The prognostic impact of magnesium in acute heart failure is different according to the presence of diabetes mellitus

Catarina Cidade-Rodrigues, MD[a],*, Filipe M. Cunha, MD[a], Catarina Elias, MD[b], Marta Carreira, MD[b], Isaac Barroso, MD[c], Paulo Bettencourt, MD, BSc, MSc, PhD[d,e,f], Patrícia Lourenço, MD, PhD[b,e,f,g]

Abstract

Background: Hypermagnesemia predicts mortality in chronic heart failure (HF); however, in acute HF, magnesium does not seem to be outcome-associated. Diabetes mellitus (DM) frequently associates with altered magnesium status. We hypothesized that DM might influence the prognostic impact of magnesium in acute HF.

Methods: This is a retrospective cohort study of hospitalized patients with acute HF. Patients without data on admission serum magnesium were excluded. Follow-up: 1 year from hospital admission. Primary end point: all-cause mortality. Patients were divided according to median serum magnesium (1.64 mEq/L). The Kaplan-Meier survival method was used to determine survival curves according to magnesium levels. The analysis was stratified according to the presence of DM. A multivariable Cox regression analysis was used to study the prognostic impact of magnesium.

Results: We studied 606 patients. The mean age was 76 ± 12 years, 44.1% were male, 50.7% had DM, and 232 (38.3%) died during follow-up. Median magnesium was 1.64 (1.48–1.79) mEq/L. Patients with magnesium ≥1.64 mEq/L had higher 1-year mortality [141 (46.4%) vs 91 (30.1%), $P < .001$]. After adjustments for age, sex, history of atrial fibrillation, systolic blood pressure, heart rate, ischemic etiology, B-type natriuretic peptide, estimated glomerular filtration rate, alcohol consumption, antihyperglycaemic agents or glycated hemoglobin, admission glycemia, New York Heart Association class IV, and severe left ventricle systolic dysfunction, serum magnesium ≥1.64 mEq/L was associated with higher mortality only in patients with DM: HR 1.89 (95% confidence interval: 1.19–3.00), $P = .007$, and 1.27 (95% confidence interval: 0.83–1.94) and $P = .26$ for non-DM patients. The results were similar if magnesium was analyzed as a continuous variable. Per 0.1 mEq/L increase in magnesium levels, patients with DM had 13% increased risk of 1-year mortality.

Conclusions: Higher magnesium levels were associated with worse prognosis only in HF patients with DM.

Keywords: diabetes mellitus, heart failure, magnesium, prognosis

Introduction

Heart failure (HF) is a common condition associated with elevated morbidity and mortality.[1] Hypomagnesemia is a frequent electrolyte abnormality in patients with HF and has been linked to premature ventricular contractions and potentially life-threatening arrhythmias.[2,3]

Magnesium is the fourth most abundant mineral in the body, and it participates in several biochemical and cellular processes, including enzymatic reactions, ribonucleic acid and protein synthesis, regulation of insulin metabolism, neuromuscular conduction, neurotransmission, and muscle cells contraction, therefore influencing cardiac excitability and vasomotor tone.[4] In addition, magnesium seems to have vasodilatory, anti-inflammatory, anti-atherosclerotic, anti-ischemic, and antiarrhythmic effects.[4]

Higher serum magnesium has been associated with lower risk of incident HF,[5–9] although a causal relationship was not supported by a recent mendelian randomization study.[10] On the contrary, a meta-analysis of patients with established HF published in 2016 found that higher serum magnesium seems to confer a higher mortality risk while hypomagnesemia does not.[11] Few studies have addressed the prognostic impact of magnesium in the acute HF setting, and the reported results are diverging.[12,13] In patients with HF, paradoxical associations have already been described for classic cardiovascular risk factors, such as blood pressure,[14] total cholesterol,[15] and obesity.[16]

Diabetes mellitus (DM) is a known risk factor for HF[17] and determines poorer prognosis in those with the condition.[18] Patients with DM, especially those with poorer glycemic control, may have

[a] Endocrinology Department, Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal, [b] Internal Medicine Department, Centro Hospitalar e Universitário do São João, Porto, Portugal, [c] Clinical Pathology Department, Centro Hospitalar e Universitário do São João, Porto, Portugal, [d] Internal Medicine Department, Hospital CUF, Porto, Portugal, [e] Faculty of Medicine, University of Porto, Porto, Portugal, [f] Cardiovascular R&D Unit (UnIC), Faculty of Medicine, University of Porto, Porto, Portugal, [g] Heart Failure Clinic, Internal Medicine Department, Centro Hospitalar e Universitário do São João, Porto, Portugal

*Corresponding author: Endocrinology Department, Centro Hospitalar do Tâmega e Sousa, Avenida do Hospital Padre Américo 210, 4564-007 Guilhufe, Penafiel, Portugal. E-mail address: catarinacidaderodrigues@gmail.com (Catarina Cidade-Rodrigues).

C. Cidade-Rodrigues and F.M. Cunha contributed equally to the manuscript.

altered magnesium status; this can be due both to urinary losses and to nutritional factors.[19] Furthermore, HF patients with DM seem to be a very particular group within patients with HF, a group in which some of the classical paradoxes do not apply.[20–22] Taken together, it seems plausible that the presence of DM can influence magnesium homeostasis and consequently HF prognosis. To the best of our knowledge, no previous study has focused on the role of serum magnesium in acute HF prognosis according to the presence of DM.

Our hypothesis was that DM might influence the prognostic impact of serum magnesium in patients with acute HF.

Methods

We conducted a retrospective study of a group of patients hospitalized due to acute HF in the internal medicine department of a tertiary care, academic hospital in the North of Portugal, between March 2009 and December 2010, who were part of an acute HF registry which took place in that department. All consecutive patients admitted with the primary diagnosis of acute HF, both de novo or chronic decompensated, were eligible for study inclusion. The HF diagnosis was made according to the then current 2008 European Society of Cardiology guidelines. Patients were excluded if an acute coronary syndrome was the cause underlying decompensation or if the echocardiogram showed no morphologic or physiologic abnormalities. Patients included had an admission and discharge complete physical examination and a venous blood sample drawn. An echocardiogram was performed within the first 72 h after admission. Patients with left ventricular ejection fraction (LVEF) $\geq$50% were considered to have HF with preserved ejection fraction. Severe left ventricular systolic dysfunction corresponded to LVEF <30%, and patients with LVEF between 40 and 49% were considered to have HF with mildly depressed ejection fraction.

Patients' demographic data, medications, and comorbidities were collected. Patient's treatment strategy, timing of discharge, and discharge medication depended on the decision of the attending physician. Both physicians and patients were aware of the ongoing registry.

DM was defined as previous diagnosis, use of antihyperglycaemic agents, or glycated hemoglobin (HbA1c) $\geq$6.5%. All patients were type 2 DM. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease.[23] Alcohol consumption was defined as a self-reported daily consumption of at least 1 drink per day. Serum creatinine and magnesium were determined using conventional methods with an Olympus AU5400 automated clinical chemistry analyzer (Beckman-Coulter Inc., USA), and the normal reference range for the latter was 1.55–2.05 mEq/L (0.78–1.03 mmol/L or 1.88–2.49 mg/dL). B-type natriuretic peptide (BNP) was determined using a chemiluminescent microparticle immunoassay (Abbott Lab., USA). Hemoglobin was obtained using an automated blood counter Sysmex XE-5000 (Sysmex Corp., Japan). HbA1c was determined by an ion-exchange high-performance liquid chromatography system with a D-10 Bio-Rad analyzer (Bio-Rad Inc, USA).

For this subanalysis, we additionally excluded the patients with missing data on admission serum magnesium. Patients were followed up to 1 year from hospital admission. The primary end point was all-cause mortality, and no patient was lost to follow-up. Patients' vital status was established by consulting hospital clinical records, by telephone contact with the patients or their family, or by consulting the Registo Nacional de Utentes (RNU), a national platform that has information on patient mortality date.

The registry's protocol conformed to the ethical guidelines of the Declaration of Helsinki, and it was approved by the local ethics committee.

Statistical analysis

Categorical variables are presented as counts and proportions. Continuous variables are presented as mean $\pm$ standard deviation when normally distributed and as median (interquartile range) when the distribution was highly skewed. Patients were divided according to serum magnesium using the cutoff of 1.64 mEq/L (corresponding to the median value) and compared: the chi-square test for categorical variables, the Student t test for normally distributed continuous variables, and the Mann–Whitney U test for non-normally distributed continuous variables. The Kaplan–Meier survival method was used to determine survival curves according to admission magnesium levels (< and $\geq$1.64 mEq/L). The analysis was stratified according to the presence of DM. A multivariable Cox regression analysis was used to study the independent association of magnesium (both as a continuous and as a categorical variable) with 1-year mortality. Variables included in the model were age, sex, history of atrial fibrillation, systolic blood pressure, heart rate, ischemic etiology, BNP, eGFR, history of alcohol consumption, HbA1c, admission glycemia, New York Heart Association (NYHA) class IV, and severe left ventricular systolic dysfunction.

The P value considered for statistical significance was 0.05. Data were stored and analyzed using SPSS software (IBM Corp, Armonk, NY, version 20.0).

Results

We studied 606 patients, 44.1% were male, and the mean age was of 76 $\pm$ 12 years. Approximately half of the patients had an elevated comorbidity burden. Sixty percent of the patients presented in NYHA class IV, and 37% had severe left ventricle systolic dysfunction (LVSD). Median serum magnesium was 1.64 (1.48–1.79) mEq/L. Patients' characteristics and comparison between those with magnesium levels above and below the median, as well as the comparison between patients with and without DM are depicted in Table 1. In brief, patients with higher magnesium levels had lower systolic blood pressure (SBP) and heart rate, lower eGFR, and lower glycemia. The frequency of DM, history of alcohol consumption, and LVSD were similar between groups. BNP levels, HbA1c, and NYHA class were also nondifferent between patients with higher and lower admission magnesium levels. Importantly, patients with serum magnesium $\geq$1.64 mEq/L had higher 1-year mortality: 141 (46.4%) vs 91 (30.1%), $P < .001$.

During the 1-year follow-up, 232 patients (38.3%) died. Serum magnesium above 1.64 mEq/L predicted 1-year all-cause mortality in acute HF with an HR of 1.69 [95% confidence interval (CI): 1.30–2.20], $P < .001$. However, when the analysis was stratified according to the presence of DM, this association remained valid only for patients with DM. Figure 1 illustrates the Kaplan-Meier survival curves in patients with serum magnesium <1.64 mEq/L and $\geq$1.64 mEq/L in patients with HF with and without DM diagnosis.

The association between serum magnesium and mortality is shown separately for patients with and without DM in Table 2. After adjustments for age, sex, history of atrial fibrillation, SBP, heart rate, ischemic etiology, BNP, eGFR, history of alcohol consumption, HbA1c, admission glycemia, NYHA class IV, and severe LVSD, a serum magnesium $\geq$1.64 mEq/L was associated with higher mortality only in patients with DM: HR 1.89 (95%

Table 1

Patients' characteristics and comparison between patients according to admission magnesium levels.

Characteristics	All patients n = 606	Mg <1.64 mEq/L n = 302	Mg ≥1.64 mEq/L n = 304	P	No DM n = 299	DM n = 307	P
Male sex, n (%)	267 (44.1)	123 (40.7)	144 (47.4)	.10	130 (43.5)	137 (44.6)	.81
Age, mean (SD)	76 (12)	75 (12)	77 (12)	.09	77 (14)	76 (10)	.56
DM, n (%)	307 (50.7)	163 (54.0)	144 (47.4)	.10	—	—	—
Serum Mg (mEq/L), median (IQR)	1.64 (1.48–1.79)	—	—	—	1.65 (1.49–1.78)	1.61 (1.47–1.79)	.59
Arterial hypertension, n (%)	433 (74.8)	221 (75.9)	212 (73.6)	.52	184 (64.8)	249 (84.4)	<.001
Atrial fibrillation, n (%)	278 (46.0)	129 (42.7)	149 (49.3)	.10	140 (47.0)	138 (45.1)	.68
Ischemic heart disease, n (%)	234 (38.6)	115 (38.1)	119 (39.1)	.79	104 (34.8)	130 (42.3)	.07
Alcohol consumption, n (%)	238 (39.7)	119 (39.8)	119 (39.5)	.95	117 (39.5)	121 (39.8)	1.00
NYHA class II, n (%)	8 (1.3)	4 (1.3)	4 (1.3)	.38	5 (1.7)	3 (1.0)	
NYHA class III, n (%)	235 (39.1)	109 (36.3)	126 (41.9)		122 (41.2)	113 (37.0)	
NYHA class IV, n (%)	358 (59.6)	187 (62.3)	171 (56.8)		169 (57.1)	189 (62.0)	.40
HFpEF, n (%)	228 (39.2)	118 (40.5)	110 (37.8)	.26	121 (41.6)	107 (36.8)	
HFmrEF, n (%)	64 (11.0)	37 (12.7)	37 (9.3)		28 (9.6)	36 (12.4)	
Moderate LVSD, n (%)	75 (12.9)	39 (13.4)	36 (12.4)		33 (11.3)	42 (14.4)	
Severe LVSD, n (%)	215 (36.9)	97 (33.3)	118 (40.5)		109 (37.5)	106 (36.4)	.39
SBP (mmHg), mean (SD)	133 (29)	138 (30)	129 (26)	<.001	134 (30)	133 (28)	.97
Heart rate (bpm), mean (SD)	89 (23)	91 (24)	87 (23)	.03	89 (23)	88 (24)	.64
Hemoglobin (g/dL), mean (SD)	11.8 (2.1)	11.9 (2.3)	11.7 (2.0)	.39	11.9 (2.2)	11.7 (2.1)	.11
eGFR (mL/min/1.73m^2), median (IQR)	45.6 (31.5–59.1)	48.8 (35.1–61.6)	41.5 (30.0–56.5)	<.001	48.5 (20.3)	45.3 (20.1)	.05
BNP (pg/mL), median (IQR)	1680 (932–2911)	1555 (908–2736)	1807 (962–3056)	.15	1446 (782–2608)	1223 (645–2647)	.16
Sodium (mmol/L), median (IQR)	139 (136–141)	139 (135–142)	139 (136–141)	.37	139 (136–142)	139 (136–141)	.63
Glucose (mg/dL), median (IQR)	119 (91–161)	124 (96–168)	109 (87–153)	.002	100 (85–126)	147 (108–206)	<.001
HbA1c (%), median (IQR)	6.2 (5.7–6.9)	6.2 (6.7–6.9)	6.2 (5.7–7.0)	.49	5.8 (5.5–6.1)	6.9 (6.4–7.7)	<.001
Death (1 year after admission), n (%)	232 (38.3)	91 (30.1)	141 (46.4)	<.001	121 (40.5)	111 (47.8)	.28

To convert serum magnesium levels from mEq/L to mmol/L, divide by 2 and from mEq/L to mg/dL, divide by 0.823.

BNP, B-type natriuretic peptide; bpm, beats per minute; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; LVSD, left ventricle systolic dysfunction; Mg, magnesium; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation.

CI: 1.19–3.00), P = .007, and 1.27 (95% CI: 0.83–1.94) and P = .26 for patients without DM. When admission serum magnesium was analyzed as a continuous variable, the results were similar. Per 0.1 mEq/L increase in serum magnesium levels in patients with DM, there would be a multivariate adjusted 13% (95% CI: 4%–23%) increased risk of 1-year mortality. No such association with mortality was evident in non-DM patients.

Discussion

In this study, elevated serum magnesium levels portended prognostic value in acute HF patients with DM. Patients with admission serum magnesium ≥1.64 mEq/L had almost two-fold higher risk of 1-year all-cause mortality. The increase in death risk was 13% per 0.1 mEq/L increase in serum magnesium. Interestingly, no such prognostic association existed in non-DM patients. As far as the authors are concerned and after review of the existing literature, this is the first study to evaluate the prognostic impact of serum magnesium levels in patients with acute HF, according to the coexistence of DM.

In our study, we found that patients with higher magnesium had lower SBP, lower heart rate, lower eGFR, and lower glycemia. These findings are consistent with those previously described by others: more severe symptoms, greater neurohormonal activation, and worse renal function.[12,24] In patients with chronic HF, higher magnesium was found to be associated with worse outcomes in
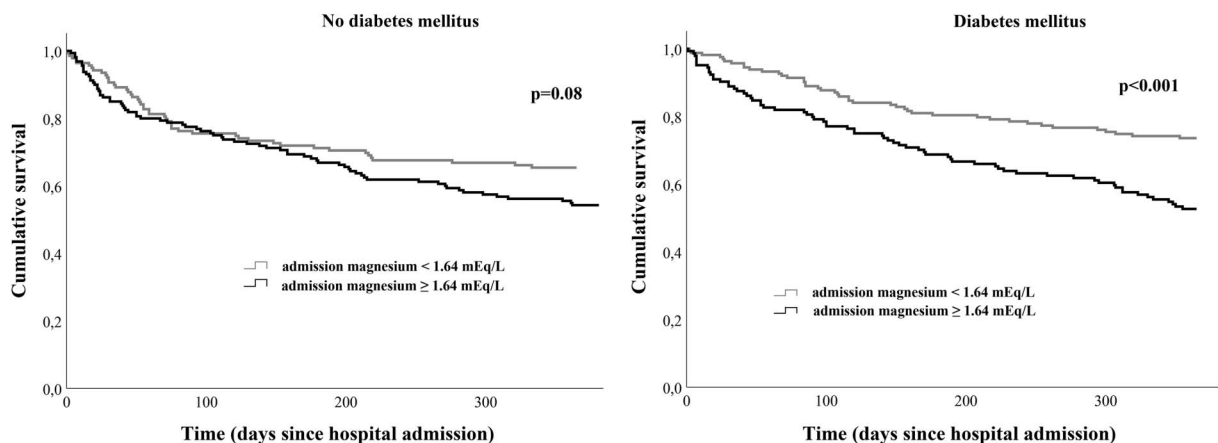

Figure 1. Kaplan–Meier curves according to admission magnesium levels in patients with and without DM.

Table 2

Multivariate Cox regression analysis stratified by DM status.

Cox regression	With DM		Without DM	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude				
Mg ≥ 1.64 mEq/L	2.05 (1.40–3.00)	<.001	1.39 (0.96–2.00)	.08
Mg, per 0.1 mEq/L	1.11 (1.04–1.19)	.002	1.03 (0.95–1.11)	.47
Multivariate adjusted				
Mg ≥ 1.64 mEq/L	1.89 (1.19–3.00)	.007	1.27 (0.83–1.94)	.26
Mg, per 0.1 mEq/L	1.13 (1.04–1.23)	.006	1.01 (0.92–1.10)	.91

Adjustments for age, sex, history of atrial fibrillation, SBP, heart rate, ischemic etiology, B-type natriuretic peptide, estimated glomerular filtration rate, history of alcohol consumption, HbA1c, admission glycemia, New York Heart Association class IV, and severe left ventricle systolic dysfunction.
To convert serum magnesium levels from mEq/L to mmol/L, divide by 2 and from mEq/L to mg/dL, divide by 0.823.
CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; Mg, magnesium.

most,[3,11,24,25] but not all,[26,27] studies. Previous studies evaluating the prognostic impact of serum magnesium in acute HF also found distinct results.[12,13] Vaduganathan et al[12] found that serum magnesium was not mortality-related after adjustment for various baselines variables in a group of patients with HF with reduced ejection fraction.[12] Their study differed from ours in some respects: Despite a similar follow-up time, the population studied (only patients with LVSF ≤40%) may justify the distinct results. More recently, a retrospective analysis of 8498 patients admitted to a cardiac care unit with the diagnosis of acute myocardial infarction (50.7%) and acute decompensated HF (42.5%) found that higher magnesium levels were associated with higher hospital mortality.[13] However, none of the studies addressed the prognostic impact of serum magnesium separately in patients with and without DM. An important note is that hypermagnesemia is more frequent than hypomagnesemia in hospitalized patients, in general, and hypermagnesemia associates with poor outcomes more strongly than hypomagnesemia.[28]

The mechanism by which higher magnesemia would adversely affect the heart might be due to altered cardiomyocytes type II isoform ryanodine channel properties by magnesium competition with calcium with impaired cardiac systolic contraction and diastolic relaxation.[29] Higher magnesium levels may also lead to electrocardiographic abnormalities such as PR interval prolongation, QRS complex widening, bradycardia, complete heart block, QT interval prolongation, and ventricular arrhythmias,[30] which can have a serious negative effect in patients with HF. QT interval prolongation, in particular, has been associated with worse prognosis in patients with HF.[31] Furthermore, patients with higher magnesium are frequently older, with worse renal function, and higher neurohumoral activation, all of which can contribute to a more ominous outcome in HF.[12,24]

In our study, we found that patients with serum magnesium levels ≥1.64 mEq/L had higher risk of 1-year all-cause mortality in those with concomitant DM. The differential association between serum magnesium and prognosis according to the presence of DM is intriguing and not readily explainable. In patients with type 2 DM, hypomagnesemia is a frequent finding, particularly in those with poorer glycemic control, longer disease duration, and chronic microvascular and macrovascular complications.[32–34] Urinary magnesium losses due to both glucosuria and hyperinsulinemia and reduced magnesium intake may all contribute to this state.[19]

Possible explanations for the association between higher magnesemia and worse HF outcome in patients with DM might be that the cardiac structural changes and remodeling,[35,36] autonomic dysfunction,[36,37] and slower nervous conduction velocity[36,38] seen in their hearts would render them more vulnerable to higher magnesium

levels, when compared with patients without DM. This could explain why only the subgroup of HF patients with DM showed grimmer prognosis with higher serum magnesium levels. Magnesium levels in the blood are primarily regulated by the kidney.[39] Chronic kidney disease associates with higher serum magnesium because there is no magnesium regulatory system other than urinary excretion.[40] Because patients with DM frequently show renal function deterioration, it is possible that higher magnesium level might simply reflect worse renal function. We did, however, take renal function into consideration in the multivariate analysis, and furthermore, this would not explain the absence of association observed in non-DM patients. Moderate hypermagnesemia has been reported to increase vascular calcifications, mainly because of a reduction in parathyroid hormone suppression.[41] This vascular remodeling, coupled with the cardiac structural changes and higher vascular calcification risk common in DM[42] might also contribute to mortality increase with higher magnesium levels in HF patients with DM. Our results sustain the general notion that HF patients with DM are a particular group within patients with HF, a group in which prognostic determinants seem to apply differently.[20–22,43]

We did not find an association between DM status and higher mortality in our patient population. Although most studies found that acute HF patients with DM had worse prognosis,[18,44] some studies did not report such association[45] and others found lower mortality risk.[46] DM is more than a categorical variable, and its association with HF mortality is probably more complex because DM duration, metabolic control and its variability throughout time, chronic DM complications, and comorbidities are expected to contribute.

There are limitations to our study that should be mentioned. It is a single-center retrospective study with all its inherent shortcomings. Information regarding magnesium supplementation or the presence of malabsorptive gastrointestinal diseases was not available. Alcohol consumption was self-reported by patients, and this data may not be accurate. In addition, one of the major pitfalls of our study is the lack of data regarding serum calcium levels; serum calcium is influenced by magnesium levels; it is involved in magnesium renal handling and can itself affect neuromuscular activity.[47] However, calcium levels are more affected by magnesium levels when these are very low (<0.8 mEq/L) or when above the reference range.[45–47] Although 33.7% of patients had hypomagnesemia, only 1 patient had severe hypomagnesemia (<0.8 mEq/L), 1.4% had magnesium levels <1.0 mEq/L, and 17.8% <1.4 mEq/L. Only 4% of patients had magnesium levels >2.05 mEq/L. Thus, it is unlikely that calcium levels were seriously affected by hypomagnesemia to impact our results.

Despite the limitations acknowledged, we were able to detect a negative impact of increasing serum magnesium levels in HF

patients with DM. Clinical implications are difficult to foresee; however, our results suggest that magnesium supplementation should not be performed widely in acute HF patients with DM. Ionic disturbances are common in hospitalized patients, and clinicians tend to be proactive in their correction, although care should be taken regarding magnesium supplementation in patients with DM hospitalized with acute HF.

Conclusions

Higher magnesium levels seem to be associated with worse prognosis only in acute HF patients with DM.

Acknowledgments

Paulo Bettencourt died on September 4, 2021.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

All authors have contributed to, and read, the paper.

References

[1] Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep. 2017;14:385–392.

[2] Douban S, Brodsky MA, Whang DD, Whang R. Significance of magnesium in congestive heart failure. Am Heart J. 1996;132:664–671.

[3] Eichhorn EJ, Tandon PK, DiBianco R, et al. Clinical and prognostic significance of serum magnesium concentration in patients with severe chronic congestive heart failure: the PROMISE study. J Am Coll Cardiol. 1993;21:634–640.

[4] Kolte D, Vijayaraghavan K, Khera S, Sica DA, Frishman WH. Role of magnesium in cardiovascular diseases. Cardiol Rev. 2014;22:182–192.

[5] Kunutsor SK, Khan H, Laukkanen JA. Serum magnesium and risk of new onset heart failure in men: the Kuopio Ischemic Heart Disease Study. Eur J Epidemiol. 2016;31:1035–1043.

[6] Lutsey PL, Alonso A, Michos ED, et al. Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. Am J Clin Nutr. 2014;100:756–764.

[7] Wannamethee SG, Papacosta O, Lennon L, Whincup PH. Serum magnesium and risk of incident heart failure in older men: the British Regional Heart Study. Eur J Epidemiol. 2018;33:873–882.

[8] Oost LJ, van der Heijden AA, Vermeulen EA, et al. Serum magnesium is inversely associated with heart failure, atrial fibrillation, and microvascular complications in type 2 diabetes. Diabetes care. 2021;44:1757–1765.

[9] Wu WC, Huang M, Taveira TH, et al. Relationship between dietary magnesium intake and incident heart failure among older women: the WHI. J Am Heart Assoc. 2020;9:e013570.

[10] Helte E, Akesson A, Larsson SC. Assessing causality in associations of serum calcium and magnesium levels with heart failure: a two-sample mendelian randomization study. Front Genet. 2019;10:1069.

[11] Angkananard T, Anothaisintawee T, Eursiriwan S, et al. The association of serum magnesium and mortality outcomes in heart failure patients: a systematic review and meta-analysis. Medicine. 2016;95:e5406.

[12] Vaduganathan M, Greene SJ, Ambrosy AP, et al. Relation of serum magnesium levels and postdischarge outcomes in patients hospitalized for heart failure (from the EVEREST Trial). Am J Cardiol. 2013;112: 1763–1769.

[13] Naksuk N, Hu T, Krittanawong C, et al. Association of serum magnesium on mortality in patients admitted to the intensive cardiac care unit. Am J Med. 2017;130:229.e5–229.e13. e5-

[14] Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296:2217–2226.

[15] Velavan P, Huan Loh P, Clark A, Cleland JGF. The cholesterol paradox in heart failure. Congest Heart Fail. 2007;13:336–341.

[16] Shah R, Gayat E, Januzzi JL, Jr., et al. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. J Am Coll Cardiol. 2014;63:778–785.

[17] Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34:29–34.

[18] Carrasco-Sanchez FJ, Gomez-Huelgas R, Formiga F, et al. Association between type-2 diabetes mellitus and post-discharge outcomes in heart failure patients: findings from the RICA registry. Diabetes Res Clin Pract. 2014;104:410–419.

[19] de Valk HW. Magnesium in diabetes mellitus. Neth J Med. 1999;54: 139–146.

[20] Adamopoulos C, Meyer P, Desai RV, et al. Absence of obesity paradox in patients with chronic heart failure and diabetes mellitus: a propensity-matched study. Eur J Heart Fail. 2011;13:200–206.

[21] Cunha FM, Lourenco P, Couto M, et al. Is the blood pressure paradox observed in all heart failure patients? BioMed Res Int. 2013;2013: 350289.

[22] Cunha FM, Pereira J, Ribeiro A, et al. The cholesterol paradox may be attenuated in heart failure patients with diabetes. Minerva Med. 2019;110: 507–514.

[23] Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145: 247–254.

[24] Gottlieb SS, Baruch L, Kukin ML, Bernstein JL, Fisher ML, Packer M. Prognostic importance of the serum magnesium concentration in patients with congestive heart failure. J Am Coll Cardiol. 1990;16:827–831.

[25] Corbi G, Acanfora D, Iannuzzi GL, et al. Hypermagnesemia predicts mortality in elderly with congestive heart disease: relationship with laxative and antacid use. Rejuvenation Res. 2008;11:129–138.

[26] Cohen N, Almoznino-Sarafian D, Zaidenstein R, et al. Serum magnesium aberrations in furosemide (frusemide) treated patients with congestive heart failure: pathophysiological correlates and prognostic evaluation. Heart. 2003;89:411–416.

[27] Madsen BK, Rasmussen V, Hansen JF. Predictors of sudden death and death from pump failure in congestive heart failure are different. Analysis of 24 h Holter monitoring, clinical variables, blood chemistry, exercise test and radionuclide angiography. Int J Cardiol. 1997;58:151–162.

[28] Cheungpasitporn W, Thongprayoon C, Qian Q. Dysmagnesemia in hospitalized patients: prevalence and prognostic importance. Mayo Clin Proc. 2015;90:1001–1010.

[29] Li J, Imtiaz MS, Beard NA, et al. ß-adrenergic stimulation increases RyR2 activity via intracellular Ca2+ and Mg2+ regulation. PLoS One. 2013;8:e58334.

[30] Tangvoraphonkchai K, Davenport A. Magnesium and cardiovascular disease. Adv Chron Kidney Dis. 2018;25:251–260.

[31] Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM, Radovancevic B. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. Circulation. 2003;107:1764–1769.

[32] Mather HM, Levin GE. Magnesium status in diabetes. Lancet. 1979;313: 924.

[33] Ramadass S, Basu S, Srinivasan AR. SERUM magnesium levels as an indicator of status of Diabetes Mellitus type 2. Diabetes Metab Syndr: Clin Res Rev. 2015;9:42–45.

[34] Sales CH, Pedrosa LdFC. Magnesium and diabetes mellitus: their relation. Clin Nutr. 2006;25:554–562.

[35] Tadic M, Cuspidi C. Type 2 diabetes mellitus and atrial fibrillation: from mechanisms to clinical practice. Arch Cardiovasc Dis. 2015;108:269–276.

[36] Grisanti LA. Diabetes and arrhythmias: pathophysiology, mechanisms and therapeutic outcomes. Front Physiol. 2018;9:1669.

[37] Oberhauser V, Schwertfeger E, Rutz T, Beyersdorf F, Rump LC. Acetylcholine release in human heart atrium: influence of muscarinic autoreceptors, diabetes, and age. Circulation. 2001;103:1638–1643.

[38] Ramirez AH, Schildcrout JS, Blakemore DL, et al. Modulators of normal electrocardiographic intervals identified in a large electronic medical record. Heart Rhythm. 2011;8:271–277.

[39] Houillier P. Mechanisms and regulation of renal magnesium transport. Annu Rev Physiol. 2014;76:411–430.

[40] Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of calcium, phosphorus, and magnesium dysregulation in chronic kidney disease. Semin Dial. 2015;28:564–577.

[41] Massy ZA, Drueke TB. Magnesium and outcomes in patients with chronic kidney disease: focus on vascular calcification, atherosclerosis and survival. Clin Kidney J. 2012;5:i52–i61.

[42] Yahagi K, Kolodgie FD, Lutter C, et al. Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. Arterioscl Thromb Vasc Biol. 2017;37:191–204.

[43] Cidade-Rodrigues C, Cunha FM, Elias C, Oliveira D, Bettencourt P, Lourenco P. The prognostic impact of uric acid in acute heart failure according to coexistence of diabetes mellitus. Nutrition, metabolism, and cardiovascular diseases. NMCD; 2021.

[44] Sarma S, Mentz RJ, Kwasny MJ, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. Eur J Heart Fail. 2013;15:194–202.

[45] Greenberg BH, Abraham WT, Albert NM, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). Am Heart J. 2007;154:647–654.

[46] Masip J, Povar-Echeverria M, Peacock WF, et al. Impact of diabetes and on-arrival hyperglycemia on short-term outcomes in acute heart failure patients. Intern Emerg Med. 2022;17:1503–1516.

[47] Quamme GA, Dirks JH. The physiology of renal magnesium handling. Kidney Blood Press Res. 1986;9:257–269.