

# Low serum magnesium is associated with faster decline in kidney function: the Dallas Heart Study experience

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## ABSTRACT

Hypomagnesemia associates with inflammation and risk of diabetes and hypertension, which may contribute to kidney function decline. We hypothesized that low serum magnesium (SMg) levels independently associate with a significant decline in estimated glomerular filtration rate (eGFR). We analyzed SMg levels in 2056 participants from the Dallas Heart Study, a longitudinal, population-based, multiethnic, cohort study involving residents of Dallas County, Texas, USA. The primary study outcome was the change in eGFR using multivariable linear regression models adjusted for demographics, anthropometric and biochemical parameters, medications, C reactive protein levels, prevalent hypertension and diabetes. During a median follow-up of 7.0 years (25th, 75th percentile: 6.5, 7.6), the median decrease in eGFR was  $-0.71$  (25th, 75th percentile:  $-2.43$ ,  $+0.68$ ) mL/min/1.73 m<sup>2</sup> per year in the entire cohort. In a fully adjusted model, the lowest SMg quintile ( $\leq 1.9$  mg/dL or  $\leq 0.8$  mM) was associated with a  $-0.50$  mL/min/1.73 m<sup>2</sup> per year drop in eGFR (95% CI  $-0.95$  to  $-0.05$ ;  $p=0.028$ ) compared with the highest SMg quintile ( $\geq 2.3$  mg/dL or  $\geq 1.0$  mM). Every 0.2 mg/dL (0.08 mM) decrease in SMg was associated with an eGFR decline of  $-0.23$  mL/min/1.73 m<sup>2</sup> per year (95% CI  $-0.38$  to  $-0.08$ ;  $p=0.003$ ), a decline that was more pronounced in participants with prevalent diabetes compared with patients without diabetes ( $-0.51$  vs  $-0.18$  mL/min/1.73 m<sup>2</sup> per year, respectively). In conclusion, low SMg was independently associated with eGFR decline. Further studies are needed to determine whether Mg repletion can ameliorate inflammation, lower blood pressure and serum glucose and ultimately prevent or retard kidney function decline.

## INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem with an overall prevalence in the general population of approximately 14%–20%.<sup>1,2</sup> Diabetes and hypertension are major risk factors for the development of CKD and nearly two-thirds of cases of end-stage renal disease (ESRD) in the USA are attributed to these underlying prevalent conditions.<sup>3</sup> The mechanisms governing CKD onset and progression

## Significance of this study

### What is already known about this subject?

- ▶ Both low magnesium (Mg) intake and low serum Mg (SMg) levels are associated with an increased incidence of diabetes and hypertension, two major risk factors for the development of chronic kidney disease (CKD).
- ▶ Low SMg levels independently associate with incidence and progression of CKD after controlling for potential socioeconomic and clinical confounders of kidney function decline.
- ▶ Mg supplementation inhibits the expression of profibrotic and proinflammatory cytokines in endothelial and renal tubular cells in vitro.

### What are the new findings?

- ▶ This is the first study to show that every 0.2 mg/dL (0.08 mM) decrease in SMg was independently associated with an estimated glomerular filtration rate (eGFR) decline of  $-0.23$  mL/min/1.73 m<sup>2</sup> per year (95% CI  $-0.38$  to  $-0.08$ ;  $p=0.003$ ) in a multiethnic cohort with approximately 50% African-Americans.
- ▶ The lowest SMg quintile ( $\leq 1.9$  mg/dL or  $\leq 0.8$  mM) was associated with a  $-0.50$  mL/min/1.73 m<sup>2</sup> per year drop in eGFR (95% CI  $-0.95$  to  $-0.05$ ;  $p=0.028$ ) compared with the highest SMg quintile ( $\geq 2.3$  mg/dL or  $\geq 1.0$  mM).
- ▶ The eGFR decline was more pronounced in participants with prevalent diabetes compared with patients without diabetes ( $-0.51$  vs  $-0.18$  mL/min/1.73 m<sup>2</sup> per year, respectively).

### How might these results change the focus of research or clinical practice?

- ▶ The modulation of SMg levels through Mg supplementation could represent a novel therapeutic target for the prevention of kidney function decline in patients with and without diabetes, who are at high risk of developing CKD.



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## Original research

are only partially understood. Besides early detection by biomarkers of kidney dysfunction or injury, the identification of novel risk factors for incidence or progression of CKD may improve our understanding of the pathogenesis of CKD, allow more accurate risk stratification and lead to the development of new therapies.

Magnesium (Mg) is essential for human health, being the second most abundant intracellular cation after potassium, and is involved in virtually every biologic process in the cell.<sup>4</sup> In the general population, both low Mg intake and low serum Mg (SMg) levels are associated with an increased incidence of diabetes,<sup>5</sup> hypertension,<sup>6</sup> metabolic syndrome,<sup>7</sup> inflammation<sup>8–9</sup> and cardiovascular disease (CVD).<sup>10–13</sup> Hypomagnesemia is postulated to contribute

to the development of diabetes by impairing the insulin receptor downstream signaling and increasing inflammation,<sup>14–16</sup> which further increases insulin resistance. In addition, both in vivo and in vitro studies showed that hypomagnesemia may increase blood pressure and promote CVD by enhancing the production of vasoconstrictor agents and cytokines (eg, endothelin-1 and interleukin-8),<sup>17–18</sup> decreasing the production of endothelial-derived vasodilators (eg, prostacyclin and nitric oxide)<sup>19–20</sup> and increasing oxidative stress.<sup>21</sup> Observational studies have shown that low SMg levels independently associate with incidence and progression of CKD in patients with or without diabetes,<sup>22–26</sup> as well as cardiovascular events and mortality in patients with CKD or undergoing hemodialysis.<sup>27–32</sup> The molecular

**Table 1** Baseline characteristics of study participants at DHS-1 in the entire cohort according to serum magnesium quintiles (mg/dL)

Characteristics	Entire cohort n = 2056	Q1 ≤1.9 n=460	Q2 2.0 n=440	Q3 2.1 n=483	Q4 2.2 n=403	Q5 ≥2.3 n=270	P trend
<b>Demographics</b>							
Age, years	44.2±10.0	42.9±10.3	43.4±9.7	43.9±9.6	45.1±10.2	46.5±9.8	<0.001
Gender (male), %	41.9	26.5	41.6	42.2	51.6	53.7	<0.001
Race, %							<0.001*
Hispanic	14.0	11.3	13.4	15.1	15.1	15.9	
Non-Hispanic black	48.9	65.9	53.0	45.8	37.7	35.6	
Non-Hispanic white	35.1	22.0	33.2	35.2	44.9	45.6	
BMI, kg/m <sup>2</sup>	30.5±7.5	31.8±8.5	30.5±7.3	30.4±7.8	30.0±6.7	29.1±6.0	<0.001
<b>Comorbidities</b>							
Prevalent diabetes, %	9.1	18.5	8.9	5.4	7.0	3.3	<0.001
Prevalent hypertension, %	37.2	42.8	34.8	34.2	34.2	41.1	0.27
SBP, mm Hg	126.8±17.8	127.2±18.0	125.9±17.6	126.1±17.2	127.4±19.2	128.1±17.1	0.45
DBP, mm Hg	79.0±9.9	79.0±9.6	78.9±10.1	78.6±9.4	79.0±10.7	79.9±9.8	0.66
Current smoker, %	25.8	27.5	28.7	25.1	23.6	23.0	0.009*
Current alcohol user, %	71.4	66.7	72.7	72.5	74.4	71.0	0.12*
<b>Medications</b>							
Diuretics, %	9.1	12.2	6.4	8.7	8.7	9.3	0.32
ACEI, %	17.5	22.8	17.0	16.8	15.1	14.1	0.001
ARB, %	9.5	11.1	8.6	8.5	9.4	10.4	0.73
Dietary supplements, %	23.7	18.7	23.0	23.4	28.5	26.7	0.001
<b>Laboratory values</b>							
Magnesium, mg/dL	2.1±0.2	1.8±0.1	2.0±0.0	2.1±0.0	2.2±0.0	2.4±0.1	
eGFR, mL/min/1.73 m <sup>2</sup>	99.9±20.7	105.5±22.4	101.1±20.0	98.7±19.8	97.7±21.0	93.8±17.7	<0.001
ΔeGFR, mL/min/1.73 m <sup>2</sup> per year	−0.7 (−2.4, 0.7)	−1.1 (−3.1, 0.5)	−0.8 (−2.5, 0.7)	−0.6 (−2.2, 0.9)	−0.6 (−2.2, 0.6)	−0.5 (−2.0, 1.0)	<0.001
Urine ACR, mg/g	2.7(1.8, 4.5)	2.9(1.9, 4.9)	2.8 (1.8, 4.9)	2.6 (1.7, 4.6)	2.7(1.8, 4.1)	2.5(1.8, 3.9)	0.009
Albumin, g/dL	4.0±0.3	3.8±0.3	4.0±0.3	4.0±0.3	4.1±0.3	4.1±0.3	<0.001
Glucose, mg/dL	100.5±37.9	113.2±60.6	99.9±37.8	96.0±23.0	96.9±23.1	93.2±16.7	0.08
Calcium, mg/dL	9.2±0.4	9.2±0.4	9.2±0.4	9.2±0.4	9.3±0.3	9.3±0.4	<0.001
Phosphate, mg/dL	3.2±0.6	3.2±0.6	3.2±0.5	3.2±0.5	3.2±0.6	3.2±0.7	0.32
Sodium, mEq/L	137.7±2.4	136.9±2.4	137.6±2.3	137.7±2.3	138.2±2.4	138.3±2.5	<0.001
Potassium, mEq/L	4.3±1.7	4.2±1.6	4.4±1.4	4.3±1.8	4.2±2.1	4.5±1.6	<0.001
Bicarbonate, mEq/L	27.2±2.2	26.8±2.2	27.1±2.1	27.1±2.2	27.5±2.1	27.7±2.3	<0.001
iPTH, pg/mL	37.2(28.3, 49.9)	35.8 (26.1, 49.1)	38.0 (28.7, 48.6)	37.2(28.7, 50.2)	37.1 (29.1, 51.1)	38.2(29.2, 52.1)	0.01
Total cholesterol, mg/dL	180.6±37.8	172.9±38.3	181.4±36.6	181.2±37.1	181.3±36.8	190.6±38.8	<0.001
HDL, mg/dL	50.4±14.6	52.1±15.5	51.1±14.5	50.6±14.5	48.1±13.7	49.5±14.6	0.001
CRP, mg/L	2.7 (1.1, 6.4)	3.2 (1.0, 8.4)	2.7 (1.1, 6.6)	2.7 (1.2, 6.7)	2.2 (0.9, 5.3)	2.5 (1.1, 4.9)	<0.001

\* $\chi^2$  Data are presented as mean±SD, median (25th, 75th percentile) or per cent for categorical variables.

eGFR was calculated according to the MDRD study equation. Microalbuminuria was calculated as ACR. Dietary supplements consisted of any combination or single treatment with Mg, calcium, active vitamin D and/or multivitamins. Conversion factors for units: phosphate in mg/dL to mmol/L,  $\times 0.3229$ ; calcium in mg/dL to mmol/L,  $\times 0.2495$ ; cholesterol in mg/dL to mmol/L,  $\times 0.02586$ ; HDL in mg/dL to mmol/L,  $\times 0.0258$ .

ACEI, ACE inhibitors; ACR, microalbumin/creatinine ratio; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DHS, Dallas Heart Study; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone.

**Table 2** Analysis of the cross-sectional correlations relevant to this study in the entire cohort at DHS-1 (baseline)

	Spearman's correlation coefficients Prob>r under HO: Rho=0		
	ΔeGFR	CRP	SMg
SMg	0.09	−0.08	1.00
	<0.001	<0.001	–
SBP	−0.09	0.24	−0.04
	<0.001	<0.001	0.09
DBP	−0.04	0.23	−0.04
	0.11	<0.001	0.04
SGlu	−0.05	0.23	−0.04
	0.02	<0.001	0.04
ΔeGFR	1.00	−0.03	0.09
	–	0.23	<0.001

Spearman's correlation coefficients (top) and p values (bottom) are reported. CRP, C reactive protein; DBP, diastolic blood pressure; DHS, Dallas Heart Study; DHS-1, DHS phase 1 (2000–2002); ΔeGFR, eGFR at DHS-2 minus eGFR at DHS-1; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SGlu, serum glucose; SMg, serum magnesium.

mechanisms underlying possible deleterious effects of low SMg on renal function are largely unknown.

In this study, we tested the hypothesis that low SMg levels are independently associated with kidney function decline in the Dallas Heart Study (DHS) cohort participants who did not have CKD at baseline. The DHS is a large multi-ethnic population characterized by standardized longitudinal data collection methodology with a comprehensive biochemical phenotype assessment, and the availability of biomarkers of inflammation, blood pressure and glycemic parameters.

MATERIALS AND METHODS

Study population

The DHS is a multiethnic, population-based, cohort study of Dallas County adults aged 30–65 years in which deliberate oversampling of African-Americans was performed. Written informed consent was provided by all participants. Baseline data collection during DHS phase 1 (DHS-1) was conducted in three visits between 2000 and 2002. The design and detailed methods of DHS-1 have been previously described.<sup>33</sup> In DHS phase 2 (DHS-2), participants who already completed DHS-1 underwent follow-up testing in a single visit to UT Southwestern Medical Center between 2007 and 2009. Participants were followed for predefined clinical events and death. For this study, the observation period was 7.0 years (25th, 75th percentile: 6.5, 7.6). We excluded participants with prevalent CKD (n=244) to avoid confounding effects from comorbidity, those with missing SMg measurements at DHS-1 (n=6) and/or with missing serum creatinine levels at either DHS-1 or DHS-2 (n=1382), resulting in a final cohort of 2056 participants. According to the latest Kidney Disease Improving Global Outcomes (KDIGO) guidelines, prevalent CKD at DHS-1 was defined as an microalbumin/creatinine ratio ≥30 mg/g and/or an eGFR <60 mL/min/1.73 m<sup>2</sup>.<sup>3</sup> The number of deaths that occurred during the follow-up period was limited to 241 and baseline SMg levels were clinically comparable in those excluded because of death and all

**Table 3** Linear regression for the decline in eGFR in the entire cohort according to SMg quintiles (mg/dL)

SMg quintiles	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Q1	−0.93	−1.35 to 0.50	<0.001	−0.78	−1.22 to −0.34	<0.001	−0.71	−1.16 to −0.27	0.002	−0.64	−1.08 to −0.20	0.005	−0.50	−0.95 to −0.05	0.028
Q2	−0.41	−0.82 to 0.01	0.06	−0.27	−0.70 to 0.15	0.21	−0.24	−0.67 to 0.18	0.26	−0.21	−0.64 to 0.21	0.33	−0.15	−0.58 to 0.27	0.48
Q3	−0.25	−0.66 to 0.15	0.22	−0.18	0.60 to 0.23	0.39	−0.18	−0.60 to 0.24	0.41	−0.15	−0.56 to 0.27	0.48	−0.12	−0.53 to 0.30	0.58
Q4	−0.27	−0.69 to 0.14	0.2	−0.20	−0.62 to 0.23	0.36	−0.20	−0.63 to 0.22	0.35	−0.17	−0.59 to 0.26	0.44	−0.12	−0.54 to 0.30	0.58
Q5	Ref.	–	–	Ref.	–	–	Ref.	–	–	Ref.	–	–	Ref.	–	–

Model 1 was adjusted for age, gender, race/ethnicity, body mass index at DHS-1.

Model 2 was adjusted for variables in model 1 plus serum phosphorus, calcium, bicarbonate, albumin, intact parathyroid hormone, total cholesterol and high-density lipoprotein at DHS-1.

Model 3 was adjusted for variables in model 2 plus use of diuretics, dietary supplements, ACEI and ARB at DHS-1.

Model 4 was adjusted for variables in model 3 plus prevalent hypertension and CKD at DHS-1.

Model 5 was adjusted for variables in model 4 plus prevalent type 2 diabetes at DHS-1.

β, change in eGFR in reference to the highest quintile of SMg levels. eGFR was calculated according to the MDRD study equation. ΔeGFR was calculated as eGFR at DHS-2 minus eGFR at DHS-1.

ACEI, ACE inhibitors; ARB, angiotensin II receptor blockers; CRP, C reactive protein; DHS, Dallas Heart Study; eGFR, estimated glomerular filtration rate; SMg, serum magnesium.

**Table 4** Baseline characteristics of participants without and with prevalent diabetes at DHS

Characteristics	Without prevalent DM	With prevalent DM	
	(n=1869)	(n=187)	P value
Demographics			
Age, years	43.5±9.9	50.4±8.8	<0.001
Gender (male), %	42.1	40.6	0.71
Race			<0.001
Hispanic	13.9	15.4	
Non-Hispanic black	47.2	65.2	
Non-Hispanic white	37	17.1	
BMI, kg/m <sup>2</sup>	29.9±7.2	35.9±8.2	<0.001
Comorbidities			
Prevalent hypertension (%)	33.7	72.2	<0.001
SBP, mm Hg	125.8±17.6	136.9±17.3	<0.001
DBP, mm Hg	78.8±9.9	81.5±9.1	<0.001
Current smoker, %	25.8	25.7	0.95*
Current alcohol user, %	73.4	51.4	<0.001*
Medications			
Diuretics, %	7.3	26.2	<0.001
ACEI, %	15.2	40.6	<0.001
ARB, %	7.5	30	<0.001
Dietary supplements, %	24.3	17.1	0.03
Laboratory values			
Magnesium, mg/dL	2.08±0.17	1.96±0.20	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	99.4±20.3	104.6±24.2	0.01
ΔeGFR, mL/min/1.73 m <sup>2</sup> per year	−0.6 (−2.3, 0.7)	−2.0 (−3.8, −0.1)	<0.001
Urine ACR, mg/g	2.7 (1.8–4.3)	3.4 (1.9–8.1)	<0.001
Albumin, g/dL	4.0±0.3	3.8±0.3	<0.001
Glucose, mg/dL	91.9±11.7	185.9±80.3	<0.001
Calcium, mg/dL	9.2±0.4	9.3±0.3	0.73
Phosphate, mg/dL	3.2±0.5	3.3±0.6	0.07
Sodium, mEq/L	137.8±2.3	136.5±2.8	<0.001
Potassium, mEq/L	4.3±1.8	4.4±1.3	0.31
Bicarbonate, mEq/L	27.1±2.2	27.6±2.3	0.003
iPTH, pg/mL	37.3 (28.4, 49.6)	34.6 (26.8, 51.2)	0.19
Total cholesterol, mg/dL	180.1±36.8	186.5±45.8	0.17
HDL, mg/dL	50.8±14.8	46.6±12.8	<0.001
CRP, mg/L	2.4 (1.0, 5.7)	6.8 (2.4, 14.3)	<0.001

\* $\chi^2$  Data are presented as mean±SD, median (25th, 75th percentile) or per cent for categorical variables.

eGFR was calculated according to theMDRD study equation. Microalbuminuria was calculated as ACR. Dietary supplements consisted of any combination or single treatment with Mg, calcium, active vitamin D and/or multivitamins. Conversion factors for units: phosphate in mg/dL to mmol/L,  $\times 0.3229$ ; HDL in mg/dL to mmol/L,  $\times 0.02586$ . ACEI, ACE inhibitors; ACR, microalbumin/creatinine ratio; ARB, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; CRP, C reactive protein; DHS, Dallas Heart Study; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone.

survivors at DHS-2 included in the study. Moreover, there were no major differences in medical history, demographics or biomarker data between eligible DHS-1 participants who did and did not complete DHS-2 (follow-up).<sup>34</sup>

### Independent variable/predictor

The exposure of interest was SMg at DHS-1 analyzed according to statistical quintiles or as a continuous variable per 0.2 mg/dL decline. SMg was measured in the UT Southwestern General Clinical Research Center laboratory using a SYNCHRON CX9 ALX system (Beckman Coulter,

Fullerton, California, USA) (normal SMg range: 1.7–2.8 mg/dL or 0.69–1.15 mM).

### Primary study outcome

The primary study outcome was the change in eGFR ( $\Delta$ eGFR) during the observation period calculated as the values at DHS-2 minus the values at DHS-1. eGFR was estimated using the four-variable Modification of Diet in Renal Disease equation (p. 63).<sup>35</sup>

### Variable definitions and measurements

Race/ethnicity and medication usage were self-reported. Prevalent hypertension (n=764) at DHS-1 was defined by need for pharmacological treatment for hypertension, or a systolic blood pressure (SBP) of  $\geq 140$  mm Hg or a diastolic blood pressure (DBP) of  $\geq 90$  mm Hg. Prevalent diabetes (n=187) was defined by pharmacological treatment for diabetes, fasting blood glucose  $\geq 126$  mg/dL (7 mM) or non-fasting blood glucose level  $\geq 200$  mg/dL (11.1 mM). All baseline laboratory parameters were measured from the fasting blood samples obtained at a second in-home visit during DHS-1 with the exception of n=45 samples that were obtained non-fasting. High-sensitive C reactive protein (CRP) measurements were performed using the Roche/Hitachi 912 System, Tina-quant assay (Roche Diagnostics, Indianapolis, Indiana, USA), a latex-enhanced immunoturbidimetric method.<sup>36</sup> Diuretic use included thiazide-like diuretics, loop diuretics, potassium-sparing diuretics and/or aldosterone antagonists. Dietary supplements consisted of any combination or single treatment with Mg, calcium, vitamin D and/or multivitamins.

### Statistical analysis

Baseline characteristics at DHS-1 in the entire cohort stratified by SMg quintiles were analyzed by Jonckheere-Terpstra and Cochran-Armitage for continuous and dichotomous categorical variables, respectively. Data are presented as the mean±SD or median (25th, 75th percentile) for continuous variables and as the number (%) for categorical variables, respectively. To investigate the relationship between SBP, DBP, serum glucose (SGlu),  $\Delta$ eGFR, CRP and SMg levels, Spearman's correlation analysis was performed. Multivariable linear regression models were constructed to examine the association between baseline SMg and the study outcome of  $\Delta$ eGFR. Model 1 was adjusted for age, gender, race/ethnicity and body mass index (BMI). Model 2 was adjusted for variables in model 1 plus serum phosphorus, calcium, bicarbonate, albumin, intact parathyroid hormone, total cholesterol and high-density lipoprotein. Model 3 was adjusted for variables in model 2 plus use of diuretics, dietary supplements, ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB). Model 4 was adjusted for variables in model 3 plus prevalent hypertension and CRP at DHS-1. Model 5 was adjusted for variables in model 4 plus prevalent diabetes at DHS-1. For interaction analyses, a p value of  $<0.10$  was considered to be statistically significant. All other statistical analyses used two-sided  $\alpha$ -values at the significance level of 0.05. Analyses were performed using SAS V9.4 (Cary, North Carolina, USA).



**Table 5** Analysis of the cross-sectional correlations relevant to this study in participants without and with prevalent diabetes at DHS-1

Spearman's correlation coefficients Prob>r under H0: Rho=0						
	Without prevalent DM			With prevalent DM		
	$\Delta$ eGFR	CRP	SMg	$\Delta$ eGFR	CRP	SMg
SMg	0.06	−0.04	1.00	0.25	−0.14	1.00
	0.01	0.06		<0.001	0.06	–
SBP	−0.05	0.21	−0.00	−0.10	0.15	0.03
	0.02	<0.001	0.99	0.16	0.04	0.66
DBP	−0.02	0.21	−0.02	−0.01	0.14	0.06
	0.39	<0.001	0.29	0.90	0.05	0.43
SGlu	0.004	0.15	0.06	−0.22	0.20	−0.37
	0.86	<0.001	0.01	0.003	0.007	<0.001
$\Delta$ eGFR	1.00	0.004	0.06	1.00	−0.05	0.25
	–	0.87	0.01		0.47	<0.001

Spearman's correlation coefficients (top) and p values (bottom) are reported.

CRP, C reactive protein; DBP, diastolic blood pressure; DHS, Dallas Heart Study; DHS-1, DHS phase 1 (2000–2002);  $\Delta$ eGFR, eGFR at DHS-2 minus eGFR at DHS-1; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SGlu, serum glucose; SMg, serum magnesium.

## RESULTS

### Baseline characteristics

Of the 2056 participants without pre-existing CKD who had SMg measurements at DHS-1 (baseline) and serum creatinine measurements available both at DHS-1 and DHS-2 (follow-up visit), 41.9% were male, 48.9% were black, 35.1% were white and 14% were Hispanic (table 1). Mean baseline eGFR $\pm$ SD in the entire cohort was 99.9 $\pm$ 20.7 mL/min/1.73 m<sup>2</sup> at DHS-1 (table 1), and 93.5 $\pm$ 22.7 mL/min/1.73 m<sup>2</sup> at DHS-2 (data not shown). The prevalence of diabetes and hypertension were 9.1% and 37.3%, respectively. SMg was normally distributed with a mean $\pm$ SD value of 2.10 $\pm$ 0.20 mg/dL (0.86 $\pm$ 0.08 mM) in the entire cohort. The comparison of baseline characteristics according to SMg quintiles revealed that patients in the lowest SMg quintile were mostly female (73.5%), included a greater proportion of non-Hispanic black (65.9%), and had a higher prevalence of diabetes (18.5%) and hypertension (42.8%; table 1). Consequently, the use of diuretics, ACEI inhibitors or ARB was significantly higher in the lowest SMg quintile. Lower serum bicarbonate and albumin levels and higher BMI and CRP levels were also observed in the lowest SMg quintile (table 1).

### Univariable association of SMg levels with kidney function decline

During a median follow-up of 7.0 years (25th, 75th percentile: 6.5, 7.6), the median eGFR change ( $\Delta$ eGFR) was −0.71 (25th, 75th percentile: −2.43, +0.68) mL/min/1.73 m<sup>2</sup> per year in the entire cohort. When analyzing  $\Delta$ eGFR across SMg quintiles, the group with the lowest SMg quintile had a greater decline in eGFR compared with the highest SMg quintile during follow-up (−1.08 [25th, 75th percentile: −3.06, 0.46] vs −0.53 [25th, 75th percentile: −1.96, 0.97] mL/min/1.73 m<sup>2</sup> per year, respectively; p<0.001; table 1).

There was a significant positive correlation between SMg levels and  $\Delta$ eGFR (table 2). Moreover, there was an inverse relationship between baseline SMg levels and CRP, DBP and SGlu levels (table 2). We also found that SBP and SGlu levels inversely correlated with  $\Delta$ eGFR, and positively correlated with CRP (table 2).

### Multivariable association of SMg levels and decline in eGFR

The lowest SMg quintile ( $\leq$ 1.9 mg/dL, or  $\leq$ 0.8 mM) was associated with a −0.50 mL/min/1.73 m<sup>2</sup> per year decline in eGFR (95% CI −0.95 to −0.05; p=0.028 for lowest vs highest quintile) after adjustment for the major traditional risk factors for kidney function decline, including demographics, anthropometric and biochemical parameters, medications, CRP and prevalent hypertension and diabetes (table 3). In the same fully adjusted model, every 0.2 mg/dL (0.08 mM) decrease in SMg was associated with an eGFR decline of −0.23 mL/min/1.73 m<sup>2</sup> per year (95% CI −0.38 to −0.08; p=0.003; table 6).

### Sensitivity analysis examining the association of SMg levels and decline in eGFR in study participants with and without prevalent diabetes

Although the association remained significant after the inclusion of prevalent diabetes, a significant interaction between SMg and prevalent diabetes on the association between SMg levels and eGFR decline was observed (p=0.02). Therefore, we stratified the study cohort based on prevalent diabetes at DHS-1. Participants with prevalent diabetes were older, mostly female (59.4%), and a greater proportion was non-Hispanic black (65.2%; table 4). They had higher BMI, SGlu, HDL, CRP; higher prevalence of comorbidities, including prevalent hypertension, and higher use of diuretics, ACEI and ARB. Mean SMg levels were significantly lower in participants with and without diabetes (1.96 $\pm$ 0.20 vs 2.08 $\pm$ 0.17 mg/dL, or 0.81 $\pm$ 0.08 vs 0.86 $\pm$ 0.07 mM, p<0.001, respectively), whereas serum calcium and phosphate were similar. There was a significant positive correlation between SMg levels and  $\Delta$ eGFR in both subgroups, which was stronger in patients with diabetes than in patients without diabetes (r=0.25 vs 0.06, respectively; table 5). CRP was inversely correlated with SMg, and positively correlated with SBP, DBP and SGlu in both subgroups. SGlu was inversely correlated with  $\Delta$ eGFR and SMg only in patients with diabetes.

**Table 6** Linear regression for the decline in eGFR in the entire DHS cohort and in participants without and with prevalent diabetes according to SMg per 0.2 mg/dL decrease

	Model 1			Model 2			Model 3			Model 4			Model 5		
	$\beta$	95% CI	P value	$\beta$	95% CI	P value	$\beta$	95% CI	P value	$\beta$	95% CI	P value	$\beta$	95% CI	P value
Entire cohort	-0.40	0.53 to -0.25	<0.001	-0.34	0.49 to -0.19	<0.001	-0.31	0.47 to -0.16	<0.001	-0.30	-0.44 to -0.14	<0.001	-0.23	0.38 to -0.08	0.003
Without prevalent DM	-0.24	0.39 to -0.09	0.001	-0.22	0.37 to -0.06	0.008	-0.21	0.36 to -0.05	0.01	-0.18	-0.34 to -0.02	0.02	-	-	-
With prevalent DM	-0.78	1.31 to -0.24	0.005	-0.58	1.16 to -0.002	0.05	-0.60	1.20 to -0.01	0.05	-0.51	-1.09 to 0.08	0.09	-	-	-

Model 1 was adjusted for age, gender, race/ethnicity, body mass index at DHS-1.

Model 2 was adjusted for variables in model 1 plus serum phosphorus, calcium, bicarbonate, albumin, intact parathyroid hormone, total cholesterol and high-density lipoprotein at DHS-1.

Model 3 was adjusted for variables in model 2 plus use of diuretics, dietary supplements, ACEI and ARB at DHS-1.

Model 4 was adjusted for variables in model 3 plus prevalent hypertension and CRP at DHS-1.

Model 5 was adjusted for variables in model 4 plus prevalent type 2 diabetes at DHS-1.

$\beta$ , change in eGFR in reference to the highest quintile of SMg levels. eGFR was calculated according to the MDRD study equation.  $\Delta$ eGFR was calculated as eGFR at DHS-2 minus eGFR at DHS-1.

ACEI, ACE inhibitors; ARB, angiotensin II receptor blockers; CRP, C reactive protein; DHS, Dallas Heart Study; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SMg, serum magnesium.

During follow-up, the decline in eGFR in participants with prevalent diabetes was higher than in participants without prevalent diabetes ( $-1.97$  [25th, 75th percentile:  $-3.79$ ,  $-0.13$ ] vs  $-0.64$  [25th, 75th percentile:  $-2.28$ ,  $+0.71$ ] mL/min/1.73 m<sup>2</sup> per year, respectively,  $p<0.001$ ; table 4). Every 0.2 mg/dL (0.08 mM) decrease in SMg was associated with a greater eGFR decline in participants with prevalent diabetes ( $-0.51$  mL/min/1.73 m<sup>2</sup> per year [95% CI  $-1.09$  to  $+0.08$ ;  $p=0.09$ ]) vs those without prevalent diabetes ( $-0.18$  mL/min/1.73 m<sup>2</sup> per year [95% CI  $-0.34$ , to  $-0.02$ ;  $p=0.02$ ]) in fully adjusted models (table 6).

## DISCUSSION

The principal finding of this study is that, in a large multi-ethnic population-based cohort, low SMg levels were associated with a greater decline in eGFR even after adjustment for the major traditional risk factors for kidney function decline, suggesting that low SMg may contribute to the pathogenesis of kidney disease and loss of renal function in a direct independent manner. Specifically, every 0.2 mg/dL (0.08 mM) decrease in SMg was independently associated with an eGFR decline of  $-0.23$  mL/min/1.73 m<sup>2</sup> per year during a median follow-up of 7.0 years in the entire cohort of DHS participants who did not have CKD at baseline. Moreover, the lowest SMg quintile ( $\leq 1.9$  mg/dL or  $\leq 0.8$  mM) was associated with a  $-0.50$  mL/min/1.73 m<sup>2</sup> per year drop in eGFR (95% CI  $-0.95$  to  $-0.05$ ;  $p=0.028$ ) compared with the highest SMg quintile ( $\geq 2.3$  mg/dL or  $\geq 1.0$  mM) despite the lowest SMg quintile had the highest eGFR at baseline. Of note, the variations in SMg being evaluated in this study are within normal values (1.6–2.6 mg/dL). Only 16 out of 460 participants (3.5%) in the lowest quintile had SMg  $\leq 1.6$  mg/dL, and 4 out of 460 participants (0.9%) had SMg  $< 1.6$  mg/dL. Thus, it is unlikely that study participants with SMg below the normal limit may drive the results observed in this study.

This eGFR decline was greater in participants with prevalent diabetes compared with those without prevalent diabetes ( $-0.51$  vs  $-0.18$  mL/min/1.73 m<sup>2</sup> per year, respectively). However, the adjusted association in participants with prevalent diabetes was borderline significant ( $p=0.09$ ) probably due to the small number of subjects ( $n=187$  subjects with prevalent diabetes vs  $n=1869$  subjects without prevalent diabetes), which may have limited statistical power.

Other studies showed the association of SMg with markers of kidney function decline after controlling for diabetes.<sup>22 25 26</sup> Tin *et al* identified a large number of incident CKD cases ( $n=1965$ ) in the Atherosclerosis Risk in Communities (ARIC) study.<sup>22</sup> They found that low SMg associated with incident CKD over a median follow-up of 21 years and after stratification by diabetes and hypertension.<sup>22</sup> Compared with DHS, participants in the ARIC study were older (45–64 years in ARIC vs 30–65 years in DHS) and had longer follow-up (21 years in ARIC vs 7 years in DHS). In a multivariable regression analysis, Pham *et al* showed that in a small cohort of patients with diabetes ( $n=550$ ), low SMg associated with a faster rate of kidney function deterioration, as determined by the slope of serum creatinine over a mean follow-up of  $5.2 \pm 1.9$  years.<sup>25</sup> In an

adjusted analysis, Sakaguchi *et al* found that in a cohort of 455 patients with CKD those with diabetic CKD (n=144) and low SMg levels had a significant higher risk of progression to renal replacement therapy compared with those with high SMg levels over a median follow-up of 1.9 years.<sup>26</sup> In subjects with CKD and without diabetes, there was no significant difference in outcome between the low and high SMg groups.<sup>26</sup>

In our study, the decline in eGFR during follow-up was greater in participants with prevalent diabetes compared with subjects without prevalent diabetes as expected due to the underlying comorbidity. The positive correlation between SMg levels and  $\Delta$ eGFR was stronger in patients with diabetes than in patients without diabetes, which supports the observation of a greater eGFR decline for every 0.2 mg/dL (0.08 mM) decrease in SMg in patients with diabetes than in patients without diabetes, even in a fully adjusted model. Of note, SMg levels were lower in participants with diabetes compared with participants without diabetes, a finding that has been previously shown in this patient population.<sup>37,38</sup> Whether low SMg is causative or a consequence of diabetes cannot be determined from this study, but epidemiological studies support a potential causal role of Mg in the development of diabetes possibly through hyperglycemia and/or inflammation.<sup>39,40</sup>

Overall, the independent association of lower SMg levels with kidney function decline observed in the DHS cohort and in other cohorts may be explained at the molecular level by direct effects of Mg on renal and/or vascular cells.<sup>17,24,41</sup> Sakaguchi *et al* reported that, in a small group of non-diabetic CKD patients, subjects with high serum phosphate had a higher risk of ESRD when they had concomitant low SMg levels at baseline.<sup>24</sup> They demonstrated that Mg suppresses phosphate-induced apoptosis of renal tubular cells in vitro experiments by inhibiting the expression of profibrotic and proinflammatory cytokines, and by inhibiting mitochondria-mediated cell death.<sup>24</sup> In our study, the association of low SMg with eGFR decline was independent of serum phosphate, which was included as a confounding variable in our models. Besides a direct nephrotoxic effect, low extracellular Mg induces production of inflammatory and proatherogenic cytokines in endothelial cells,<sup>17</sup> and promote vascular calcification in both in vitro and in vivo studies.<sup>41–43</sup> Together these multiple molecular pathways can contribute to intrarenal chronic inflammation and impaired hemostasis that have been previously linked to kidney function decline.<sup>44–48</sup>

Some limitations of our study warrant mention. First, the number of patients with prevalent diabetes in our cohort is small. This may have limited statistical power after stratification for prevalent diabetes status. Second, this study is observational and thus cannot provide evidence of a causal relationship between SMg and kidney function decline. Our study has also several strengths. First, we used a large multiethnic population-based cohort with approximately 50% African-Americans, a population at high risk of CKD. Second, our cohort has an adequate median follow-up of 7.0 years for the observation of the outcome of eGFR decline, and is characterized by standardized longitudinal data collection methodology with a comprehensive biochemical phenotype assessment. Third, the availability of biomarkers of inflammation, BP and glycemic parameters

underpinned important observations to construct plausible biological hypotheses that can guide further bench and clinical research.

In summary, we identified that low SMg is independently associated with eGFR decline in a large multiethnic cohort, and that the eGFR decline was greater in subjects with prevalent diabetes. Future studies are required to determine whether the modulation of SMg levels could represent a novel therapeutic target for the prevention of CKD in patients with and without diabetes who are at high risk of developing CKD.

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