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Original article

Drug use is associated with lower plasma magnesium levels in geriatric outpatients; possible clinical relevance

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SUMMARY

Background: Hypomagnesemia has been associated with diabetes, cardiovascular disease, and other disorders. Drug use has been suggested as one of the risk factors for low magnesium (Mg) levels. In the elderly population, prone to polypharmacy and inadequate Mg intake, hypomagnesemia might be relevant. Therefore, we aimed to investigate associations between drug use and plasma Mg.

Methods: Cross-sectional data of 343 Dutch geriatric outpatients were analysed by Cox and linear regression, while adjusting for covariates. Drug groups were coded according to the Anatomical Therapeutic Chemical classification system; use was compared to non-use. Hypomagnesemia was defined as plasma Mg < 0.75 mmol/l and <0.70 mmol/l.

Results: Prevalence of hypomagnesemia was 22.2% (Mg < 0.75 mmol/l) or 12.2% (Mg < 0.70 mmol/l); 67.6% of the patients used ≥5 medications (polypharmacy). The number of different drugs used was inversely linearly associated with Mg level (beta −0.01; p < 0.01). Fully adjusted Cox regression showed significant associations of polypharmacy with hypomagnesemia (Mg < 0.75 mmol/l) (prevalence ratio (PR) 1.81; 95%CI 1.08–3.14), proton pump inhibitors (PR 1.80; 95%CI 1.20–2.72), and metformin (PR 2.34; 95%CI 1.56–3.50). Moreover, stratified analyses pointed towards associations with calcium supplements (PR 2.26; 95%CI 1.20–4.26), insulins (PR 3.88; 95%CI 2.19–6.86), vitamin K antagonists (PR 2.01; 95%CI 1.05–3.85), statins (PR 2.44; 95%CI 1.31–4.56), and bisphosphonates (PR 2.97; 95%CI 1.65–5.36) in patients <80 years; selective beta blockers (PR 2.01; 95%CI 1.19–3.40) if BMI <27.0 kg/m^2; and adrenergic inhalants in male users (PR 3.62; 95%CI 1.73–7.56). Linear regression supported these associations.

Conclusion: As polypharmacy and several medications are associated with hypomagnesemia, Mg merits more attention, particularly in diabetes, cardiovascular disease, and in side-effects of proton pump inhibitors and calcium supplements.

1. Introduction

Magnesium (Mg) is the most abundant intracellular cation and essential for numerous physiologic functions. Inadequate dietary Mg intake and hypomagnesemia have been related to a diversity of clinical complaints related to chronic inflammation such as dyslipoproteinemia, increased insulin resistance, diabetes and diabetes complications, cardiac arythmias, hypertension, coronary artery disease, coronary spasms, asthma, osteoporosis, stroke, and all-cause mortality [1–3]. However, dietary or supplemental Mg is hardly recognized as treatment option next to pharmacological agents.

Mg is not commonly assessed by clinicians, as diagnosis of Mg status is complicated. The Mg loading test as gold standard is too

Abbreviations: ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical classification system; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Mg, magnesium; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; PPIs, proton pump inhibitors; PR, prevalence ratio; SD, standard deviation; SE, standard error; SSRIs, selective serotonin reuptake inhibitors; 25(OH)D, 25-hydroxyvitamin D.

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burdensome for daily practice [4], just as the best alternative to combine blood Mg with measurement of 24-hour Mg excretion in urine and dietary Mg intake [5]. If a clinician is interested in the Mg status of a patient, diagnostic investigation is mostly confined to measurement in blood. Although 0.75 mmol/l is generally accepted as cutoff for hypomagnesemia, also levels between 0.75 and 0.85 mmol/l are associated with complaints of chronic inflammation and trials indicate that in this range and lower, Mg suppletion would be effective [5–7]. At the same time, it should be noted that circulating Mg represents only 1% of total body reservoirs.

An important risk factor for hypomagnesemia is inadequate Mg intake. It is remarkable that although dietary Mg intake of half of the general US population is below the Estimated Average Requirement, Mg inadequacy is not considered a public health problem [9]. Other risk factors for hypomagnesemia are decreased Mg intestinal absorption, intestinal or renal Mg loss, alcohol, stress, exercise, diabetes, and drug use [8,10]. Elaborating on the latter, drug groups known for their Mg-lowering properties are proton pump inhibitors (PPIs) and diuretic, antineoplastic, immunosuppressant, and antimicrobial medications [2,11–17]. However, detailed data on the impact of drug use on Mg levels are scarce, which is especially important for the older adults. Their predisposition to polypharmacy and inadequate Mg intake together with their physical vulnerability, increase the risk of hypomagnesemia and its clinical consequences. Therefore, we conducted a cross-sectional study to explore associations of drug use with hypomagnesemia and plasma Mg levels. Our study population consisted of geriatric outpatients of a large non-academic hospital in The Netherlands.

2. Methods

2.1. Study population

For this study we used data of the 'PanDeMics Study' (Polypharmacy and Deficiencies of Micronutrients), designed by the Gelderse Vallei Hospital in Ede and Wageningen University & Research in The Netherlands to explore associations between drug use and outcomes of nutritional status in geriatric outpatients. Data for this study were collected during the first visit of community living elderly people to one of the outpatient clinics of the Geriatric Department of the hospital, between February 2014 and June 2016. Main indications for geriatric consultation were cognitive problems (60%) and falling (14%).

Initially, all patients of whom Mg level and drug use had been registered were included (N = 358). Subsequently, patients were excluded if they were younger than 55 years (N = 0), had an estimated glomerular filtration rate (eGFR) below 30 ml/min (indicating renal insufficiency) (N = 7), or missing data (N = 8). This resulted in a final study population of 343 individuals. As analyses were conducted with anonymized patient data, no ethical approval was needed according to the Dutch Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen).

2.2. Patient data

At their first visit, patients were thoroughly screened by the geriatricians, physician assistant, and trained nurses according to standardized protocols. The complete results of anamnesis and heteroanamnesis, physical examination, laboratory measurements, and other clinical assessments were reported in the hospital electronic patient file system NeoZis. ICT specialists of the hospital extracted raw patient data from the patient records. Data were additionally checked, coded, and where necessary adjusted and/or completed by the first author (AvO) and a co-author (EV).

2.2.1. Drug use

Drug use was assessed by (hetero)anamnesis and, if available, by the referring physician's medication list and pharmacy dispensing records. In addition, patients were asked to bring all prescribed and over-the-counter drugs as well as their supplements to the clinic. Compliance was checked by asking the patient and/or his (her) companion during consultation. Subsequently, medications and supplements were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [18]. The following variables of drug use were investigated: the number of different ATC-coded substances used (medications); polypharmacy (concomitant use of ≥5 medications); severe polypharmacy (≥10 medications); twenty different ATC-coded drug groups or dietary supplements that were used by at least 10% of the patients: proton pump inhibitors (PPIs), osmotically active laxatives, biguanides (metformin), multivitamins and minerals, vitamin D, calcium, potassium, vitamin K antagonists, platelet aggregation inhibitors, thiazide diuretics, loop diuretics, selective beta-blocking agents, dihydropyridines, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 antagonists, statins, anilides (paracetamol), benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), adrenergic inhalants; and next to these, 3 extra groups that were used by less than 10% of the study population: insulins, bisphosphonates, and Mg-containing ATC-coded substances.

2.2.2. Laboratory measurements

Laboratory tests were performed by the hospital's clinical laboratory. Laboratory markers and Mg were measured in non-fasting routine blood samples collected in the hospital at the day of first visit, without any prior selection. Mg was standardly applied for by one geriatrician and the physician assistant (N = 297). The other physicians were responsible for 46 extra Mg samples. After blood collection, samples were immediately analysed for total Mg in plasma (Dimension Vista 1500, Siemens Healthineers, USA), using a modification of the methylthymol blue complexometric procedure (coefficient of variation 1.7% at 1.44 mmol/L and 3.0% at 0.62 mmol/L). The hospital clinical laboratory's reference range of total Mg in plasma was 0.70–1.10 mmol/l. Assessment of calcium, potassium, sodium, glucose, vitamin D, and eGFR is briefly described in the supplementary material.

2.2.3. Other parameters

Height was measured to the nearest 0.1 cm by a telescopic height rod (Seca 220), weight to the nearest 0.1 kg by a digital floor scale (Seca 770). If a patient was not able to stand straight up, weight was determined using a chair scale (Seca D94-09-033). Before measuring height and weight, patients were asked to take their coat and shoes off. BMI was calculated by dividing weight (kg) by squared height (m^2). Patients aged 65 years or older were screened for malnourishment by the Mini Nutritional Assessment (MNA). A screening score of 12–14 is classified as normal nutritional status, 8–11 indicates risk of malnutrition, and 0–7 malnutrition. Alcohol use was categorized according to the Alcohol Consumption Index according of Garretsen into not or light, moderate, and (very) excessive [19]. The Mini Mental State Examination (MMSE) was used to screen for cognitive impairment. A score of 24–30 indicates normal cognition, 18–23 mild impairment, and 0–17 severe impairment. Education was classified as primary (≤6 years) or higher (>6 years). Smoking as never, ever, or current.

2.3. Statistics

Patient characteristics were determined for the total population and for the patient subgroups being either or not hypomagnesemic and presented as means with standard deviation (SD), medians

with interquartile range (IQR), or frequencies (%). Hypomagnesemia was defined as plasma Mg < 0.75 mmol/l. As there is still no consensus on this definition, we did extra analyses with a second cut-off value of <0.70 mmol/l, used by the hospital laboratory. Characteristics of the subgroups were compared by the independent samples t-test (numerical variables with normal distribution), the non-parametric Mann–Whitney U-test test (numerical variables with non-normal distribution), or the chi-squared test (categorical variables).

Crude mean Mg levels were determined for users and non-users of the drug groups and for yes and no (severe) polypharmacy. Associations between drug use and the dichotomous variable hypomagnesemia were estimated by Cox proportional hazards regression with robust error variance and with prevalence ratio (PR) as outcome measure. Because of the cross-sectional design, an artificial, constant time period was assigned [20]. Reference category for drug use was either non-use of a medication or no polypharmacy. Associations between drug use and the continuous variable plasma Mg were determined by linear regression. The regression model was constructed by stepwise backward regression with total number of medications used as fixed independent variable. Potential covariates were age, sex, BMI, MNA screening score, alcohol use, eGFR, and blood level of 25-hydroxyvitamin D (25(OH)D), albumin, calcium, sodium, potassium, glucose, and use of Mg-containing ATC-coded substances (oral Mg). Included covariates were tested for interaction with each individual drug group. If statistical significance of interaction was <0.02, the interacting covariate was not included in the model and analysis was stratified.

Table 1
Characteristics[a] of total population 343 geriatric outpatients and stratified for hypomagnesemia (Mg < 0.75 mmol/l).

Characteristic	Category	Total study population	Mg < 0.75 mmol/l (N = 76)	Mg ≥ 0.75 mmol/l (N = 267)	P-value[b]
Sex	men	142 (41)	22 (28.9)	120 (44.9)	0.01
	women	201 (59)	54 (77.1)	147 (55.1)	
Age (yr)		79.3 ± 7.5	79.4 ± 7.3	79.3 ± 7.6	0.93
	<75	91 (26.5)	24 (31.6)	67 (25.1)	0.45
	75–79	66 (19.2)	12 (15.8)	54 (20.2)	
	≥80	186 (54.2)	40 (52.6)	146 (54.7)	
BMI (kg/m^2)[c]		26.5 ± 4.4	27.6 ± 5.1	26.2 ± 4.2	0.03
	<21.0	23 (6.7)	7 (9.2)	16 (6.0)	0.13
	21.0–26.9	192 (56.0)	35 (46.1)	157 (58.8)	
	≥27.0	128 (37.3)	34 (44.7)	94 (35.2)	
MNA screening (score)[d]		12 [11–13]	12 [10–13]	12 [11–13]	0.03
	0–11	117 (36.0)	32 (44.4)	85 (33.6)	0.09
	12–14	208 (64.0)	40 (55.6)	168 (66.4)	
Alcohol use[e]	not/light	290 (8–5.8)	64 (85.3)	226 (85.9)	0.39
	moderate	41 (12.1)	8 (10.7)	33 (12.5)	
	excessive	7 (2.1)	3 (4.0)	4 (1.5)	
Smoking status	never	240 (70.8)	54 (72.0)	186 (70.5)	0.96
	former	65 (19.2)	14 (18.7)	51 (19.3)	
	current	34 (10.0)	7 (9.3)	27 (10.2)	
Education level	primary	79 (24.8)	20 (28.6)	59 (23.7)	0.40
	> primary	240 (75.2)	50 (71.4)	190 (76.3)	
MMSE (score)[f]		24 [20–27]	26 [20–28]	24 [19–27]	0.28
	0–17	54 (16.4)	14 (18.9)	40 (15.7)	0.06
	18–23	99 (30.1)	14 (18.9)	85 (33.3)	
	24–30	176 (53.5)	46 (62.2)	130 (51.0)	
Medications (number)[g]		6 [4–9]	9 [5–11]	6 [3–9]	<0.01
Use (≥1)	no	17 (5.0)	1 (1.3)	16 (6.0)	0.10
	yes	326 (95.0)	75 (98.7)	251 (94.0)	
Polypharmacy (≥5)[h]	no	111 (32.4)	15 (19.7)	96 (36.0)	0.01
	yes	232 (67.6)	61 (80.3)	171 (64.0)	
Severe polypharmacy (≥10)	no	259 (75.5)	47 (61.8)	212 (79.4)	<0.01
	yes	84 (24.5)	29 (38.2)	55 (20.6)	
Magnesium (oral)[i]	no	295 (86.0)	69 (90.8)	226 (84.6)	0.17
	yes	48 (14.0)	7 (9.2)	41 (15.4)	
Magnesium (mmol/l)		0.80 ± 0.10	0.66 ± 0.09	0.84 ± 0.06	<0.01
Calcium (mmol/l)		2.37 ± 0.11	2.39 ± 0.1	2.36 ± 0.1	0.05
Potassium (mmol/l)		4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.82
Sodium (mmol/l)		137.8 ± 3.6	137.0 ± 4.0	138.1 ± 3.5	0.02
Glucose, non sober (mmol/l)		5.7 [5.2–6.4]	5.9 [5.4–7.2]	5.6 [5.2–6.2]	0.01
Vitamin D (nmol/l)[j]		70 [43–93]	74 [42–93]	69 [43–93]	0.56
eGFR (ml/min)[k]	30–60	84 (24.5)	16 (21.1)	68 (25.5)	0.43
	≥61	259 (75.5)	60 (78.9)	199 (74.5)	

Missing values: MNA screening n = 18, alcohol use n = 5, smoking status n = 4, education level n = 24, MMSE n = 14.

[a] Values are expressed as a mean ± standard deviation, median [interquartile range], or as number (%).

[b] The difference between means is tested with the independent samples t-test, between medians with the non-parametric Mann Whitney U test, and between frequencies with the chi squared test.

[c] Body mass index.

[d] Mini Nutrition Assessment.

[e] Alcohol consumption index according to Garretsen [19].

[f] Mini Mental State Examination.

[g] ATC-coded substances (Anatomical Therapeutic Chemical classification).

[h] Concomitant use of multiple medications.

[i] Mg-containing ATC-coded substances: ATC 4-level groups A02AA, A06AD, A12CC, and multivitamins and minerals[d].

[j] 25-hydroxyvitamin D (25(OH)D).

[k] Estimated glomerular filtration rate.

Restricted cubic spline regression was used to test the association between the number of different medications used and Mg level for non-linearity and to visualize the association.

Furthermore, we tested for interaction between use of PPIs and loop diuretics, based on a recent publication [21]. Also, we did a subgroup analysis in users and non-users of diabetic medications, including multiple medications in the model, to be able to make a comparison with another recent publication [22]. Extra candidate variables for inclusion were drug groups that were significantly associated with Mg in the analyses before. Finally, as one of the five geriatricians and the physician assistant standardly applied for Mg measurement, we performed a sensitivity analysis including their patients only.

The statistical software used for Cox regression was SAS, version 9.3, for linear regression SPSS version 21.0, and restricted cubic spline regression was performed with 'R' version 3.3.1. Statistical tests were two-tailed and unless mentioned otherwise, $p < 0.05$ was considered statistically significant and $p < 0.10$ borderline significant.

3. Results

3.1. Characteristics

Table 1 illustrates the characteristics of the final study population (N = 343). Prevalence of hypomagnesemia (Mg < 0.75 mmol/l) was 22.2%. In patients with hypomagnesemia, prevalence of polypharmacy was higher compared to patients with normal Mg levels, 80.3% vs. 64.0% ($p = 0.01$).

If a lower cut-off value of Mg < 0.70 mmol/l was used, prevalence of hypomagnesemia was 12.2%. Prevalence of polypharmacy in patients either or not hypomagnesemic was respectively 83.3% and 65.4% ($p = 0.01$), proportion of female patients 71.4% and 56.8% ($p = 0.01$), mean BMI 27.7 ± 5.4 and 26.3 ± 4.3 kg/m^2 ($p = 0.05$), and MNA screening score <12 respectively 46.3% and 34.5% ($p = 0.14$) (Table 1a, supplementary material).

3.2. Drug use and hypomagnesemia

In Table 2 the unadjusted mean Mg levels are given for use/non-use of specific drug groups and for yes/no polypharmacy. Table 3 shows the crude and adjusted associations between variables of drug use and hypomagnesemia (<0.75 mmol/l); associations are expressed as prevalence ratios (PRs). Seventy-six events of hypomagnesemia were observed. In the fully adjusted model, medication, age, sex, BMI, and albumin were included as independent variables. After full adjustment, patients using 5 or more medications (polypharmacy) had a 84% higher probability of hypomagnesemia (PR 1.84; 95%CI 1.08–3.14) compared to patients using fewer medications. Probability of hypomagnesemia was also increased among patients using PPIs (PR 1.80; 95%CI 1.20–2.72), metformin (PR 2.34; 95%CI 1.56–3.50), and platelet aggregation inhibitors (PR 1.52; 95%CI 1.03–2.23), compared to non-users. In patients younger than 80 years, we saw an increased probability of hypomagnesemia if using calcium supplements (PR 2.26; 95%CI 1.20–4.26), insulins (PR 3.88; 95%CI 2.19–6.86), vitamin K antagonists (PR 2.01; 95%CI 1.05–3.85), statins (PR 2.44; 95%CI 1.31–4.56), bisphosphonates (PR 2.97; 95%CI 1.65–5.36), and in severe polypharmacy (PR 2.06; 95%CI 1.17–3.62). In participants with a BMI <27.0 kg/m^2, PRs were increased in users of vitamin K antagonists (PR 2.00; 95%CI 1.11–3.63), and selective beta blockers (PR 2.01; 95%

Table 2
Crude mean Mg levels (mmol/l) by drug use in 343 geriatric outpatients.

Drug use			Mean Mg ± SD[c] (mmol/l)	
ATC[a]	Medication[b]	N (use)	Users	Non-users
Any	Polypharmacy[d]	232	0.79 ± 0.11	0.82 ± 0.08
	Severe polypharmacy[e]	84	0.77 ± 0.11	0.81 ± 0.10
A02BC	Proton pump inhibitors	161	0.78 ± 0.12	0.82 ± 0.09
A06AD	Osmotically acting laxatives	63	0.80 ± 0.10	0.80 ± 0.10
A10A	Insulins	17	0.72 ± 0.13	0.81 ± 0.10
A10BA	Biguanides (metformin)	47	0.71 ± 0.15	0.82 ± 0.09
A11A	Multivitamins and minerals	35	0.82 ± 0.07	0.80 ± 0.11
More[f]	Magnesium[f]	48	0.82 ± 0.08	0.80 ± 0.11
A11CC	Vitamin D	149	0.79 ± 0.11	0.81 ± 0.10
A12AA	Calcium	60	0.79 ± 0.12	0.80 ± 0.10
A12BA	Potassium	37	0.79 ± 0.11	0.80 ± 0.10
B01AA	Vitamin K antagonists	55	0.78 ± 0.12	0.81 ± 0.10
B01AC	Platelet aggregation inhibitors	114	0.79 ± 0.11	0.81 ± 0.10
C03AA	Thiazide diuretics	54	0.79 ± 0.10	0.80 ± 0.10
C03CA	Loop diuretics	39	0.78 ± 0.09	0.81 ± 0.11
C07AB	Selective beta blockers	95	0.78 ± 0.12	0.81 ± 0.10
C08CA	Dihydropyridines	64	0.79 ± 0.10	0.81 ± 0.11
C09AA	ACE inhibitors[g]	74	0.79 ± 0.10	0.81 ± 0.11
C09CA	Angiotensin-2 antagonists	51	0.77 ± 0.09	0.81 ± 0.11
C10AA	Statins	115	0.78 ± 0.12	0.81 ± 0.09
M05BA	Bisphosphonates	22	0.76 ± 0.11	0.81 ± 0.10
N02BE	Anilides (paracetamol)	55	0.80 ± 0.11	0.80 ± 0.10
N05[h]	Benzodiazepines	63	0.80 ± 0.12	0.80 ± 0.10
N06AB	SSRIs[i]	38	0.77 ± 0.12	0.81 ± 0.10
R03A	Adrenergics, inhalants	39	0.79 ± 0.10	0.80 ± 0.11

[a] Anatomical Therapeutic Chemical classification code.
[b] All ATC-coded substances (ATC-coded supplements included).
[c] Standard deviation.
[d] Use of ≥5 medications concomitantly.
[e] Use of ≥10 medications concomitantly.
[f] Mg-containing ATC-coded substances from ATC 4-level groups A02AA, A06AD, A12CC and multivitamins and minerals.
[g] Angiotensin-converting enzyme inhibitors.
[h] ATC codes N05BA, N05CD.
[i] Selective serotonin reuptake inhibitors.

Table 3
Prevalence ratios (PR) of hypomagnesemia (<0.75 mmol/l) by drug use in 343 geriatric outpatients; PR reference value of non-use = 1.00.

Drug use			Crude model			Adjusted model[a]				
ATC[b]	Medication[c]	N (use)	PR	95% CI	P-value	Strata	N	PR	95% CI	P-value
Any	Polypharmacy[d]	232	1.95	1.16–3.27	0.01			1.84	1.08–3.14	0.03
	Severe polypharmacy[e]	84	1.90	1.29–2.82	<0.01	age <80	37	2.06	1.17–3.62	0.01
						age ≥80	47	1.43	0.84–2.44	0.18
A02BC	Proton pump inhibitors	161	1.93	1.21–2.76	<0.01			1.80	1.20–2.72	<0.01
	C03CA[f] no	139	2.21	1.39–3.53	<0.01	C03CA[f] no	37	2.28	1.42–3.65	<0.01
	C03CA[f] yes	22	0.66	0.27–1.61	0.36	C03CA[f] yes	47	0.50	0.18–1.39	0.19
A06AD	Osmotically acting laxatives	63	1.09	0.67–1.79	0.72			1.02	0.64–1.63	0.95
A10A	Insulins	17	2.91	1.85–4.57	<0.01	age <80	10	3.88	2.19–6.86	<0.01
						age ≥80	7	1.35	0.34–5.32	0.67
A10BA	Biguanides (metformin)	47	2.57	1.74–3.79	<0.01			2.34	1.56–3.50	<0.01
A11A	Multivitamins and minerals	35	0.62	0.27–1.43	0.26			0.64	0.28–1.48	0.30
More[g]	Magnesium[g]	48	0.66	0.35–1.24	0.20			0.66	0.34–1.29	0.22
A11CC	Vitamin D	149	1.45	0.97–2.15	0.07			1.37	0.92–2.03	0.12
A12AA	Calcium	60	1.06	0.64–1.77	0.81	age <80	24	2.26	1.20–4.26	0.01
						age ≥80	36	0.46	0.17–1.23	0.12
A12BA	Potassium	37	1.40	0.82–2.40	0.22	age <80	14	1.13	0.55–2.32	0.74
						age ≥80	23	1.48	0.78–2.83	0.23
						BMI <27.0	22	0.42	0.11–1.60	0.20
						BMI ≥27.0	15	2.49	1.52–4.09	<0.01
B01AA	Vitamin K antagonists	55	1.40	0.87–2.24	0.16	age <80	16	2.01	1.05–3.85	0.04
						age ≥80	39	1.39	0.76–2.53	0.29
						BMI <27.0	32	2.00	1.11–3.63	0.02
						BMI ≥27.0	23	0.93	0.40–2.15	0.86
B01AC	Platelet aggregation inhibitors	114	1.46	0.98–2.17	0.06			1.52	1.03–2.23	0.03
C03AA	Thiazide diuretics	54	1.21	0.73–2.00	0.46			1.11	0.69–1.79	0.67
C03CA	Loop diuretics	39	1.61	0.98–2.64	0.06			1.31	0.81–2.13	0.27
	A02BC[h] no	17	3.09	1.55–6.15	<0.01	A02BC[h] no	17	2.96	1.34–6.56	0.01
	A02BC[h] yes	22	0.93	0.45–1.92	0.83	A02BC[h] yes	22	0.71	0.40–1.25	0.24
C07AB	Selective beta blocking agents	95	1.61	1.08–2.40	0.02	BMI <27.0	58	2.01	1.19–3.40	0.01
						BMI ≥27.0	37	1.12	0.64–1.95	0.69
C08CA	Dihydropidines	64	1.48	0.95–2.30	0.08			1.32	0.87–2.01	0.20
C09AA	ACE inhibitors[i]	74	1.68	1.11–2.53	0.01			1.55	1.03–2.34	0.04
C09CA	Angiotensin-2 antagonists	51	1.41	0.87–2.28	0.16			1.26	0.79–2.01	0.34
C10AA	Statins	115	1.61	1.08–2.38	0.02	age <80	63	2.44	1.31–4.56	0.01
						age ≥80	52	0.94	0.53–1.67	0.84
M05BA	Bisphosphonates	22	1.80	1.01–3.24	0.05	age <80	10	2.97	1.65–5.36	<0.01
						age ≥80	12	0.40	0.06–2.75	0.35
N02BE	Anilides (paracetamol)	55	1.29	0.79–2.09	0.36			1.07	0.66–1.74	0.79
N05[j]	Benzodiazepines	63	1.28	0.80–2.04	0.30			1.10	0.70–1.73	0.67
N06AB	SSRIs[k]	38	1.08	0.59–1.98	0.81			0.99	0.54–1.81	0.97
R03A	Adrenergics, inhalants	39	1.66	1.01–2.71	0.05	sex men	20	3.62	1.73–7.56	<0.01
						sex women	19	1.29	0.66–2.49	0.46

[a] Adjusted for age, sex, BMI, and albumin.
[b] Anatomical Therapeutic Chemical classification code.
[c] All ATC -coded substances (ATC-coded supplements included).
[d] Use of ≥5 medications concomitantly.
[e] Use of ≥10 medications concomitantly.
[f] Stratification for use of loop diuretics based on literature [21].
[g] Mg -containing ATC-coded substances: ATC 4-level groups A02AA, A06AD, A12CC, and multivitamins and minerals.
[h] Stratification for use of proton pump inhibitors based on literature [21].
[i] Angiotensin-converting enzyme inhibitors.
[j] N05BA, N05CD.
[k] Selective serotonin reuptake inhibitors.

CI 1.19–3.40). Finally, in male users of adrenergic inhalants, probability of hypomagnesemia was increased (PR 3.62; 95%CI 1.73–7.56).

If hypomagnesemia was defined as Mg < 0.70 mmol/l, the number of hypomagnesemic events was 42. The results of Cox regression in Table 3a (supplementary material) are comparable to the results in Table 3.

3.3. Drug use and Mg level

Spline regression suggested a negative linear relationship between the total number of ATC-coded substances used and plasma Mg concentration, as shown in the graph (Fig. 1). Tables 4a and 4b in the supplementary material give an overview of crude and adjusted linear associations between drug use and Mg level. Regression coefficient beta is equal to the difference in mean Mg level between users and non-users of a medication. Determinants of drug use associated with hypomagnesemia in Cox regression were also associated with Mg level in linear regression.

3.4. Subgroup analyses

Sensitivity analyses, including only the patients of physicians that standardly requested for Mg measurement at the first visit (N = 297), did not show different associations compared to the results of the total study population. In this subgroup prevalence of hypomagnesemia was 22.6% (<0.75 mmol/l) or 11.8% (<0.70 mmol/l), mean Mg level 0.80 ± 0.10 mmol/l.

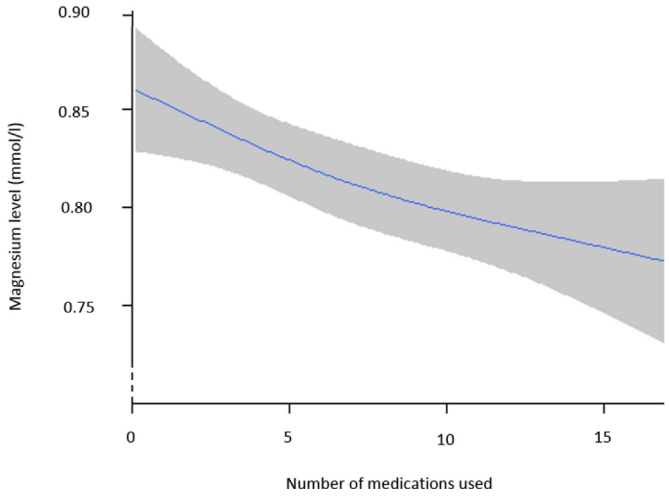

Fig. 1. Association between the number of different medications used and blood magnesium level adjusted for age, gender, and BMI, in 351 Dutch geriatric outpatients.

In the subgroup of patients not using diabetic medications (N = 280), prevalence of hypomagnesemia was 17.9% (<0.75 mmol/l) or 8.6% (<0.70 mmol/l), mean Mg was 0.82 ± 0.08 mmol/l. A linear regression model with multiple medications included non-selective beta blockers, angiotensin-2 antagonists, bisphosphonates, and adrenergic inhalants, which explained 7.7% (R^2 adjusted) of the total variation. In users of diabetic medications (N = 63), prevalence of hypomagnesemia was 41.4% (<0.75 mmol/l) or 28.6% (<0.70 mmol/l); mean Mg was 0.73 ± 0.14 mmol/l. The regression model included sex, eGFR, vitamin K antagonists, statins, and adrenergic inhalants. R^2 adjusted was 33.1%; 15.9% of the total variation in Mg level was explained by drug use.

4. Discussion

In our population of community-living geriatric outpatients, polypharmacy, the number of different drugs used, and several specific drug groups were inversely associated with plasma Mg. Possible explanations of these observed associations, as also illustrated in Fig. 2, are:

I. drug use changes Mg level (causal relationship)
II. indication for drug prescription changes Mg level (confounding by disease)
III. symptoms of hypomagnesemia lead to drug prescription (reverse causation)

Because of the high number of reported outcomes, we will focus on PPIs, calcium supplements, antidiabetics, and drugs used for cardiovascular disease. For a discussion of the other medications we refer to the supplementary material.

The inverse association between *PPIs* and Mg as observed in this study is in line with a meta-analysis of nine studies showing a 43% increased risk of hypomagnesemia in PPI users [14]. Mechanistic studies indicate that PPIs decrease Mg absorption by inhibiting pH-sensitive Mg transport via the transient receptor potential melastins (TRPM) 6 and 7 ion channels in the colon [23]. Interestingly, administration of the prebiotic inulin increased plasma Mg in 11 patients with PPI-induced hypomagnesemia, which might be explained by a decrease of intestinal pH [24]. The increased risk of hypomagnesemia seen in long-term users of PPIs may contribute to the increased risk of myocardial infarction and other cardiovascular problems in users [25–27]. Magnesium controls contractility of heart and vessels by modulating transport of calcium and other cations in cardiovascular tissues [2,6], and Mg deficiency accounted for atherogenesis and other cardiovascular pathologies in various pre-clinical studies [28–30].

The inverse association observed between the antidiabetic drug *metformin* and plasma Mg might be caused by metformin-related diarrhea [31], result from confounding by diabetes [32], or reverse causation might play a role. Hypomagnesemia increases insulin resistance by decreasing Mg-mediated phosphorylation of insulin receptors [32] or by induction of ceramide formation [28,33]. In line with this, Mg suppletion has been shown to improve glucose metabolism and lipid profiles [34–39], and diabetic patients with higher Mg levels displayed fewer diabetic complications [40–42].

Calcium may cause lower Mg levels in *calcium supplement* users <80 years. A plausible mechanism for this interaction is

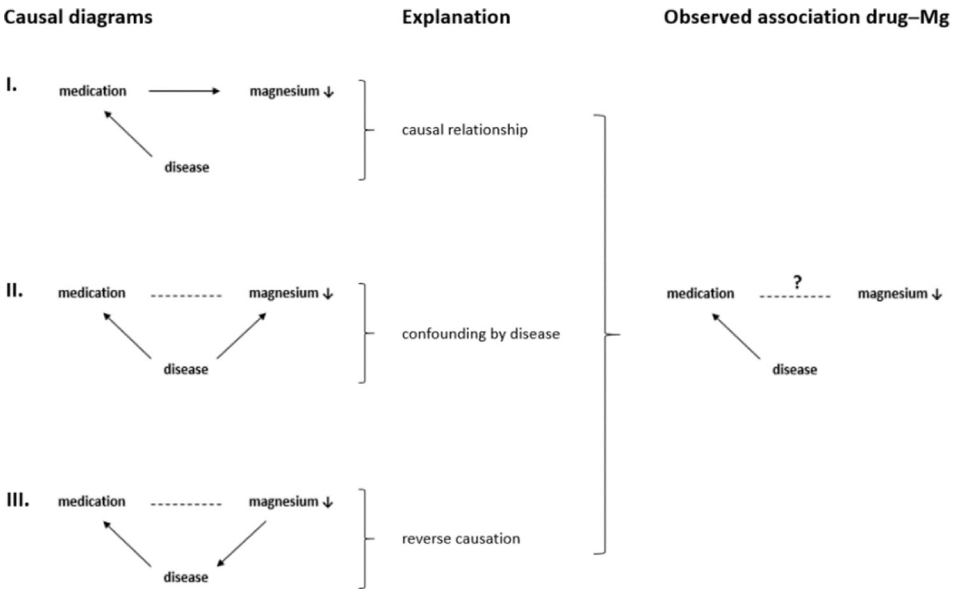

Fig. 2. Explanations of observed associations between drug use and Mg level.

competition between calcium and Mg for reabsorption from the glomerular filtrate. In the thick ascending loop of Henle, 50–70% of Mg is reabsorbed via the epithelial tight junctions. When calcium in the glomerular filtrate increases, calcium sensing receptors stimulate expression of tight junction blocking claudins [2], resulting in decreased reabsorption of both calcium and Mg and increase of their urinary elimination. Preclinical research suggests that expression of kidney claudins decreases with age [43]. Although speculative, this might explain why we did not see an association in 80 plus patients. Interestingly, according to recent publications use of calcium supplements leads to increased risk of myocardial infarction and other cardiovascular events [44–51]. Proposed mechanisms include changes in vascular function, increased arterial calcification, and increased coagulation of red blood cells, all attributed to increased circulating calcium. Notably, to the best of our knowledge, involvement of decreased Mg levels has never been suggested.

Normal-weight users of *selective beta blockers* also showed an increased probability of having low Mg levels. Reverse causation may explain this association, as Mg has a mechanistic role in the indications for prescription of these drugs (*i.e.* hypertension, arrhythmias, angina pectoris, and myocardial infarction) [2,6,52–55]. As such, reverse causation may also explain the increased probability of hypomagnesemia in users of vitamin *K antagonists* and *platelet aggregation inhibitors;* their primary indications include thrombosis risk in cardiac arrhythmias and myocardial infarction. Recent publications have shown Mg deficiency to stimulate ceramide synthesis and downregulate telomere repair, both involved in atherogenesis, hypertension, and cardiac failure [28,30]. At the same time, for *dihydropyridines, ACE inhibitors,* and *angiotensin-2 antagonists,* also prescribed for hypertension, no consistent associations were found.

Major drawback of our study is the cross-sectional design, which does not allow conclusions on causality. Explanations of observed associations are hypomagnesemia as drug side effect (causal relationship), hypomagnesemia as unrecognized cause of the complaints (reverse causation), or hypomagnesemia as consequence of the complaints (confounding by disease). Another limitation is the minimum number of 10 hypomagnesemic 'events' required per predictor for valid outcomes in Cox regression. In analyses with Mg < 0.70 mmol/l as dependent variable, the number of hypomagnesemic 'events' was 42 which limited the maximum number of predictors in the regression models [56,57]. Inadequate dietary Mg intake might also have influenced associations, as MNA scores were lower in hypomagnesemia. Furthermore, Mg assessments were not randomly requested for by all geriatricians. Despite, sensitivity analysis including random measurements only (N = 297) did not lead to different results. Another major limitation is that, we had no structured data on disease diagnoses or data of CRP level or other markers of inflammatory disease to take into account in our analyses. Also, only non-fasted blood samples were available because patients were not required to be sober. Finally, although 24-hour urine Mg, combined with blood measurement and dietary intake would have been a more reliable method to measure individual Mg status, or, ideally, the Mg loading test as gold standard [4,58], we were dependent on plasma Mg. This limited the quality of estimations of Mg status.

Strength of our study is the accurate registration of pharmacologically active substances used. This enabled us to systematically screen for associations with medications and ATC-coded dietary supplements. We make the remark that compliance was only asked for, not validated. The high prevalence of polypharmacy in our study population is another strength, which enabled us to explore a large number of drug groups. Furthermore, application of Cox regression with an artificial constant time factor resulted in prevalence ratios as outcome measures, which are easier to interpret than odds ratios in logistic regression. Finally, analysis by Cox as well as linear regression gives a broader insight in observed associations. We also applied a second cut-off value of <0.70 mmol/l, as there is still no consensus on the clinical definition of hypomagnesemia [6].

In summary, in hypomagnesemia risk of malnourishment was increased and Mg supplements were hardly prescribed. The observed inverse associations between drug use and Mg level could be explained by the drug causing a low Mg level, the underlying disease causing a low Mg level, or by a low Mg level causing the disease (=indication for drug prescription). The latter might be the case for antithrombotics, beta blockers, antidiabetics, adrenergic inhalants, and bisphosphonates as low Mg level can play an etiological role in pathophysiology of arrhythmias, atherosclerosis, stroke, diabetes, asthma, and osteoporosis. In contrast, in users of (again) adrenergic inhalants, PPIs, and calcium supplements, decreased Mg levels can be a drug side effect. Hypomagnesemia as side effect might explain the increased risk of myocardial infarction, stroke, and other cardiovascular problems in users of proton pump inhibitors and calcium supplements, giving new input in the ongoing debate on safety of these agents.

To conclude, our data indicate a potential clinical relevance of adequate Mg intake and measurement of Mg status in elderly people. This holds particularly true for elderly with diabetes, cardio-metabolic disorders, osteoporosis, or using proton pump inhibitors or calcium supplements. An interesting perspective for future research would be to explore the etiological role of Mg in indications for drug prescription in patients with chronic inflammatory disease and in drug side effects. Although it may be too early to speculate about causality, such a role of low Mg status might lead to a reappraisal of pharmacotherapy in chronic disease and more attention for magnesium.

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Conflicts of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

A.C.B. van Orten-Luiten: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing - original draft, Writing - review & editing. **A. Janse:** Conceptualization, Data curation, Methodology, Resources, Supervision, Writing - review & editing. **E. Verspoor:** Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **E.M. Brouwer-Brolsma:** Conceptualization, Methodology, Supervision, Writing - review & editing. **R.F. Witkamp:** Conceptualization, Methodology, Project administration, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.11.018.

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