Blood Mg^{2+} is more closely associated with hyperglycaemia than with hypertriacylglycerolaemia: the PREVEND study

Peter R. van Dijk¹ · Joëlle C. Schutten² · Elias J. Jeyarajah³ · Jenny E. Kootstra-Ros⁴ · Margery A. Connelly³ · Stephan J. L. Bakker² · Robin P. F. Dullaart¹

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Abbreviation

PREVEND Prevention of Renal and Vascular End-stage Disease

To the Editor: Mg^{2+} affects beta cell function and insulin signalling and the relevance of abnormalities in Mg^{2+} regulation for the development of type 2 diabetes mellitus is being increasingly appreciated [1–3]. Kurstjens et al recently reported that an increase in serum non-esterified fatty acids and triacylglycerols in response to an oral fat challenge is paralleled by reduced Mg^{2+} concentrations, thereby linking triacylglycerol metabolism to Mg^{2+} homeostasis [4]. In 285 individuals with a BMI >27 kg/m², they also observed that circulating Mg^{2+} levels, measured with a routinely available colourimetric assay (Roche/Hitachi, Tokyo, Japan), were inversely correlated with triacylglycerols and with large very-low-density lipoproteins, but not significantly so with plasma glucose [4]. In a cohort of 395 participants with type 2 diabetes, the same group showed inverse correlations of plasma Mg^{2+} with both triacylglycerols and glucose [5].

Uncertainties regarding the associations of Mg^{2+} with glucose and triacylglycerols prompted us to determine the relationships of Mg^{2+} with glucose and triacylglycerols in a large population-based cohort. We used the Roche Modular system (Roche Diagnostics, Mannheim, Germany) to measure Mg^{2+} in lithium heparin plasma and we used a recently developed nuclear magnetic resonance (NMR) spectroscopy-based technique, which uses an excess of ethylenediaminetetraacetic acid (EDTA) to chelate plasma Mg^{2+} and is believed to measure EDTA-bound Mg^{2+} in EDTA-anticoagulated plasma. Measurements were performed in the Prevention of Renal and Vascular End-stage Disease (PREVEND) population, which comprises a large and well-characterised cohort of predominantly white individuals from the north of the Netherlands. The design of the PREVEND cohort has been reported in detail elsewhere [3, 6]. Pregnant women, individuals with type 1 diabetes and those with type 2 diabetes using insulin were excluded. The initial study population of the PREVEND study consisted of 8592 participants who completed the total study screening programme.

For the current post hoc analysis, data from participants who completed the second screening round of PREVEND were collected on demographics, lifestyle factors, anthropometric measurements, medical history and medication use ($n = 6892$). Participants with missing measurements of Mg^{2+} , with non-fasting samples or using statins (which have triacylglycerol-lowering effects) were excluded, leaving 5568 individuals for the present analysis. Information on medication use was combined with information from a pharmacy-dispensing registry, which has complete information on drug usage for >95% of individuals in the PREVEND study. Type 2 diabetes was defined as a fasting serum glucose >7.0 mmol/l, a self-report of a physician diagnosis or the use of glucose-lowering medication. The revised National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III

✉ Peter R. van Dijk
p.r.van.dijk@umcg.nl

¹ Department of Endocrinology, University of Groningen, University Medical Centre Groningen, Hanzeplein 1, 9700 RB, HP AA30, Groningen, the Netherlands

² Department of Nephrology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

³ Laboratory Corporation of America® Holdings (LabCorp), Morrisville, NC, USA

⁴ Department of Laboratory Medicine, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

criteria were applied to categorise individuals with the metabolic syndrome; participants were categorised with the metabolic syndrome when at least three out of the five criteria were present. Glucose, lipids and lipoproteins, as well as estimated glomerular filtration rate, were measured, as previously described [3, 6]. Plasma samples were prepared by centrifugation at 4°C and kept frozen at −80°C until analysis. EDTA-anticoagulated plasma samples were sent frozen to LabCorp (Morrisville, NC, USA) for testing on a Vantera Clinical Analyser (Burlington, NC, USA). As described in more detail elsewhere, the assay system for NMR spectroscopy [7] ensures complete chelation of ionised Mg^{2+} [3]. The within-laboratory imprecision is between 4.6% and 7.1%. The Roche Modular colourimetric assay measures plasma Mg^{2+} levels via xylydyl blue absorbance, which is inversely related to Mg^{2+} concentration [1, 3]. Recently, we found a strong correlation between NMR spectroscopy-measured Mg^{2+} and Mg^{2+} measured by the Roche Modular colourimetric assay ($r = 0.90$) [3]. Colourimetric-based measurements of Mg^{2+} are higher than NMR-based Mg^{2+} measurements, with a systematic bias of 0.07 mmol/l between the assay systems [3]. Between group comparisons were performed using unpaired t

tests. Univariate correlations were sought by Pearson's correlation coefficients. Multivariable linear regression analyses were carried out to determine the independent relationships between variables. Two-sided p values <0.05 were considered significant. The PREVEND study was approved by the Medical Ethics Committee of the UMC Groningen and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

In the whole population (2714 men and 2854 women), aged 53 ± 12 years, plasma NMR-based Mg^{2+} was 0.75 ± 0.05 mmol/l, whereas colourimetric-based Mg^{2+} was 0.82 ± 0.06 mmol/l. NMR- and colourimetric-based Mg^{2+} concentrations were lower in 272 individuals with type 2 diabetes (0.72 ± 0.06 mmol/l and 0.79 ± 0.06 mmol/l, respectively) than in 5296 individuals without diabetes (0.75 ± 0.06 mmol/l and 0.83 ± 0.06 mmol/l, respectively; $p < 0.001$ for both). In the whole population, NMR- and colourimetric-based Mg^{2+} levels were inversely correlated with glucose ($r = -0.155$ and $r = -0.134$, respectively; $p < 0.001$ for both). NMR-based Mg^{2+} concentration was correlated inversely with triacylglycerol levels ($r = -0.073$, $p < 0.001$) but such a relationship was not found for colourimetric-based Mg^{2+} ($r \leq 0.001$,

Table 1 Multivariable linear regression analysis showing the relationship of NMR-measured Mg^{2+} concentration and Roche Modular colourimetric-based Mg^{2+} concentration with components of the metabolic syndrome

Variable	Model 1 ^a		Model 2 ^b	
	β	p value	β	p value
NMR-based Mg^{2+}				
Age	0.106	<0.001	0.069	<0.001
Sex (men/women)	−0.020	0.15	−0.011	0.47
Enlarged waist circumference (yes/no)	−0.065	<0.001	−0.066	<0.001
High blood pressure (yes/no)	−0.035	0.02	−0.010	0.57
High plasma glucose (yes/no)	−0.102	<0.001	−0.052	0.001
High triacylglycerol (yes/no)	−0.014	0.32	−0.011	0.45
Low HDL-cholesterol (yes/no)	−0.070	0.001	−0.062	<0.001
Colourimetric-based Mg^{2+}				
Age	0.080	<0.001	0.068	0.001
Sex (men/ women)	0.060	<0.001	0.066	<0.001
Enlarged waist circumference (yes/no)	−0.055	<0.001	−0.053	<0.001
High blood pressure (yes/no)	−0.027	0.08	0.015	0.40
High plasma glucose (yes/no)	−0.102	<0.001	−0.058	<0.001
High triacylglycerol (yes/no)	0.014	0.33	0.016	0.28
Low HDL-cholesterol (yes/no)	−0.017	0.23	−0.008	0.59

$n = 5568$ PREVEND participants were included in the analysis. Data are standardised regression coefficients (β)

Components of the metabolic syndrome were categorised according to National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria: waist circumference >102 cm for men and >88 cm for women; plasma triacylglycerols ≥ 1.7 mmol/l; HDL-cholesterol <1.0 mmol/l for men and <1.3 mmol/l for women; hypertension (blood pressure $\geq 130/85$ mmHg or the use of antihypertensive medication); hyperglycaemia (fasting glucose ≥ 5.6 mmol/l or the use of glucose-lowering drugs)

^a Model 1 includes age, sex and the five components of the metabolic syndrome

^b Model 2 includes age, sex and the five components of the metabolic syndrome, with additional adjustment for current cigarette smoking, alcohol consumption, previous history of cardiovascular disease, eGFR, urinary albumin excretion, use of antihypertensive medication and use of glucose lowering drugs

$p = 0.99$). In individuals with type 2 diabetes, NMR- and colourimetric-based magnesium concentrations were inversely correlated with glucose levels ($r = -0.181$, $p = 0.003$ and $r = -0.204$, $p = 0.001$, respectively), as well as with triacylglycerols ($r = -0.184$, $p = 0.002$ and $r = -0.194$, $p = 0.001$, respectively). In people without diabetes with a BMI >27 kg/m² ($n = 2000$), NMR- and colourimetric-based Mg²⁺ levels were weakly correlated with glucose levels ($r = -0.040$, $p = 0.074$ and $r = -0.047$, $p = 0.037$, respectively) and not with triacylglycerols ($r = 0.002$, $p = 0.94$ and $r = 0.038$, $p = 0.092$, respectively). In the whole population, multivariable linear regression analysis, including the five individual components of the metabolic syndrome as covariates, demonstrated an independent inverse association of NMR- and colourimetric-based Mg²⁺ level with an elevated glucose level but not with hypertriacylglycerolaemia (Table 1). In alternative analyses with glucose, triacylglycerols and the other components of the metabolic syndrome as continuous variables (cf. Table 1, Model 1 and Model 2) there was also an independent association of both NMR- and colourimetric-based Mg²⁺ level with glucose ($\beta = -0.091$ and $\beta = -0.098$; $p < 0.001$ for both; data not shown). There was a borderline significantly positive association of colourimetric-based Mg²⁺ concentration with triacylglycerol levels ($\beta = 0.030$, $p = 0.049$), whereas there was no association with NMR-based Mg²⁺ levels ($\beta = -0.002$, $p = 0.90$).

From the current findings in a large population-based cohort, we conclude that Mg²⁺ level is inversely associated with fasting glucose, a finding that persisted when taking account of other components of the metabolic syndrome and relevant covariates. Notably, in the whole population, we observed no independent inverse associations of Mg²⁺ with hypertriacylglycerolaemia. The inverse correlation of plasma Mg²⁺ with triacylglycerols appears particularly relevant in individuals with type 2 diabetes. Our current findings would, however, question the overall clinical relevance of the effect of triacylglycerols on circulating Mg²⁺ levels.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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References

1. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A (2000) Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta Int J Clin Chem* 294(1–2):1–26. [https://doi.org/10.1016/S0009-8981\(99\)00258-2](https://doi.org/10.1016/S0009-8981(99)00258-2)
2. Gommers LMM, Hoenderop JGJ, Bindels RJM, de Baaij JHF (2016) Hypomagnesemia in type 2 diabetes: a vicious circle? *Diabetes* 65(1):3–13. <https://doi.org/10.2337/db15-1028>
3. Schutten JC, Gomes-Neto AW, Navis G et al (2019) Lower plasma magnesium, measured by nuclear magnetic resonance spectroscopy, is associated with increased risk of developing type 2 diabetes mellitus in women: results from a Dutch prospective cohort study. *J Clin Med* 8(2):169. <https://doi.org/10.3390/jcm8020169>
4. Kurstjens S, de Baaij JHF, Overmars-Bos C et al (2019) Increased NEFA levels reduce blood Mg²⁺ in hypertriacylglycerolaemic states via direct binding of NEFA to Mg²⁺. *Diabetologia* 62(2):311–321. <https://doi.org/10.1007/s00125-018-4771-3>
5. Kurstjens S, de Baaij JHF, Bouras H, Bindels RJM, Tack CJJ, Hoenderop JGJ (2017) Determinants of hypomagnesemia in patients with type 2 diabetes mellitus. *Eur J Endocrinol* 176(1):11–19. <https://doi.org/10.1530/EJE-16-0517>
6. Gruppen EG, Connelly MA, Vart P, Otvos JD, Bakker SJ, Dullaart RP (2016) GlycA, a novel proinflammatory glycoprotein biomarker, and high-sensitivity C-reactive protein are inversely associated with sodium intake after controlling for adiposity: the Prevention of Renal and Vascular End-Stage Disease study. *Am J Clin Nutr* 104(2):415–422. <https://doi.org/10.3945/ajcn.116.133744>
7. Matyus SP, Braun PJ, Wolak-Dinsmore J et al (2014) NMR measurement of LDL particle number using the Vantara Clinical Analyzer. *Clin Biochem* 47(16–17):203–210. <https://doi.org/10.1016/j.clinbiochem.2014.07.015>

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