magnesium (per 0.1 mmol/L decrease)	1.40 (0.95, 2.07)	0.09	1.47 (1.07, 2.00)	0.02
	Average magnesium in the first month post-translant	1.49 (0.95, 2.32)	0.08	-	-
	Rolling average magnesium in the previous 3 months	-	-	1.45 (0.97, 2.16)	0.07
	Hypomg (Yes vs. No)	1.50 (0.64, 3.52)	0.36	1.45 (0.71, 2.97)	0.31
Binary magnesium	Average magnesium in the first month post-translant	2.15 (0.90, 5.10)	0.08	-	-
	Rolling average magnesium in the previous 3 months	-	-	1.59 (0.77, 3.30)	0.21

Unit conversion for serum magnesium: 1 mmol/L = 2.43 mg/dL.

Models were adjusted for recipient age, sex, race, body mass index, peak PRA, time on dialysis, eGFR, pre-transplant hypomagnesemia, cause of end-stage renal disease, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, regraft, type of CNI at baseline, and transplant era.

SA-6. Cox Proportional Hazards Model for the Risk of New-Onset Diabetes Mellitus by Time-Fixed (A) and Time-Dependent (B) Serum Magnesium Adjusting for Exposure to Supratherapeutic Calcineurin Inhibitor Levels in the First Month Post-Transplant

(A)

Exposure variables		Origin: one-month post-transplant Baseline magnesium	
		HR (95% C.I.)	*P* value
Continuous magnesium	Magnesium (per 0.1 mmol/L decrease)	1.24 (1.05, 1.46)	0.01
	Average magnesium in the first month post-translant	1.21 (1.02, 1.45)	0.03
Dichotomous magnesium	Hypomagnesemia (Yes vs. No)	1.58 (1.06, 2.34)	0.02
	Average magnesium in the first month post-translant	1.39 (0.93, 2.06)	0.10

Unit conversion for serum magnesium: 1 mmol/L = 2.43 mg/dL.

Models were adjusted for recipient age, sex, race, body mass index, peak PRA, time on dialysis, eGFR, pre-transplant hypomagnesemia, cause of end-stage renal disease, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, regraft, type of CNI at baseline, proportion of CNI levels over therapeutic threshold within first month post-transplant, and transplant era.

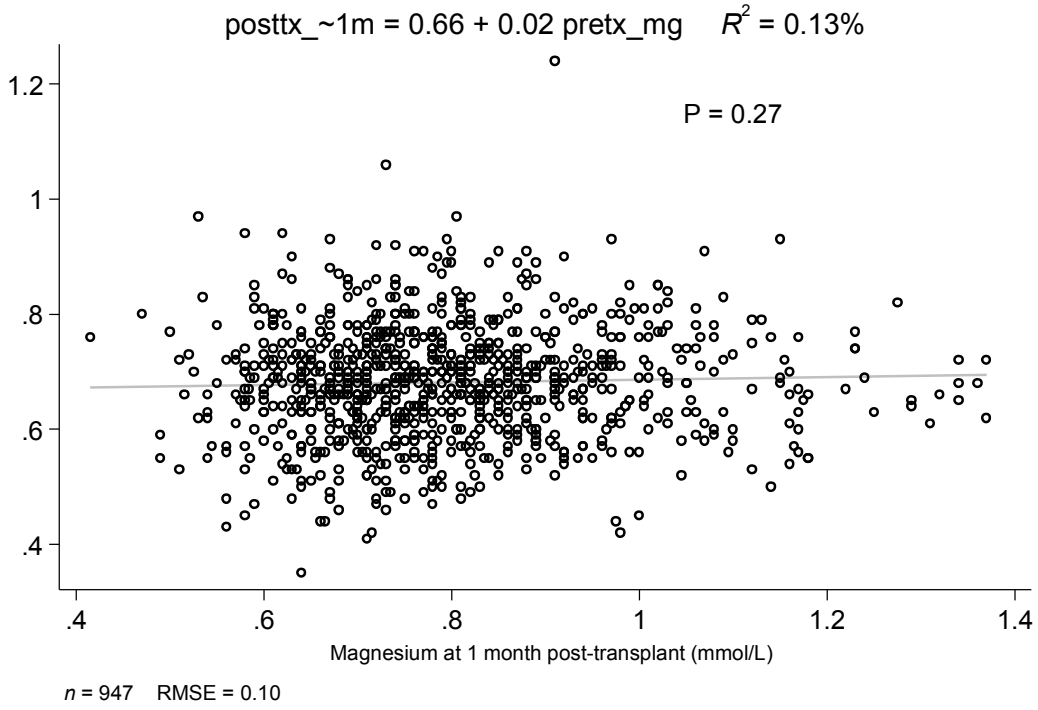
(B)

Exposure variables		Origin: one-month post-transplant Time-varying magnesium	
		HR (95% C.I.)	*P* value
Continuous magnesium	Magnesium (per 0.1 mmol/L decrease)	1.31 (1.14, 1.52)	< 0.001
	Rolling average magnesium in the previous 3 months	1.33 (1.13, 1.57)	0.001
Dichotomous magnesium	Hypomagnesemia (Yes vs. No)	1.77 (1.28, 2.44)	0.001
	Rolling average magnesium in the previous 3 months	1.82 (1.29, 2.56)	0.001

Unit conversion for serum magnesium: 1 mmol/L = 2.43 mg/dL.

Models were adjusted for recipient age, sex, race, body mass index, peak PRA, time on dialysis, eGFR, pre-transplant hypomagnesemia, cause of end-stage renal disease, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, regraft, type of CNI at baseline, proportion of CNI levels over therapeutic threshold within first month post-transplant, and transplant era.

SA-7. Correlation Plots Between Pre-Transplant Serum Magnesium and Serum Magnesium at One-Month Post-Transplant



SA-8. Cox Proportional Hazards Models for the Association Between Pre-Transplant Serum Magnesium and the Risk of New-Onset Diabetes Mellitus After Kidney Transplantation

Exposure variables	Origin: at transplant		Origin: one-month post-transplant	
	HR (95% C.I.)	*P* value	HR (95% C.I.)	*P* value
Pre-transplant magnesium (per 0.1 mmol/L decrease)	0.99 (0.90, 1.09)	0.83	0.99 (0.90, 1.10)	0.910
Hypomagnesemia (Yes vs. No)	0.81 (0.59, 1.12)	0.21	0.83 (0.60, 1.14)	0.249

Unit conversion for serum magnesium: 1 mmol/L = 2.43 mg/dL

Models were adjusted for post-transplant serum magnesium, recipient age, sex, race, body mass index, peak PRA, time on dialysis, eGFR, pre-transplant hypomagnesemia, cause of end-stage renal disease, donor age, sex, history of hypertension, body mass index, donor type, delayed graft function, regraft, type of CNI at baseline, and transplant era

SA-9. Immunosuppression and Patient Follow-Up Protocols at the Toronto General Hospital Kidney Transplant Program During the Study Period

During the study period, all kidney transplant recipients at the Toronto General Hospital received either depleting or non-depleting induction therapy. Maintenance immunosuppression included a calcineurin inhibitor, mycophenolate mofetil, and prednisone. Prior to 2007, the first-line calcineurin inhibitor was cyclosporine microemulsion with C2 level monitoring. Subsequently, tacrolimus with trough level monitoring became the first-line calcineurin inhibitor. After hospital discharge, routine outpatient blood work (including blood glucose and serum magnesium) was performed three times per week for 4 weeks, two times per week for 4 weeks, weekly for 8 weeks, biweekly from months 3 to 6, monthly from months 7 to 12, and then every 2 to 3 months beyond 12 months. Additionally, patients were followed at the Toronto General Hospital Kidney Transplant Clinic weekly for 1 month, biweekly for 2 months, monthly from months 4 to 6, bimonthly from months 7 to 12, every 3 to 4 months from 13 to 24 months, and then every 6 to 12 months beyond 24 months.

SA-10. Data Sources for the Study

Data for this study were retrieved from our in-center research database, the Comprehensive Renal Transplant Research Information System (CoReTRIS), which houses an extensive set of recipient, donor, transplant, laboratory, pathology, treatment, and follow-up data on all patients receiving kidney transplants at the Toronto General Hospital since 1 Jan 2000 [44]. All data housed in CoReTRIS have been abstracted from patient charts (electronic and paper), entered into the database, and audited for completeness and accuracy.