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Prevalence and risk factors of long-term proton pump inhibitors-associated hypomagnesemia: a cross-sectional study in hospitalized patients

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Abstract

Background Proton pump inhibitors (PPI)-related hypomagnesemia is a potentially life-threatening adverse event first described in 2006. PPIs are widely used in the general population. Information regarding prevalence and risk factors is scarce. We conducted a cross-sectional study in inpatients to evaluate prevalence and associated factors with hypomagnesemia in chronic PPIs users. This is a cross-sectional study of hospitalized adult patients with chronic use of PPIs from January 01, 2012, to December 31, 2018. Chronic use was defined as taking PPIs at least 6 months before hospital admittance. Data were collected from informatized medical records from a University Hospital (Hospital Italiano de Buenos Aires). Hypomagnesemia was defined as a value equal to or less than 1.7 mg/dl. The first hospitalization measurement was retrieved. Thirty-six percent of patients (95% CI 30–43) with chronic PPI use presented hypomagnesemia at admission. Patients with hypomagnesemia presented a higher prevalence of chronic kidney disease (18.6% vs 8%, $p<0.05$), more use of oral magnesium supplementation (20.9% vs 8%, $p<0.05$), use of corticosteroids (32.6% vs 19.3%, $p=0.06$) and calcineurin inhibitors (17.4% vs 6.7%, $p<0.05$). Regarding laboratory findings, they presented lower hematocrit (28.7% vs 32.8%, $p<0.05$), phosphatemia (3 mg/dl vs 3.4 mg/dl, $p<0.05$), natremia (135 mg/dl vs 136 mg/dl, $p<0.05$) and albumin levels (2.8 g/dl vs 3.2 g/dl $p<0.05$) when compared to those who presented normomagnesemia. Hypocalcemia was more frequent among patients with hypomagnesemia (57% vs 38.7%, $p<0.05$). In the multivariate analysis, hyponatremia, decreasing levels of hematocrit (odds ratio, OR 0.93–CI 95% 0.88–0.98) and malignant bone compromise (OR 2.83–CI 95% 1.04–7.7) were associated with hypomagnesemia. Adult patients with long-term use of PPIs have a high prevalence of hypomagnesemia. Increasing age, female sex, concomitant use of drugs that impair tubular function and chronic kidney disease may enhance this phenomenon. Anemia, hyponatremia and malignant bone compromise were associated factors with PPIs-related hypomagnesemia.

Keywords Hypomagnesemia · Proton pump inhibitor use · Drug safety

Abbreviations

ATC	Anatomical therapeutic chemical
CI	Confidence intervals
CKD	Chronic kidney disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HIMSS	Healthcare Information and Management Systems Society
IQR	Interquartile range
OR	Odds ratio
PPI	Proton pump inhibitor
SD	Standard deviation
TRPM6/7	Transient receptor potential melastatin type 6 and 7 channels

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Introduction

Proton pump inhibitors (PPI)-related hypomagnesemia is a potentially life-threatening adverse event that was first described in 2006 in relation to two patients that developed severe magnesium deficiency while on chronic PPI use [1]. Overtime approximately 45 case reports were published [2] leading to the US Food and Drug Administration (FDA) issuing a safety communication in 2011 warning about hypomagnesemia when PPIs are consumed during prolonged periods of time [3, 4]. A recent meta-analysis of 15 studies described that PPIs users exhibited roughly 40% higher risk of developing hypomagnesemia compared with non-PPIs users [5]. Furthermore, in a 2018 study, long-term treatment by PPI was seen as the most frequent potential iatrogenic cause of extreme hypomagnesemia referred to as a value of blood magnesium lower than 0.3 mmol/L (0.73 mg/dl) [6]. Several PPIs have been associated with hypomagnesemia, and it is considered a class effect [2].

PPIs are widely used by the general population for treating conditions related to augmented gastric acid production over histamine-2 receptor antagonists [7]. Its extensive use comes from sales as an over-the-counter drug and from medical prescription. In Argentina, between January and August 2019, 12.662.024 units were sold as an over-the-counter medicine and 4.007.315 units were sold as prescribed drugs by physicians becoming the most prescribed drug in that period of time [8].

Magnesium is the second most abundant intracellular ion, and its regulation is determined by intake and renal excretion [9]. It is theorized that PPIs cause hypomagnesemia by lowering the absorption of magnesium at the gastrointestinal wall [10]. By increasing the luminal pH, the affinity for the magnesium transient receptor potential melastatin type 6 and 7 channels (TRPM6/TRPM7) is reduced [11]. It has been observed that the deficiency is increased with the complementary intake of diuretics, malabsorptive disorders and a low magnesium diet [12]. Clinical manifestations of hypomagnesemia may vary from paresthesias and muscular weakness to arrhythmias and seizures [13, 14] that may lead to death.

Observational studies were published that evaluate the association between hypomagnesemia and PPIs in different healthcare settings [15–17] with variable and scarce findings regarding associated factors and prevalence which to this day is not clearly established [18, 19]. We conducted a cross-sectional study in inpatients to evaluate prevalence and associated factors with hypomagnesemia in chronic PPIs users.

Methods:

Data source and study population

We performed a cross-sectional study based on electronic medical records of all consecutive adult patients admitted at Hospital Italiano de Buenos Aires from January 01, 2012, to December 31, 2018. The Hospital Italiano de Buenos Aires is a third-level teaching university hospital accredited and certified by the Joint Commission International. Patient information was retrieved from electronic medical charts that collect comprehensive clinical, demographic and laboratory data using ITALICA software. ITALICA is a computerized medical record from the Hospital Italiano de Buenos Aires certified by the Healthcare Information and Management Systems Society (HIMSS) Electronic Medical Record Adoption Model (EMRAM) with the highest Stage 7 status.

Patients aged 18 or older with chronic use of PPI and at least one serum magnesium level dosage during hospital admission were eligible for the present study. Patients with previous diagnosis of chronic kidney disease (CKD) defined as glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2 of at least 3 months duration with concomitant creatinine level > 2 mg/dl were excluded since among these patients tubular function may be severely impaired leading to hypomagnesemia due to renal excretion.

The present study was approved by the local ethics review board (protocol 3920) and was conducted according to the amended declaration of Helsinki.

Measures

PPIs

Chronic PPI intake was defined as PPIs use at least 6 months before hospital admittance. Chronic use of PPIs was captured from ambulatory purchases 6 months prior to hospital admission. Further, PPIs prescription was manually corroborated by reviewing electronic medical charts.

Serum magnesium levels

Study population was categorized into two groups: patients with hypomagnesemia and patients with normomagnesemia. Hypomagnesemia was defined as a blood magnesium value equal or lower than 1.7 mg/dl. Magnesium values higher than 1.7 mg/dl were defined as normomagnesemia. Patients' first magnesium-level measurement during their first hospitalization during the study period was considered, and additional hospitalizations were disregarded for the present study. For patients with multiple measurements during

hospital admission, only the first one was considered. For patients admitted to intensive or intermediate care units, only those with magnesium dosages taken from the general ward were included.

Other covariates

Patients' characteristics such as demographic variables, comorbidities and regular medication were retrieved. Data regarding concomitant drug use of furosemide, spironolactone, eplerenone, hydrochlorothiazide, nonsteroidal anti-inflammatory drugs, corticosteroids, magnesium compounds, laxatives, immunosuppressants such as cyclosporine and tacrolimus, lithium, digoxin, cisplatin, pentamidine, amphotericin B and aminoglycoside were retrieved from pharmacy records and electronic medical charts using anatomical therapeutic and chemical (ATC) classification codes. Inhospital factors and laboratory results were also retrieved. If more specific laboratory data were not available during patient's hospitalization (e.g., human thyrotropin), the closest result to the magnesium value was retrieved including outpatient results. Bone compromise was defined as bone compromise by primary bone tumors, oncohematologic disease or metastases at the time of admittance. Hypocalcemia was defined as a corrected serum total calcium concentration below 8 mg/dl. Inhospital factors were defined as new events during hospitalization, including symptoms or newly administered drugs. We also captured admission to intensive care units and all-cause mortality during hospitalization.

Statistical methods

Quantitative variables were described according to distribution with their mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were summarized using proportions. Prevalence of hypomagnesemia was calculated as a proportion with its confidence interval. Categorical variables were compared between patients with and without hypomagnesemia using Chi-square or Fisher's exact test and quantitative variables with *T* test or Mann–Whitney test. We conducted univariate analysis for prespecified covariates, including age, sex, sodium serum levels, hemoglobin levels, malignant bone compromise, use of amphotericin, aminoglycosides, diuretics (each considered individually), lithium, calcineurin inhibitors, pentamidine, cisplatin, corticosteroids and nonsteroidal anti-inflammatory drugs. In addition, we fitted a multiple logistic regression model in order to identify potential PPI-induced hypomagnesemia independently associated factors. Variables were introduced into the model based primarily on clinical subject matter knowledge and a significant association in the aforementioned univariate analysis. Crude and adjusted coefficients were expressed with their corresponding confidence interval. All analyses were performed using STATA v13.0, and a threshold of 0.05 was set to define statistical significance.

Results

Two hundred and fifty-nine patients met the inclusion criteria. Twenty-three patients were excluded for chronic kidney disease and creatinine level > 2 mg/dl. Two hundred and thirty-six patients were included in the final analysis (see Fig. 1).

Overall, 86 (36%, 95% CI 30–43) patients presented hypomagnesemia and 150 patients had normal blood magnesium levels. The median time between admission and the magnesium dosage was 1 day (IQR 0–2). Patient's characteristics, comorbidities and hospital stay characteristics are summarized in Table 1. The median age was 73.5 (IQR 58–85) years old with a higher proportion of women (59.3%). Hypertension was the most frequent comorbidity, followed by osteoporosis, diabetes and malignant disease with bone involvement. Of note, 16.1% of patients were admitted to critical care units and 16.5% of patients died during hospitalization.

Patients with hypomagnesemia had a higher prevalence of chronic kidney disease (18.6% vs 8%, $p < 0.05$) and bone compromise (13.9% vs 6%, $p < 0.05$) when compared to patients with normomagnesemia. We found no differences regarding hospital stay, admission to intensive care units or all-cause mortality between groups.

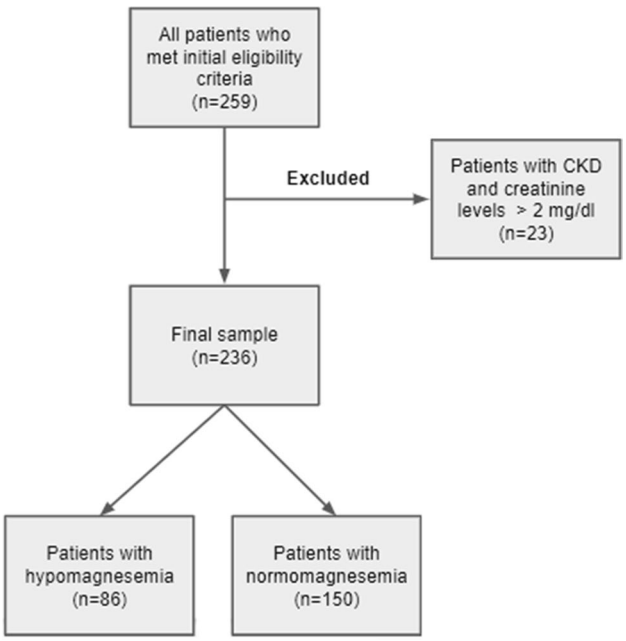

Fig. 1 Flowchart

Table 1 Patients' characteristics, comorbidities and inhospital factors ($n=236$)

Variable	Global ($n=236$)	Hypomagnesemia ($n=86$)	Normomagnesemia ($n=150$)	P value
Women (%)	140 (59.3)	53 (61.6)	87 (58)	0.58
Age	73.5 (58–85)	68.5 (57–84)	76.5 (60–85)	0.13
Hypertension (%)	126 (53.4)	44 (51.2)	82 (54.7)	0.60
Diabetes (%)	39 (16.5)	17 (19.8)	22 (14.7)	0.31
Congestive heart failure (%)	19 (8)	3 (3.5)	16 (10.7)	0.05
Chronic kidney disease (%)	28 (11.9)	16 (18.6)	12 (8)	<0.05
Bone metastases/bone compromise (%)	21 (8.9)	12 (13.9)	9 (6)	<0.05
Smoking (%)	14 (5.9)	3 (3.5)	11 (7.3)	0.23
Alcoholism (%)	3 (1.3)	1 (1.2)	2 (1.3)	0.91
Acute or chronic diarrhea/vomiting (%)	27 (11.4)	11 (12.8)	16 (10.7)	0.62
Malabsorption (%)	4 (1.7)	2 (2.3)	2 (1.3)	0.57
Inflammatory bowel disease (%)	1 (0.4)	0	1 (0.7)	0.45
Refeeding syndrome (%)	0	0	0	–
Osteoporosis (%)	38 (16.1)	14 (16.3)	24 (16)	0.69
Days of hospitalization	8 (4–12)	9 (8–14)	7 (4–11)	0.07
Death (%)	39 (16.5)	12 (13.9)	27 (18)	0.42
Closed unit hospitalization (%)	38 (16.1)	18 (20.9)	20 (13.3)	0.12

Patient's regular medication other than PPIs is described in Table 2. Patients with hypomagnesemia had a higher prevalence of immunosuppressants (17.4% vs 6.7%, $p<0.05$) and oral magnesium supplementation use (20.9% vs 8%, $p<0.05$). Regarding laboratory findings, patients with hypomagnesemia presented lower hematocrit (28.7% vs 32.8%, $p<0.05$), phosphatemia (3 mg/dl vs 3.4 mg/dl, $p<0.05$), natremia (135 mg/dl vs 136 mg/dl, $p<0.05$) and albuminemia (2.8 g/dl vs 3.2 g/dl $p<0.05$) and higher proportion of hypocalcemia (57% vs 38.7%, $p<0.05$) compared to patients with normomagnesemia (Table 3). No differences were found regarding diarrhea, vomiting, refeeding syndrome or use of aminoglycosides.

When evaluating factors associated with hypomagnesemia, after adjusting for potential confounders, multivariate analysis showed that lower sodium and hematocrit levels (odds ratio, OR 0.93–CI95% 0.88–0.98) were factors associated with lower levels of magnesemia and patients with bone compromise were nearly three times more likely to present hypomagnesemia (OR 2.83–CI95%

Table 2 Regular medication other than PPIs and administered drugs during hospital stay ($n=236$)

Variable	Global ($n=236$)	Hypomagnesemia ($n=86$)	Normomagnesemia ($n=150$)	p value
Diuretics (%)	53 (22.5)	19 (22.1)	34 (22.7)	0.92
Furosemide (%)	33 (14)	13 (15.1)	20 (13.3)	0.85
Spironolactone/eplerenone (%)	17 (7.2)	5 (5.8)	12 (8)	0.76
Thiazides (%)	15 (6.36)	5 (5.8)	10 (6.7)	0.89
Nonsteroidal anti-inflammatory drugs (%)	54 (22.9)	21 (24.4)	33 (22)	0.83
Corticosteroids (%)	57 (24.1)	28 (32.6)	29 (19.3)	0.06
Supplementary magnesium (%)	30 (12.7)	18 (20.9)	12 (8)	<0.05
Laxatives (%)	15 (6.4)	7 (8.14)	8 (5.3)	0.69
Immunosuppressants (cyclosporine and tacrolimus) (%)	25 (10.6)	15 (17.4)	10 (6.7)	<0.05
Lithium (%)	0	0	0	–
Digoxin (%)	3 (1.3)	1 (1.2)	3 (2)	0.41
Cisplatin (%)	6 (2.5)	4 (4.6)	2 (1.3)	0.25
Pentamidine (%)	0	0	0	–
Amphotericin B (%)	0	0	0	–
Aminoglycosides (%)	2 (0.8)	2 (2.33)	0	0.17

Table 3 Laboratory measurements ($n=236$)

Variable	Global ($n=236$)	Hypomagnesemia ($n=86$)	Normomagnesemia ($n=150$)	p value
Magnesemia (mg/dl)	1.9 (1.6–2.1)	1.5 (1.4–1.7)	2 (1.9–2.2)	< 0.05
Hematocrit (%)	31.2 (27.2–35.9)	28.7 (26.1–33.2)	32.8 (28.3–37.6)	< 0.05
Blood glucose (mg/dl)	108 (94–134)	105.5 (93–134)	111.5 (94.5–134)	0.63
Phosphate (mg/dl)	3.2 (2.7–3.8)	3 (2.5–3.7)	3.4 (2.8–3.9)	< 0.05
Calcium (mg/dl)	8.5 (8–9)	8.2 (7.8–8.9)	8.6 (8.2–9)	< 0.05
Hypocalcemia (%)	107 (45.3)	49 (57)	58 (38.7)	< 0.05
Ionized calcium (mg/dl)	1.1 (1–1.2)	1.1 (1–1.2)	1.1 (1–0.12)	0.09
Potassium (mg/dl)	4 (3.6–4.4)	3.9 (3.6–4.3)	4.1 (3.7–4.4)	0.06
Sodium (mg/dl)	136 (133–138)	135 (131–137)	136 (134–139)	< 0.05
Chloride (mg/dl)	103 (99–106)	102 (99–107)	104 (100–106)	0.73
Albumin (g/dl)	3.1 (2.7–3.5)	2.8 (2.4–3.4)	3.2 (2.8–3.5)	< 0.05
Parathormone (pg/mL)	82.4 (49.8–142.4)	93.3 (52.6–188.1)	76.7 (48.1–111.9)	0.21
Vitamin D (ng/ml)	17.6 (14–27.8)	16.9 (11.9–27.8)	18 (14.6–27.2)	0.24
Thyrotropin (uUI/mL) (TSH)	1.7 (1–2.6)	1.5 (1.1–2.5)	1.8 (1–2.6)	0.56

Table 4 Associated factors with hypomagnesemia ($n=236$)

Variable	OR	p value	Confidence interval 95%
Hematocrit (%)	0.93	0.01	0.88–0.98
Chronic kidney disease	2.26	0.1	0.86–5.95
Calcium (mg/dl)	1.25	0.49	0.66–2.39
Hypocalcemia (mg/dl)	1.97	0.17	0.75–5.17
Sodium (mg/dl)	0.93	0.01	0.88–0.98
Albumin (g/dl)	0.60	0.09	0.34–1.07
Congestive heart failure	0.40	0.19	0.10–1.61
Bone metastases/bone compromise	2.83	0.041	1.04–7.7
Supplementary magnesium	2.19	0.2	0.67–7.16
Immunosuppressants (ciclosporin and tacrolimus)	1.49	0.55	0.39–5.61

1.04–7.7) than patients without malignant bone compromise (Table 4).

Discussion

Our cross-sectional study is the first to report the prevalence of hypomagnesemia in hospitalized patients with PPIs chronic consumption in nonintensive care units. The results of our study revealed a high prevalence of hypomagnesemia in this population, which is in keeping with previous meta-analysis that evaluated the association between the use of PPI and the risk of developing hypomagnesemia. Across all included studies among patients taking PPIs, the median proportion of patients with hypomagnesemia was 27.1% (range, 11.3–55.2%) [20]. As expected, no difference between PPIs types and hypomagnesemia was observed supporting the class effect concept [2, 21].

In addition, we were able to identify several factors associated with the occurrence of hypomagnesemia. Patients with hypomagnesemia were more frequently women, a finding that contrasts with previous studies where female sex was associated with increased risk of PPI-related adverse events, but no specifically hypomagnesemia [21]. Further, despite that prevalence of CKD was higher in the hypomagnesemia group, it is worth noting that the group of patients with severely impaired (i.e., GFR below 30 m/kg/min) renal disease were excluded. Therefore, this differential prevalence of CKD may in turn reflect a higher burden of comorbidities rather than impaired tubular function [22, 23]. Of note, patients in the hypomagnesemia group presented a higher prevalence of corticosteroids and calcineurin inhibitors use. This finding highlights the importance of serum magnesium dosage among patients with PPI treatment and concomitant drugs that can impair tubular function [24, 25]. In that sense, we could not assess for differences between groups regarding diuretic drug use that has been reported in previous studies [12, 15]. As expected, levels of hypocalcemia were lower in the group of patients with hypomagnesemia, since magnesium deficiency induces an end-organ PTH-resistant state [21, 26, 27]. Finally, in our multivariate analysis, the presence of bone compromise and that of lower hematocrit and natremia levels were associated factors with hypomagnesemia. The role of hyponatremia, anemia and hypomagnesemia in PPIs use was not previously analyzed, and we could not find reasonable biological plausibility for such an effect. Regarding bone compromise, studies in rodents revealed that magnesium deficiency might influence early and late phases of tumorigenesis and enhance

metastases [28, 29] through an increased inflammatory response [30]. Low magnesium promotes oxidative stress and inflammation, which generate genetic instability and increase the risk of mutations [28]. The underpinnings of these associations could not be assessed in the present study, and future research may enlighten the causal pathways involved.

Several limitations must be accounted for when considering our findings. First, since our study design was based on retrospective evaluation of electronic medical records and PPIs are widely sold over the counter, misclassification of patients and missing data cannot be ruled out. Thus, patients with chronic use of PPIs acquired outside the hospital's pharmacy could not be identified and included in our study. Nevertheless, we found complete data for all the included patients regarding the prespecified variables and we performed manual review of patients' records in order to correctly categorize them as chronic users of PPI. Second, since we conducted a cross-sectional study, causal relationships cannot be established. Third, we evaluated patients presenting a hospital admission, where factors that can alter magnesium levels may be magnified and influence the occurrence of hypomagnesemia. However, more than half of patients presented their magnesium measurement before 24 h of hospital admission, lessening the impact of inhospital factors on hypomagnesemia. Finally, since our study only included patients belonging to the hospital's private Health Plan, the findings of the present study may not be generalizable to patients outside this specific population.

Conversely, strengths are worth highlighting regarding our study. First, it is the first study designed to specifically evaluate the prevalence of hypomagnesemia among chronic users of PPIs. Second, our population presented a high prevalence of old and very old patients, a population of interest where the dangers of PPI-associated hypomagnesemia can be magnified resulting from polypharmacy, higher prevalence of comorbidities and increased risk of adverse clinical outcomes [21]

In conclusion, our study shows that adult patients with long-term use of PPIs have a high prevalence of hypomagnesemia. We consider that a magnesium measurement at 6 months of PPIs treatment might identify potentially at-risk patients, especially those with factors such as increasing age, concomitant use of drugs that impair tubular function and chronic kidney disease [21]. Supporting this idea, indefinite prescription of PPIs without a specific indication is becoming a major concern and campaigns recommending evaluation and eventual discontinuation of long-term PPIs prescriptions have gained importance [31, 32]. Further research and analysis of anemia, hyponatremia and malignant bone compromise as risk factors associated with hypomagnesemia and chronic use of proton pump inhibitors might exhibit a novel at-risk population.

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Author contributions DAR: study concept, study design, data analysis and interpretation. Drafting of the manuscript. AF: data interpretation, drafting of the manuscript. CIP: study concept, study design. MAS: data acquisition, data interpretation. MBB: data interpretation, critically reviewed the manuscript. MLPM: study design, data acquisition, data interpretation, critically reviewed the manuscript. All authors read and approved the final version of this manuscript. DAR, MLPM and MBB are guarantors of the present manuscript paper and take responsibility for the integrity of the work as a whole.

Compliance with ethical standards

Conflicts of interest The authors (DAR, AF, CIP, MAS, MBB, MLPM) declare no potential conflict of interest relevant to the content of this manuscript.

Statement of human and animal rights The present study was approved by the ethics committee Comité de Ética y Protocolos de Investigación with protocol number 3920 and was conductedaccording to the amended declaration of Helsinki.

Informed consent In view of the retrospective nature of the study a waiver of consent was acquired from the ethics committee.

Ethics approval The present study was approved by the local ethics review board (protocol 3920) and was conducted according to the amended declaration of Helsinki.

Consent for publication The authors grant the publisher permission to publish the work named herein. All authors read and approved the final version of this manuscript. DAR, MAS, MBB, MLPM are guarantors of the present manuscript paper and take responsibility for the integrity of the work as a whole.

Availability of data and material The data that support the findings of this study are available from the corresponding author, Delfina Ana Recart, upon reasonable request.

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