Low magnesium is not a significant predictor of hard events in acute myocardial infarction

Cristina Vassalle *, Debora Battaglia, Alessandro Vannucci, Kyriazoula Chatzianagnostou, Patrizia Landi, Caterina Arvia, Clara Carpeggiani

Fondazione G. Monasterio CNR-Regione Toscana and Institute of Clinical Physiology-CNR, Pisa, Italy

1. Introduction

Magnesium (Mg) is an essential element and an activator of a number of enzymes, which retains β-adrenoreceptor blocking action, antiplatelet effects, and antiarrhythmic, antivasospastic and other important cardiovascular (CV) protective effects, supporting the rationale for its use in acute myocardial infarction (AMI) [12]. From first promising results in experimental studies, several other clinical trials evaluated the efficacy of Mg adjuvant therapy in the secondary prevention of CV disease [18]. Nonetheless, whether some previous, relatively small randomized clinical trials demonstrated improved survival, other trials could not demonstrate any benefit [18]. In particular, two published large-scale randomized studies – the Fourth International Study of Infarct Survival and Magnesium in Coronaries – did not evidence any advantage in terms of survival of intravenous Mg over placebo [8,15]. Also the relationship between dietary Mg and CV risk has not been clearly established [4,9]. In a meta-analysis of 5 studies, dietary Mg intake was not associated with total CV disease risk (RR comparing high versus low Mg intake, 0.86; 95% CI, 0.67 to 1.10) [21]. Other population-based studies, that have evaluated the relationship between Mg and CV events, also reported conflicting result [10,17,21]. Mg represents a low-tech, low-cost and easily accessible biomarker to be used in the clinical setting. However, a direct relationship between blood and/or dietary Mg and CV disease risk has not been clearly established. Moreover, despite the numerous reports on its potential CV benefits and the use as an adjuvant therapy in AMI, its effective prognostic value in AMI is still not cleared.

The aim of the present study was to evaluate the predictive value of Mg for hard events (HE: mortality and non fatal myocardial infarction, MI) in AMI patients.

* Corresponding author at: Fondazione G. Monasterio CNR-Regione Toscana and Istituto di Fisiologia Clinica-CNR, Via Moruzzi 1, I-56124 Pisa, Italy.
E-mail address: cristina.vassalle@ftgm.it (C. Vassalle).

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TABLE 1

Clinical characteristics according to magnesium 25th percentile.

| Characteristic                          | Mg ≤ 0.783 mmol/L | Mg > 0.783 mmol/L | p  |
|----------------------------------------|-------------------|-------------------|----|
| Number of pts                          | 101               | 305               |    |
| Age (years)                            | 67 ± 11           | 68 ± 13           | ns |
| Males                                  | 70 (69)           | 236 (77)          | ns |
| Body mass index (kg/m²)                | 26 ± 4            | 27 ± 4            | <0.05|
| Mean arterial pressure (mm Hg)         | 92 ± 15           | 94 ± 15           | ns |
| Total cholesterol (mg/dL)              | 137 ± 65          | 119 ± 43          | <0.001|
| High density lipoproteins (mg/dL)      | 187 ± 46          | 193 ± 41          | ns |
| Triglycerides (mg/dL)                  | 40 ± 12           | 41 ± 11           | ns |
| Low density lipoproteins (mg/dL)       | 128 ± 111         | 128 ± 78          | ns |
| Smoking habit                          | 121 ± 39          | 127 ± 35          | ns |
| Family history of coronary artery disease | 60 (56)          | 143 (48)          | ns |
| Multi-vessel disease                   | 55 (51)           | 170 (57)          | ns |

Data presented are mean ± SD or number (%) of patients.

Diabetes mellitus = fasting plasma glucose ≥ 126 mg/dL or use of antidiabetic treatment.

Hypertension = systolic blood pressure > 140 mm Hg or diastolic pressure > 90 mm Hg or by the use of antihypertensive medication.

Dyslipidemia = total cholesterol concentration ≥ 200 mg/dL, or triglyceride concentration ≥ 150 mg/dL, or current use of lipid-lowering drugs.

ns = not significant.

2. Materials and methods

2.1. Subjects

Subjects selected to participate in the study were 406 patients (306 males, age: 67 ± 12 years, mean ± SD), consecutively admitted (period 2002–2008) to the Coronary Care Unit of the CNR Institute of Clinical Physiology in Pisa within 48 h after onset of symptoms of AMI symptoms.

In this retrospective study, information were extracted from the IMAGE database, which contains detailed information on demographic, clinical, laboratory, instrumental, therapeutical and follow-up data of all consecutive patients admitted to the Coronary Unit [3,22].

Left ventricular function was estimated by echocardiography at discharge. Data on smoking habit (never smokers, ex-smokers – who had quit smoking for at least 6 months – and current smokers), family history of ischemic heart disease, arterial hypertension (systolic blood pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg or antihypertensive medication), diabetes (twice fasting plasma glucose > 126 mg/dL or antidiabetic treatment), obesity (body mass index, BMI; >30 kg/m²), and dyslipidemia (total cholesterol ≥ 200 mg/dL, or triglycerides ≥150 mg/dL, or lipid-lowering treatment) were coded in a dichotomized fashion. Medical therapy included ACE inhibitors, beta-blockers, lipid-lowering, anti-diabetic agents, diuretics, aspirin, nitrates and calcium-channel antagonists.

2.2. Follow-up

Following discharge, the follow-up program included an annual telephone interview with patients or family members and validation of HE [3]. The endpoints included cardiac death, all-cause death, and new myocardial infarction. Patients were censored after the first major event during follow-up. The cause of death was derived from medical records or death certificates provided by local health authorities. The diagnosis of AMI was based on the documentation of persistent electrocardiographic ST segment changes or new Q wave development, associated with increase of cardiac specific biomarkers.

2.3. Statistical analysis

Data were expressed as the mean ± SD. Statistical analysis performed included Student’s t test, χ² test, and linear regression.

Fig. 1. Levels of Mg in patients with and without events. Median, interquartile, outliers and extremes of Mg are given.

Owing to skewness, log transformations of glycemia and glycated hemoglobin, were used for statistical analyses. Log-transformed values were then back-transformed for data presentation.

The multiple regression analysis was performed to determine independent correlates of Mg levels. Cumulative event rates were estimated by Kaplan–Meier survival curves and probability values determined with the log-rank test. For survival analysis, only one event was considered in each patient. Statistical analysis also included Cox proportional hazard models to determine independent predictors of HE.

Variables were selected if they had a p value 0.05 on univariate analyses and added for multivariate adjustment. A p value 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of patients and Mg determinants

In the study, 406 patients with AMI were enrolled. The average age of the whole population was 67 ± 12 years and 75% (n = 306) of them were males.

Characteristics of Mg distribution were: mean (SD), 0.842 (0.1) mmol/L; range 0.52–1.2 mmol/L; skewness −0.1; and kurtosis 0.7. The prevalence of baseline risk factors according to Mg 25th quartile (corresponding to 0.783 mmol/L) is reported in Table 1.

Glycated hemoglobin, available in a subset of 143 patients, inversely correlated with Mg values (r = −0.18, p < 0.05). After the adjustment at the multivariate regression analysis, glycemia (T value = −2.8,
In the ISIS-4 trial the incidence of heart failure was even significantly lower in the Mg-treated arm compared to the control arm. This was also true for the 5-week mortality in myocardial infarction patients [8, 15]. The ISIS-4 (n = 58,050 patients) and MAGIC (n = 6213 patients) studies did not report any advantage conferred by adjuvant Mg therapy to the all-cause mortality rate in the Mg-treated group [23]. Subsequent meta-analysis of these patients showed a 16% reduction in the 28-day mortality rate in patients receiving Mg therapy compared with control subjects (n = 2316 patients), evidencing a reduction in the 28-day mortality rate in patients receiving Mg therapy compared with control subjects [23]. Long-term follow-up of these patients showed a 16% reduction in the 28-day mortality rate in patients receiving Mg therapy compared with control subjects [23].

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3.2. Outcome

During a mean follow-up period of 21 ± 18 months, the combined endpoint accounted for 63 events; there were 44 (11%) deaths (35 cardiac deaths), and 19 (5%) patients had nonfatal myocardial infarctions. No differences were observed regarding the Mg level between patients with and without events (Fig. 1). The Kaplan-Meier survival estimate for HE failed to show a significantly worst outcome in patients presenting low Mg (<0.783 mmol/L) (25th percentile) (Fig. 2). Aging (>67 yrs-50th percentile), and ejection fraction (~<40%) remained as significant prognostic factors for HE in the adjusted Cox multivariate proportional hazard model (HR = 2.8, 95% CI = 1.6-5, p < 0.001; HR = 3.2, 95% CI = 1.9-5.3 p < 0.001, respectively) (Table 2).

4. Discussion

We did not find a significant association between Mg levels and subsequent HE in AMI patients. Mg, which is the physiological calcium antagonist, protects from oxidative damage, improves endothelial function and inhibits platelet aggregation and adhesion [18]. Mg supplementation improves myocardial metabolism, inhibits calcium accumulation and myocardial cell death, improves vascular tone, peripheral vascular resistance, afterload and cardiac output, reduces cardiac arrhythmias and improves lipid metabolism [18]. Conversely, hypomagnesemia is associated with an increased incidence of CV risk factors, and arrhythmias particularly in association with congestive heart failure, and more rapid progression of kidney disease, among others adverse health consequences [18].

Levels of Mg have been documented reduced in AMI [1, 16, 20]. In this context, dated results suggested that lower Mg in AMI patients was essentially due to increased demand during AMI, rather than dietary intake differences [20]. Clinical studies investigating the role of Mg adjuvant therapy on mortality after AMI have produced conflicting results. The Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) (n = 2316 patients), evidenced a reduction in the 28-day mortality rate in patients receiving Mg therapy compared with control subjects [23]. Long-term follow-up of these patients showed a 16% reduction in the all-cause mortality rate in the Mg-treated group [23]. Subsequent ISIS-4 (n = 58,050 patients) and MAGIC studies (n = 6213 patients) did not report any advantage conferred by adjuvant Mg therapy to standard on 5-week mortality in myocardial infarction patients [8, 15]. In the ISIS-4 trial the incidence of heart failure was even significantly higher in the Mg-group [15]. Nonetheless, one main critical to ISIS-4 is in the timing of Mg administration. Indeed, more recent research has confirmed the time-dependent effect of Mg when given for both myocardial protection in experimental ischemia-reperfusion injury and for antithrombotic effects [15].

Majority of population studies that have evidenced the relationship between Mg status and CV outcomes were based on dietary intake, which may be influenced by residual confounding or recall bias [18]. The few studies focused on the relationship between Mg and CV disease events have produced controversial results. An analysis from the ARIC cohort (13,922 healthy subjects without CAD on admission) showed a significant association between Mg and coronary heart disease in women but not men [14]. However, we did not observe any difference in terms of significance on HE between men and women in our AMI population (data not shown). In the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHANES) Mg was inversely associated with CV and all-cause mortality [5, 6]. More recent data in a German population-based sample evidenced low Mg concentration as independent predictor of all-cause and CV mortality also after adjustment for CV risk factors, including diabetes and hypertension [17]. Mg was also found to be associated with CV and all-cause mortality in middle-aged men (n = 4035) in the Paris Prospective Study [13]. Notably, none of our patients showed severe hypomagnesemia (≤0.494 mmol/L), as in other cohorts of patients [5, 13], thus it is not possible for us to draw conclusions about the risk associated with a very low Mg. Moreover, a recent analysis of the Framingham Heart Offspring Cohort, did not evidence any association between Mg, incident arterial hypertension, and all cause mortality in the adjusted statistical models [10]. Recent data also suggest that low Mg is predictor of major adverse cardiac events in patients with AMI, but not in those with unstable angina [2].

Mg is a common biomarker measured in biochemical laboratory, although it is predominantly an intracellular cation [12]. Thus, it has been supposed that the measurement of circulating Mg might not reflect total body Mg stores. Accordingly, serial measurements or a measure of intracellular Mg, such as that contained in lymphocytes, erythrocytes or myocytes, may provide a more precise assessment of the true Mg status [19, 22]. Conversely, other data suggest that Mg circulating concentration may represent an effective index of Mg status given that levels well correlate with ionized Mg and intracellular Mg [7, 11].

In conclusion, actually the relationship between Mg and coronary artery disease as well as benefit from use of Mg in AMI clinical setting are not clearly delineated in view of available contrasting literature data. In this context, our findings do not support a role for low Mg as adverse prognostic factor for HE in AMI patients.

### Transparency document

The Transparency document associated with this article can be found, in online version.

**Table 2**

| Predictors                                      | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
|                                                 | Hazard ratio        | 95% confidence intervals | p     | Hazard ratio | 95% confidence intervals | p     |
| Age (>67 years—50th percentile)                | 3.2                 | 1.8–5.6               | <0.001 | 2.8          | 1.6–5                   | <0.001 |
| Males                                          | 1.05                | 0.6–1.9               | ns     |              |                        |       |
| Hypertension                                   | 1.2                 | 0.7–2.0               | ns     |              |                        |       |
| Type 2 diabetes                                | 1.02                | 0.6–1.8               | ns     |              |                        |       |
| Dyslipidemia                                   | 1.1                 | 0.6–1.9               | ns     |              |                        |       |
| Smoking habit                                  | 0.8                 | 0.5–1.3               | ns     |              |                        |       |
| Family history of coronary artery disease      | 0.8                 | 0.5–1.3               | ns     |              |                        |       |
| Obesity (BMI ≥ 30 kg/m²)                       | 0.8                 | 0.4–1.5               | ns     |              |                        |       |
| Mg (<0.783 mmol/L)                             | 0.99                | 0.6–1.7               | ns     |              |                        |       |
| Ejection fraction (<40%)                       | 3.5                 | 2.1–5.8               | <0.001 | 3.2          | 1.9–5.3                 | <0.001 |
| Multi-vessel disease                           | 1.8                 | 1.1–3.0               | <0.5   | 1.2          | 1–2.1                   | ns     |

Diabetes mellitus = fasting plasma glucose > 126 mg/dL or use of antidiabetic treatment.

Hypertension = systolic blood pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg or by the use of antihypertensive medication.

Dyslipidemia = total cholesterol concentration ≥ 200 mg/dL or triglyceride concentration ≥ 150 mg/dL or current use of lipid-lowering drugs.

ns = not significant.

standard coefficient = −0.15, p < 0.01) remained as the only independent determinant for lower Mg level.
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