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ORIGINAL CONTRIBUTION

Magnesium and C-reactive protein in heart failure: an anti-inflammatory effect of magnesium administration?

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Abstract *Background* Little is known about the relationship between serum magnesium (Mg) and C-reactive protein (CRP) in heart failure (HF). *Aim of the study* To investigate the relationship, if any, between serum Mg and CRP in HF patients and, concomitantly, to test a hypothesis that Mg supplementation might affect serum CRP levels. *Methods* Serum Mg and CRP were evaluated in 68 patients with chronic systolic HF leading to hospital admission and 65 patients requiring hospitalization for other causes. Following 5 weeks, serum Mg, CRP and intracellular Mg were reevaluated in 17 HF patients after administration of oral Mg citrate 300 mg/day (group A), and 18 untreated HF patients (group B). In order to obtain Gaussian distribution, logarithmic transformation of CRP was performed. *Results* Inverse correlation was found between serum Mg and log CRP ($r = -0.28$, $P = 0.002$). Compared to controls, patients with HF demonstrated higher baseline CRP levels, independent of coexisting conditions, and lower serum Mg values. Following Mg treatment, log CRP decreased from 1.4 ± 0.4 to 0.8 ± 0.3 in group A ($P < 0.001$). No significant changes in log CRP were demonstrable in group B. Serum Mg (mmol/l) rose significantly in group A (0.74 ± 0.04–0.88 ± 0.08, $P < 0.001$), and to a lesser extent in group B (0.82 ± 0.08–0.88 ± 0.08, $P = 0.04$). Intracellular Mg significantly increased only in Mg-treated group A ($P = 0.01$). *Conclusions* Oral Mg supplementation to HF patients significantly attenuates blood levels of CRP, a biomarker of inflammation. Targeting the inflammatory cascade by Mg administration might prove a useful tool for improving the prognosis in HF.

Key words heart failure – magnesium – CRP – inflammation

Introduction

Despite advances in the diagnosis and treatment of heart failure (HF), patients with HF are prone to high morbidity and mortality [1]. About 50% of these patients die within 5 years following diagnosis [1], commonly from cardiac arrhythmias secondary to impaired electrolyte balance [2, 3]. Magnesium (Mg) deficiency (hypomagnesemia and/or intracellular magnesium depletion, especially in the cardiomyocytes) is considered to be contributory to

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augmented rate of deaths in HF patients, as a result of cardiac arrhythmias, coronary vasospasms and progressive reduction in cardiac contractility [3–6]. Both hypomagnesemia and intracellular Mg depletion are frequent in HF [3–7]. Mg depletion in HF may result from reduced dietary intake, impaired intestinal Mg absorption and/or exaggerated urinary excretion generated by diuretics, especially furosemide [5, 6]. Furthermore, it has been shown that activation of the neurohormonal system and of the renin–angiotensin–aldosterone axis in HF may lead to stimulation of aldosterone and antidiuretic hormone secretion, which would inhibit renal tubular Mg reabsorption and thus exaggerate urinary Mg loss [5, 6]. However, since serum Mg levels do not necessarily reflect the actual state of intracellular Mg stores, intracellular Mg depletion may coexist with normomagnesemia [7].

Serum levels of C-reactive protein (CRP), a marker of ongoing inflammation, were found to be elevated in HF [8–10], especially during cardiac decompensation [9]. It has been demonstrated that elevated CRP per se might contribute to lysis of cardiocytes, and thus aggravate HF [11, 12]. Moreover, in HF patients elevated CRP and, in particular, high sensitivity CRP, have been shown to predict the development and progression of the disease [13–16] and death within 1 year, independent of other known risk factors [17].

The relationship between Mg and CRP in inflammatory conditions has been investigated only in a handful of studies. In patients with metabolic syndrome, higher levels of CRP have been demonstrated in those with hypomagnesemia [18, 19]. Low serum Mg concentrations have been shown to be associated with high levels of serum CRP in obese non-diabetic, non-hypertensive patients [20]. Furthermore, low Mg intake was found to significantly correlate with elevated CRP levels in subjects with overweight, hypertension or other metabolic abnormalities [21] as well as in healthy persons [21, 22]. Interestingly, studies based on infrared spectrometry techniques demonstrated substantial alterations in secondary structures of human CRP in the presence of Mg ions [23].

No substantial information has thus far been available regarding the interrelationship between CRP and Mg in HF. Since both, elevated serum CRP levels and Mg deficiency are very common in HF, and since any of these factors may aggravate HF, promote inflammation and predict death, it was of interest to investigate the relationship, if any, between serum Mg, intracellular Mg and CRP in HF patients and, concomitantly, to test a hypothesis that Mg supplementation might affect serum CRP levels.

Methods

Patients and study design

This investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee. All subjects gave their informed consent to participate in the study.

The first stage of the study was designed to investigate the relationship between serum Mg and CRP. We studied 133 patients referred sequentially by Emergency Department physicians to our Department of Internal Medicine due to a variety of clinical disorders (the causes of admission are listed in Table 1). Sixty-eight of them had chronic systolic HF antecedent to hospital admission (the HF group), and the remaining 65 were patients requiring hospital admission for causes other than HF (the non-HF group).

On admission, clinical and routine laboratory data were recorded. Following stabilization of the acute clinical condition, serum Mg and CRP values were determined. CRP was analyzed using immuno-turbidimetric assay (normal range 0–5 mg/dl, assay sensitivity <3.0 mg/dl, performed on Hitachi 917 autoanalyzer, Roche, Switzerland).

Effect of Mg administration on CRP, serum and intracellular Mg in HF

The second stage of the study was designed to investigate the net effect of Mg administration on CRP and included only 35 normomagnesemic (the interpretive normal range in our laboratory being 0.75–1.09 mmol/l) HF patients with systolic HF (left ventricular ejection fraction ≤40%) who were willing to proceed with the study. These patients, were randomly assigned to the following groups: group A, which included 17 HF patients treated with Mg citrate (Diasporal, Protina GMBH, Ismaning, Germany) 300 mg/day for 5 weeks, and group B (18 untreated HF patients), to serve as HF-controls.

HF was defined as a clinical syndrome in which symptoms and signs are associated with abnormalities, related to reduced cardiac output, increased pulmonary capillary wedge pressure and tissue congestion [24]. All the patients included in the study had evidence of left ventricular systolic dysfunction (LVSD) and symptoms of breathlessness and/or fatigue as well as clinical signs of fluid overload [24]. In all patients, HF was diagnosed as chronic, lasting at least 3 months, class II–IV according to New York Heart Association, and of various etiologies. Exclusion criteria were admission with infectious diseases or other conditions associated with inflammation, and

Table 1 Baseline characteristics of patients with and without HF

	HF patients (n = 68)	Non-HF patients (n = 65)	P value
Demographic parameters			
Mean age (years) ± SD	70.8 ± 10.1	69.8 ± 12.4	NS
Male/Female	39/29	21/44	0.005
Causes of admission			
Exacerbation of HF	35 (51)	0	
Acute coronary syndrome	13 (19)	18 (28)	NS
Exacerbation of chronic pulmonary disease	5 (7)	11 (17)	NS
Cerebrovascular accident	13 (19)	10 (15)	NS
Cardiac arrhythmias	5 (7)	8 (12)	NS
Syncope or faintness	3 (4)	12 (19)	<0.01
Other	3 (4)	6 (9)	NS
Comorbid conditions			
Ischemic heart disease	50 (73)	17 (26)	<0.001
Diabetes mellitus	35 (51)	15 (23)	0.003
Chronic renal failure	23 (34)	10 (15)	0.009
Hypertension	39 (57)	44 (68)	NS
Dyslipidemia	36 (53)	40 (61)	NS
Smoking/Chronic pulmonary disease	29 (43)	20 (31)	NS
Chronic anemia	18 (26)	11 (17)	NS
Past history of atrial fibrillation	8 (12)	8 (12)	NS
Peptic disease	5 (7)	12 (18)	NS
Valvular disease	8 (12)	7 (11)	NS
Overweight/Obesity	5 (7)	5 (8)	NS
Peripheral vascular disease	4 (6)	3 (5)	NS
Medications			
Diuretics	65 (96)	22 (34)	<0.001
Beta-receptor blockers	45 (66)	28 (43)	0.01
Oral hypoglycemic drugs	24 (35)	7 (11)	0.01
Calcium channel blockers	15 (22)	25 (38)	0.02
Insulin	11 (16)	2 (3)	0.04
Nitrates	26 (38)	16 (25)	0.04
Angiotensin converting enzyme inhibitors	39 (57)	29 (45)	NS
Angiotensin II receptor blockers	14 (21)	6 (9)	NS
Aspirin/Clopidogrel	51 (75)	51 (78)	NS
Digoxin	5 (7)	1 (2)	NS
Statins	31 (46)	19 (29)	NS
Anti-arrhythmic drugs	13 (19)	11 (17)	NS
Anticoagulants	10 (15)	5 (8)	NS
H_2/proton pump inhibitors	31 (46)	26 (40)	NS
Alpha-receptor blockers	7 (10)	5 (8)	NS
Corticosteroids	9 (13)	6 (9)	NS
Bronchodilators	15 (22)	7 (11)	NS
Antibiotics	10 (15)	8 (12)	NS

HF, heart failure; NS, not statistically significant. Values are number (%) of cases

specific conditions known to interfere with Mg metabolism [i.e. renal failure (creatinine ≥1.5 mg/dl), patients receiving Mg-containing drugs and patients with malignant diseases, alcoholism, thyroid, parathyroid or active liver disease].

Serum Mg, CRP and intracellular Mg were determined before discharge and following 5 weeks. On discharge, all the patients demonstrated no shortness of breath in the resting state, no orthopnea, paroxysmal nocturnal dyspnea or radiographic evidence of pulmonary congestion. Thus, their current state was designated as stabilized HF. During the second stage of the trial, the patients were instructed to strictly comply with the treatment protocol and to consult us about any changes in their medications.

Intracellular Mg was determined in peripheral blood mononuclear cells using atomic absorption spectrometry methods, as described previously [25]. Total protein of each cell sample was determined by Bradford's assay [26] and the results were presented as mmol per gram cell protein.

Statistical analysis

The data were analyzed using BMDP statistical software [27]. All the data are presented as means ± SD. Since CRP results did not yield a Gaussian distribution, we performed a log-transformation on these values. Analysis of variance (ANOVA) was used to

Table 2 Baseline serum CRP and Mg values in patients with HF vs. those without HF

Data	HF patients (n = 68)	Non-HF patients (n = 65)	P value
Serum CRP (mg/dl)	39.8 ± 50	12.2 ± 18	<0.001
Serum Mg (mmol/l)	0.78 ± 0.08	0.86 ± 0.07	<0.001
Proportion of patients with normal CRP values (≤3 mg/dl)	5/68 (7.4%)	18/65 (27.7%)	0.001

CRP, C-reactive protein; Mg, magnesium; HF, heart failure. Values are presented as mean ± SD

compare the basal results of serum CRP, serum Mg and other continuous variables between the groups. For the treatment stage, the ANOVA with repeated measurements was applied to determine the changes occurring during 5 weeks within a given group in serum log CRP, serum Mg and intracellular Mg, in relation to Mg treatment. Discrete variables were compared, where appropriate, using Pearson's χ^2 Test or Fisher's Exact Test. Pearson's correlation test was applied to determine correlation between serum Mg and log CRP. Differences yielding P-values less than 0.05 were considered statistically significant.

Results

Stage 1: the relationship between serum Mg and CRP

Baseline characteristics of the patients with and without HF are summarized in Table 1, while Table 2 demonstrates the differences in baseline serum CRP and Mg values in HF vs. non-HF patients. Only 23 out of 133 patients (17.3%) demonstrated normal serum CRP values. However, in patients diagnosed with HF, mean serum CRP was significantly higher than in non-HF subjects (39.8 ± 50 mg/dl vs. 12.2 ± 18 mg/dl, $P < 0.001$). The percentage of patients with normal CRP values was significantly lower in a group subsequently diagnosed with HF (7.4% vs. 27.7% in non-HF patients, $P < 0.001$). Mean serum Mg values were significantly decreased in HF patients compared to their non-HF counterparts (0.78 ± 0.08 mmol/l vs. 0.86 ± 0.07 mmol/l, $P < 0.001$). A significant inverse correlation was found between serum levels of Mg and log CRP within the entire patient group (Fig. 1, $r = -0.28$, $P = 0.002$).

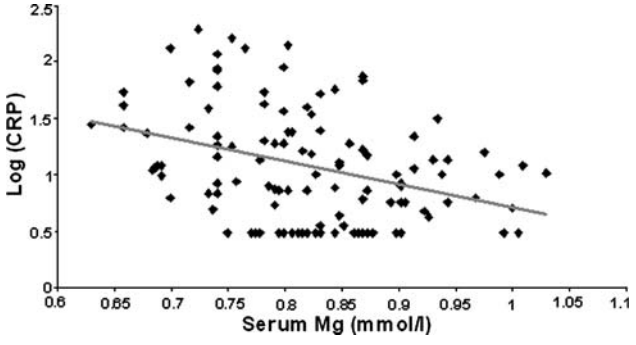

Fig. 1 The inverse correlation between serum levels of Mg and log CRP within the entire patient group ($r = -0.28$, $P = 0.002$). Log CRP, logarithmic transformation of C-reactive protein; Mg, magnesium

Stage 2: Effect of Mg administration on CRP, serum and intracellular Mg

Table 3 summarizes the clinical data of the Mg-treated or Mg non-treated HF patients. As can be seen, at this stage of the study their baseline characteristics were, irrespective of Mg treatment, comparable with regard to their age, gender, comorbid conditions, causes of admission and medications at discharge. During the study period, no significant changes in treatment protocol were performed. No participant exhibited adverse effects following Mg administration throughout the entire study period.

The results of log CRP, mean serum Mg and intracellular Mg at baseline and following 5 weeks of Mg treatment, are demonstrated in Fig. 2a–c. In the Mg-treated HF group A (Fig. 2a), log CRP decreased significantly after 5 weeks of treatment (from basal 1.4 ± 0.4 to 0.8 ± 0.3, $P < 0.001$). In group B, this difference did not reach statistical significance (1.5 ± 0.7 to 1.2 ± 0.6, $P = 0.3$). Concomitantly, mean serum Mg in Mg-treated HF patients (group A) rose from basal 0.74 ± 0.04 mmol/l to 0.88 ± 0.08 mmol/l ($P < 0.001$), while in the non-treated HF group B it increased from basal 0.82 ± 0.08 mmol/l to 0.88 ± 0.08 mmol/l (Fig. 2b, $P = 0.04$). Basal intracellular Mg rose significantly in group A (61 ± 8 to 67 ± 12 mmol/g cell protein, Fig. 2c, $P = 0.01$). By contrast, in the non-treated group B, intracellular Mg remained statistically not different from the baseline (66 ± 12 to 70 ± 12 mmol/g cell protein, Fig. 2c, $P = 0.7$).

Table 4 illustrates the percentages of the patients that responded to Mg supplementation by changes in serum Mg, CRP and intracellular Mg. Most of the Mg-treated patients (94%) demonstrated decreased CRP. Similarly, serum and intracellular Mg were increased in 94% and 82%, respectively, of these patients.

Discussion

In the present investigation, patients with HF demonstrated augmented baseline CRP and decreased Mg levels, when compared with patients acutely hospitalized for reasons other than HF. Inverse correlation

Table 3 Baseline characteristics of patients with HF treated or not treated with Mg

	Group A Treated patients (n = 17)	Group B Not treated patients (n = 18)
Demographic parameters		
Mean age (years) ± SD	71.0 ± 7.8	72.3 ± 7.7
Male/Female	9/8	10/8
Causes of admission		
Exacerbation of HF	10 (59)	9 (50)
Acute coronary syndrome	5 (29)	4 (22)
Exacerbation of chronic pulmonary disease	1 (6)	1 (6)
Cerebrovascular accident	1 (6)	2 (11)
Syncope	0	2 (11)
Comorbid conditions		
Ischemic heart disease	13 (76)	14 (78)
Diabetes mellitus	11 (65)	7 (39)
Chronic renal failure	5 (29)	5 (28)
Hypertension	12 (71)	11 (61)
Dyslipidemia	7 (41)	9 (50)
Smoking/Chronic pulmonary disease	7 (41)	9 (50)
Chronic anemia	5 (29)	4 (22)
Past history of atrial fibrillation	3 (18)	2 (11)
Valvular disease	5 (29)	1 (6)
Overweight/Obesity	3 (18)	1 (6)
Peripheral vascular disease	1 (6)	2 (11)
Medications		
Diuretics	16 (94)	17 (94)
Beta-receptor blockers	11 (65)	13 (72)
Oral hypoglycemic drugs	6 (35)	7 (39)
Calcium channel blockers	6 (35)	2 (11)
Insulin	4 (23)	2 (11)
Nitrates	5 (29)	6 (33)
Angiotensin converting enzyme inhibitors	9 (53)	9 (50)
Angiotensin II receptor blockers	5 (29)	6 (33)
Aspirin/Clopidogrel	13 (76)	14 (78)
Digoxin	0	1 (6)
Statins	10 (59)	8 (44)
Anti-arrhythmic drugs	3 (18)	3 (17)
Anticoagulants	2 (12)	5 (28)
H_2/proton pump inhibitors	8 (47)	9 (50)
Alpha-receptor blockers	3 (18)	0
Corticosteroids	2 (12)	1 (6)
Bronchodilators	3 (18)	2 (11)
Antibiotics	3 (18)	3 (17)

HF, heart failure; Mg, magnesium. Values are presented as a number (%) of cases

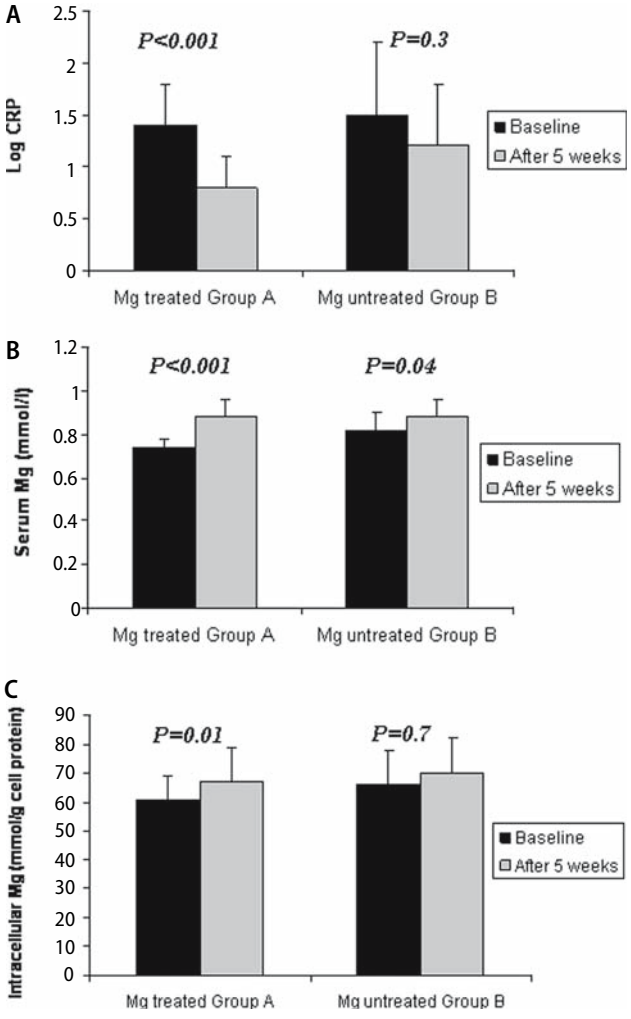

Fig. 2 The effect of Mg treatment on log CRP (**a**), serum Mg (**b**) and intracellular Mg (**c**) in patients with HF. Values are presented as means ± SD. Log CRP, logarithmic transformation of C-reactive protein; Mg, magnesium

was found between serum Mg and CRP. These parameters were reevaluated after 5 weeks in those patients who were diagnosed with HF and received, or not, oral Mg citrate. Following Mg treatment, CRP significantly decreased and, concomitantly, a significant elevation of intracellular Mg was evident. Serum Mg also rose significantly in Mg receiving HF patients. One would conclude that oral Mg supplementation to HF patients significantly attenuates blood levels of CRP, a biomarker of inflammation and, consequently, that targeting the inflammatory cascade by Mg administration might prove a useful tool for improving the prognosis in HF.

CRP, a well-known biomarker of inflammation, has been reported to play an important role in induction and/or aggravation of HF [11–17]. After myocardial insult, CRP binds to the ischemic myocardium and activates the classical cascade of the complement system [11]. As a result, ischemic myocytes undergo lysis, acquiring the appearance of eosinophilic droplets [28, 29]. Since myocyte lysis occurs in various types of cardiomyopathies [30] and following myocardial infarction [13], it is conceivable that CRP, which has been found in high concentrations in serum of HF patients, may be one of the factors contributing to the development and/or aggravation of HF. A recent study by Satoh et al. [10] demonstrated a direct correlation between augmented CRP and enhanced TNF-alpha expression in myocardium of patients with dilated car-

Table 4 Percentage of responders to Mg supplementation in patients with HF

	Group A 5 weeks of Mg treatment (n = 17)	Group B Untreated (n = 18)
Decreased serum CRP	94%	72%
Increased serum Mg	94%	61%
Increased intracellular Mg	84%	44%

Mg, magnesium; CRP, C-reactive protein; HF, heart failure

diomyopathy. Moreover, in this study both CRP and TNF-alpha mRNA levels were shown to be inversely correlated with systolic function, while any pharmacologic intervention resulting in improvement of patients' cardiac performance was followed by decrease in both CRP and TNF-alpha mRNA expression [10]. In fact, any therapy aimed to reduce the expression of proinflammatory proteins, including CRP, would seem to improve the course of HF [31–33]. However, a number of clinical studies aiming to decrease synthesis of specific pro-inflammatory cytokines in an attempt to attenuate HF progression have not only been unsuccessful, but in some cases even brought about worsening of HF [34, 35]. Two main reasons for this have been recently pointed out in an extensive review summarizing the existing clinical experience on targeting inflammatory mediators in HF [36]. First, some of the specific monoclonal antibodies and/or soluble receptors used for targeting the pro-inflammatory cytokines either act by themselves as toxic substances, or start acting as agonists for the cytokine they bind. Second, physiologic levels of some of the pro-inflammatory cytokines, such as TNF-alpha and/or its soluble receptor, proved to be mandatory for eliciting cytoprotective responses in cardiac cells in the context of HF [36].

Recently, new and thus far more successful approaches, aiming to decrease systemic inflammatory responsiveness instead of targeting the specific components of the inflammatory cytokine cascade in HF, have been proposed. The most promising treatment protocol appears to be the application of intravenous immunoglobulin to HF patients, inducing a marked increase in plasma levels of physiologic anti-inflammatory mediators accompanied by a 10% increase in left ventricular ejection performance [37].

The present investigation has been designed to test yet a different strategy, this time using Mg supplementation for non-specific targeting of the systemic inflammatory responsiveness in HF patients. The main outcome of the study was that Mg administration during a period of 5 weeks produced a significant CRP reduction in patients with HF. Anti-inflammatory effects of Mg have thus far been reported only in a limited number of studies [38–40]. They were suggested to be mediated via its antagonism to calcium, the ion playing an important role in inflammation [41] as well as in protein synthesis and transmembrane ion transport. An inverse correlation between daily Mg intake and systemic inflammation in the elderly has also been well documented [22, 42]. Recent data based on the National Health and Nutrition Examination Survey 1999–2000 (NHANES), suggest the likelihood of cardiovascular patients receiving regular and prolonged Mg supplementation to have lower CRP levels [43]. Furthermore, in a recent study by Bo et al., it has been demonstrated that not only in patients with metabolic syndrome but also in their healthy counterparts lower dietary fiber intake, which is associated with lower daily Mg consuming, is linked to augmented CRP levels [21]. To the best of our knowledge, this is the first study designed to demonstrate CRP reduction following Mg administration in HF patients. At baseline, in accordance with other investigations, our HF patients demonstrated high serum CRP and low serum Mg levels. Statistical analysis suggested that a significant drop of CRP, evident following 5 weeks of Mg treatment, was the result of interaction between the increased CRP levels associated with HF, the effect of Mg administration and, to a lesser extent, the effect of time. It seems plausible that the final outcome of Mg administration, i.e. the decrease in CRP, could be the result of a combined effect of the increase in serum Mg levels and concomitant elevation of intracellular Mg, so that even apparently small increase in both serum and intracellular Mg would result in a CRP drop.

In conclusion, the present study has demonstrated that HF patients are capable of responding to oral Mg supplementation by reduction of CRP levels. The significance of this study is limited by a small number of participants and short duration of Mg administration. However, if similar results emerge in further investigations performed on larger groups of patients, this observation might be of a great importance. Mg-containing drugs are cheap and devoid of any significant adverse effects, the only accepted contraindication being renal failure. A significant reduction of the inflammatory status represented by a drop in CRP, a known marker of inflammation, has therefore a potential to attenuate the progression of the disease and perhaps improve the prognosis of HF.

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