Magnesium citrate supplementation decreased blood pressure and HbA1c in normomagnesemic subjects with metabolic syndrome: a 12-week, placebo-controlled, double-blinded pilot trial

Kseniia Afitska[1,a], Julia Clavel[1,a], Klaus Kisters[2], Jürgen Vormann[3], Tanja Werner[1]

[1] Protina Pharmazeutische GmbH, 85737 Ismaning, Germany; [2] St. Anna Hospital, 44649 Herne, Germany; [3] Institute for Prevention and Nutrition, 85737 Ismaning, Germany

Correspondence: Tanja Werner. Protina Pharmazeutische GmbH, 85737 Ismaning, Germany <werner.tanja@protina.de>

Abstract. Magnesium (Mg) supplementation was shown to improve metabolic syndrome (MetS) parameters in hypomagnesemic patients. The current study evaluated the role of Mg in normomagnesemic individuals with MetS. Patients were randomly assigned to 400 mg Mg as Mg citrate or placebo daily for 12 weeks. Blood pressure (BP), HbA1c, plasma concentrations of glucose, Mg and Ca, blood-ionized Mg, serum concentrations of cholesterol, triglycerides, vitamin D, creatinine, interleukin-6, and C-reactive protein were measured at baseline and after 12 weeks. Data were obtained from $n = 13$ in the Mg supplemented and $n = 11$ in the placebo group. Mg supplementation led to a significant increase in plasma Mg concentration (0.78 ± 0.07 mmol/L to 0.83 ± 0.07 mmol/L) and a decrease in systolic and diastolic BP (baseline: $145 \pm 10/85 \pm 3$ mmHg; 12 weeks: $121 \pm 5/79 \pm 3$ mmHg). HbA1c decreased significantly in the Mg group ($6.43 \pm 0.64\%$ to $6.15 \pm 0.55\%$), and the difference in change between placebo and Mg group was significant. Serum vitamin D levels significantly increased only in the Mg group. In normomagnesemic individuals with MetS, oral Mg citrate supplementation reduced HbA1c and BP.

Key words: magnesium citrate, oral supplementation, metabolic syndrome, glycemic control, blood pressure

Metabolic syndrome (MetS) is a pathologic condition characterized by a set of metabolic impairments. To diagnose MetS, any three of following parameters should be met: insulin resistance, obesity, atherogenic dyslipidemia (high plasma triglyceride [TG] levels and/or low high-density lipoprotein cholesterol levels), and hypertension [1, 2]. These parameters are interrelated and share underlying mediators, mechanisms, and pathways, such as inflammation, oxidative stress, endothelial dysfunction, impaired function of β-cells, etc. [1, 3, 4]. The global prevalence of MetS can be estimated to be about one quarter of the world population [5]. This makes MetS a serious health problem,

[a] Both authors equally contributed to the manuscript

To cite this article: Afitska K, Clavel J, Kisters K, Vormann J, Werner T. *Magnes Res* 2021; 34(3): 130-139. doi: 10.1684/mrh.2021.0489

doi: 10.1684/mrh.2021.0489

taking into account that MetS increases the risk of various cardiovascular diseases [6-8], of cancer [9], and of incident diabetes [10].

Changes in the concentration of cellular magnesium (Mg) might be an underlying common mechanism of the "insulin resistance" of the MetS, essential hypertension, altered glucose tolerance, and type 2 diabetes [11]. Mg plays an important role in insulin action as it is required for the activation of the tyrosine kinase domain of the insulin receptor, an important step in transmitting the insulin signal into cells [12]. Higher Mg intake decreases the risk of incident metabolic impairments (impaired glucose tolerance, insulin resistance, or hyperinsulinemia) [13]. Almost 80% of patients with MetS also suffer from hypertension, and the optimal antihypertensive treatment is being debated [2]. Recent large meta-analysis showed a correlation between Mg deficiency and hypertension and its successful therapy with Mg as well as a positive effect on increased systolic and diastolic blood pressure (BP) values [14].

Several lines of evidence confirm that Mg plays an important role in MetS. Patients with MetS have significantly lower serum Mg levels compared to healthy people [3, 15, 16]. Dietary Mg intake among nondiabetic individuals with MetS is way below recommended dietary allowance [17], and an inverse association was found between dietary Mg intake and the prevalence of the MetS [18-20]. Moreover, Mg intake was inversely associated with metabolic biomarkers of insulin resistance [17] and with systemic inflammation [18]. A meta-analysis of five studies has shown that for every 100 mg/day increment in Mg intake, the overall risk of having MetS was lowered by 17% [21]. Mg supplementation (382 mg/day for 4 months) significantly reduced systolic and diastolic BP values, insulin resistance, fasting glucose, and TG levels in metabolically obese, normal-weight individuals [22], and in patients with MetS [23]. Another study, however, showed that Mg supplementation (400 mg/day for 3 months) had no influence on BP, insulin resistance, levels of insulin, TGs, and fasting blood glucose in women with MetS without diabetes [24]. According to systematic review, approximately half of the clinical studies show no effect of Mg supplementation on certain components of MetS (high BP, hyperglycemia, hypertriglyceridemia, high-density lipoprotein cholesterol levels, and insulin sensitivity), although the majority of studies demonstrate improvement of at least one of these parameters upon Mg supplementation [25].

In hypomagnesemic patients, the effect of Mg supplementation is modular as it includes both the improvement of hypomagnesemia and the effect of additional Mg supplementation. We were interested in the latter one; therefore, in this study, we investigated the potential benefit of Mg supplementation in normomagnesemic individuals with MetS.

Materials and methods

This single-center, randomized, double-blinded, placebo-controlled pilot study was performed to assess the effect of 400 mg Mg in the form of Mg citrate on metabolic and physiologic parameters. All participants gave their written informed consent before starting the study. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethical Committee at the Ärztekammer Westfalen-Lippe and Westfälischen Wilhelmsuniversität (2015-493-f-S). This trial was registered at clinicaltrials.gov (NCT03002545). Initially the study aimed to determine the effect of Mg supplementation on blood glucose control and insulin resistance within patients with type 2 diabetes (HbA1c > 6%). Due to low number of subjects with untreated diabetes within the prolonged recruiting phase (18 months), it was decided to change the focus and to proceed with available patients, majority of which (n = 42/50, *figure 1*) suffered from MetS.

Inclusion and exclusion criteria

Fifty patients were recruited among regular visits for different reasons in the St. Anna Hospital, Herne, Germany. Eligible individuals were men and women between 20 and 80 years of age with a MetS condition. MetS was determined by the presence of at least three of following symptoms: obesity determined as body mass index (BMI) > 25 kg/m^2, BP $\geq$ 130/85 mmHg, hyperinsulinemia determined as HbA1c $\geq$ 5.7%, and dyslipidemia determined as TG > 150 mg/dL. Patients with two or less symptoms (n = 8) were not eligible for the study (*figure 1*).

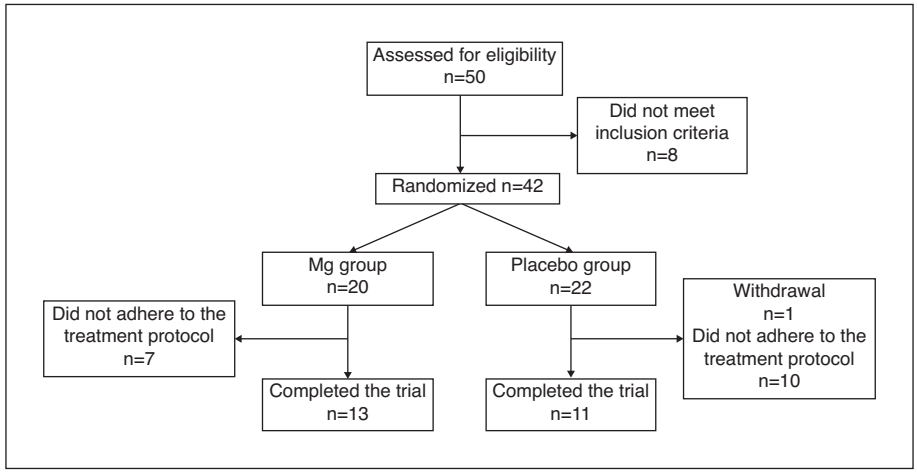

Figure 1. Flow of participants in the clinical trial.

Exclusion criteria included pregnancy and lactation, patients with severe kidney dysfunction (estimated glomerular filtration rate < 30 mL/min), anemia, the use of insulin, oral antidiabetics, diuretics, antacids, or proton pump inhibitors in the 4 week-period prior to study enrolment. Similarly, participants who had taken mineral or vitamin supplements, food supplements, or fortified foods that contain Mg in 4 weeks period prior to the study enrolment were also excluded.

Patients under hypertension treatment (n = 5 in the Mg group and n = 8 in the placebo group) were taking the following medication (single or multitherapy): Amlodipine, Aprovel Bipreterax, Beloc Zok, Candesartan, Carvedilol, Diovan, Lercanidipin, Nebilet, Ramipril, Valsartan, and Valsacor. During the study, the antihypertensive treatment was not changed.

Study design and procedures

Forty-two subjects (mean age 66 ± 9 years) were randomly assigned to receive either 400 mg Mg in the form of Mg citrate (Magnesium-Diasporal 400 EXTRA, Protina GmbH, Ismaning, Germany) or an identical looking and tasting placebo daily for 12 weeks. Mg citrate was chosen as it provides better bioavailability of Mg compared to inorganic salts such as Mg oxide [26]. Complete data set for analysis was obtained from n = 11 from the placebo group and n = 13 from the Mg group. Seventeen participants did not adhere to the treatment protocol (n = 7 in Mg group and n = 10 in placebo group), and one participant in placebo group dropped out for unknown reasons (*figure 1*).

Parameters were assessed at the beginning of the study (baseline) and after 12 weeks of supplementation. Body height (cm) was measured using a stadiometer (standard equipment) and body weight (kg) was assessed using regular scales to the nearest of 0.1 kg in nonfasting conditions with subjects wearing light clothing without shoes. BMI was calculated as body weight (kg) divided by height (m) squared. BP was determined according to recommendations proposed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [27]. The auscultatory method of BP measurement was used for participants who had sat quietly for at least 5 minutes prior to the procedure. The average of two measurements of BP was recorded.Blood samples for serum and plasma were collected in tubes without anticoagulant or in tubes containing ethylenediaminetetraacetic acid, respectively, and processed according to standard procedures. Analyses were carried out by a Cobas analyzer (Roche, Mannheim, Germany). Blood samples for measurement of whole blood ionized Mg were collected in Eppendorf tubes that contained no anticoagulants, and right after the collection were subjected to measurement by a pHOx+ analyzer (NOVA, Rödermark, Germany).

Measured parameters included: systolic and diastolic BP, HbA1c, plasma glucose (nonfasting, so-called spontaneous or random), serum cholesterol, serum TGs, plasma Mg, plasma Ca, ionized Mg (from the whole blood), serum vitamin D, serum creatinine, serum interleukin-6 (IL-6), and serum C-reactive protein. Quality of life was assessed by SF-36 questionnaire.

Statistics

Data are expressed as mean ± standard deviation. The normal distribution of our population (Gaussian distributions) was tested using the Kolmogorov and Smirnov method. Comparisons between groups were analyzed using the unpaired *T* test (equality of variances was assessed prior to the analysis). Paired *T* test was used to assess the difference between data in each group before and after intervention. For all statistical tests, $P \leq 0.05$ was considered statistically significant.

Results

Demographic data of the study population

All patients in this study were of Caucasian origin. Demographic and clinical characteristics were balanced between treatment groups (*table 1*). After several patients were removed from the analysis as they did not adhere to the treatment protocol, the difference in systolic BP between the groups became significant.

Effect of Mg supplementation on Mg levels

Subjects included in this study were normomagnesemic, with plasma Mg concentrations >0.75 mmol/L (mean concentration at baseline 0.79 ± 0.07 mmol/L) and blood-ionized Mg in the range of 0.55 to 0.75 mmol/L (mean concentration at baseline 0.62 ± 0.11 mmol/L). Plasma Mg concentrations in the Mg group significantly increased after 12 weeks (from 0.78 ± 0.07 to 0.83 ± 0.07 mmol/L, $P = 0.01$; *table 1*). There was neither a significant change in plasma Mg levels within the placebo group nor a significant difference between the groups at the baseline or at 12 weeks. In contrast to plasma Mg concentration, the change in blood-ionized Mg levels was not significant in both groups (–0.05 ± 0.08 and –0.01 ± 0.10 mmol/L in Mg and placebo groups, respectively).

Effect of Mg supplementation on glycemic control

To assess the effect of Mg supplementation on glycemic control, HbA1c and spontaneous plasma glucose levels were measured at baseline and after 12 weeks of intervention. HbA1c levels decreased significantly within the Mg group by –0.28 ± 0.27% ($P < 0.01$) but not within the placebo group (–0.04 ± 0.18%, $P = 0.53$). The difference between changes in both groups was also significant ($P = 0.02$).

Mg supplementation had no effect on the levels of plasma glucose, and there was no statistically significant difference between the groups at any time point.

Effect of Mg supplementation on BP

We observed a difference at baseline with significantly higher values for systolic BP in the Mg group compared to the placebo group, which is likely due to BP medication. Five participants in the Mg group and eight in the placebo group were receiving an antihypertensive drug at baseline. During the study, the medication regimen for BP was not changed. After removing patients receiving antihypertensive medication from the analysis, we observed no difference between Mg and placebo groups at the baseline (data not shown), but the following effect of Mg treatment remained the same as described below (and with the similar level of significance).

After 12 weeks of intervention, systolic BP values were significantly lower in Mg group (120.8 ± 4.6 vs. 133.5 ± 7.6 mmHg, $P < 0.001$). Mg supplementation led to a pronounced decrease in systolic BP compared to placebo (–24.2 ± 11.5 vs. –1.0 ± 3.8 mmHg, respectively, $P < 0.001$).

Diastolic BP was significantly decreased within the Mg group after 12 weeks when compared with baseline (–6.8 ± 3.7 mmHg, $P < 0.001$). No significant difference was found in the placebo group (–1.0 ± 2.8 mmHg). After 12 weeks of supplementation, there was a

Table 1. General and metabolic characteristics of participants with metabolic syndrome at baseline and after 12 weeks of intervention with magnesium citrate or placebo.

	Reference values	Placebo group (n = 11)				Mg group (n = 13)				P-value: placebo vs. Mg groups		
		Baseline	12 weeks	Change	P for change	Baseline	12 weeks	Change	P for change	Change	Baseline	12 weeks
Age (years)		71.9 ± 7.8				61.8 ± 10.7						
Sex		55% female				61% female						
Height (cm)		170.9 ± 8.0				170.9 ± 10.3						
Body weight (kg)		102.7 ± 18.2	102.0 ± 18.2	–0.7 ± 1.5	0.15	98.3 ± 15.9	97.6 ± 16.0	–0.7 ± 1.5	0.15	0.91	0.55	0.55
Body mass index (kg/m^2)	<25	35.2 ± 5.6	34.9 ± 5.6	–0.2 ± 0.5	0.15	33.7 ± 5.1	33.5 ± 5.1	–0.2 ± 0.6	0.17	1.00	0.53	0.53
Plasma Mg (mmol/L)	0.75–1	0.81 ± 0.07	0.79 ± 0.05	–0.01 ± 0.05	0.38	0.78 ± 0.07	0.83 ± 0.07	0.05 ± 0.06	**0.01**	**0.01**	0.38	0.15
Mg ion (blood) (mmol/L)	0.55–0.75	0.58 ± 0.09	0.56 ± 0.07	–0.01 ± 0.10	0.67	0.65 ± 0.11	0.60 ± 0.08	–0.05 ± 0.08	0.059	0.37	0.11	0.24
HbA1c (%)	4.8–5.7	6.16 ± 0.51	6.13 ± 0.42	–0.04 ± 0.18	0.53	6.43 ± 0.64	6.15 ± 0.55	–0.28 ± 0.27	**0.0036**	**0.02**	0.30	0.90
TG (mg/dL)	<200	240.9 ± 69.6	208.6 ± 81.6	–32.3 ± 37.4	**0.04**	187.6 ± 65.8	179.2 ± 52.7	–8.4 ± 64.7	0.66	0.35	0.10	0.34
Systolic BP (mmHg)	<120	134.5 ± 6.6	133.5 ± 7.6	–1.0 ± 3.8	0.42	145.0 ± 10.4	120.8 ± 4.6	–24.2 ± 11.5	**0.00001**	**0.000009**	**0.01**	**0.00008**
Diastolic BP (mmHg)	<80	84.0 ± 4.6	83.0 ± 3.6	–1.0 ± 2.8	0.28	85.4 ± 3.1	78.5 ± 2.8	–6.8 ± 3.7	**0.00003**	**0.0004**	0.41	**0.0036**
Vitamin D (ng/mL)	>20	25.6 ± 15.8	27.6 ± 14.2	2.0 ± 7.5	0.42	14.7 ± 6.9	19.9 ± 8.3	5.2 ± 4.9	0.003	0.24	0.06	0.13
Creatinin (mg/dL)	0.7–1.2	1.02 ± 0.12	1.06 ± 0.19	0.04 ± 0.10	0.27	0.94 ± 0.18	0.93 ± 0.16	–0.02 ± 0.10	0.59	0.22	0.28	0.09
Glucose (mg/dL)	82–115	119.3 ± 23.1	119.1 ± 19.1	–0.2 ± 25.1	0.98	130.9 ± 32.3	118.6 ± 33.1	–12.3 ± 35.3	0.25	0.39	0.37	0.97
Cholesterol (mg/dL)	<200	212.9 ± 32.9	204.0 ± 34.2	–8.9 ± 23.0	0.28	193.5 ± 40.7	189.5 ± 37.0	–4.0 ± 20.6	0.51	0.61	0.25	0.37
IL-6 (pg/mL)	<15	6.52 ± 6.97	5.54 ± 3.68	–0.98 ± 5.63	0.59	3.72 ± 2.41	3.30 ± 1.45	–0.42 ± 2.51	0.57	0.78	0.25	0.09
CRP (mg/dL)	<0.5	0.69 ± 0.59	0.51 ± 0.41	–0.18 ± 0.25	0.06	0.51 ± 0.58	0.57 ± 0.49	0.06 ± 0.74	0.78	0.31	0.49	0.77
Plasma Ca (mmol/L)	2.15–2.55	2.44 ± 0.15	2.44 ± 0.13	–0.01 ± 0.11	0.81	2.37 ± 0.09	2.38 ± 0.10	0.00 ± 0.07	0.83	0.74	0.19	0.25
Ca/Mg ratio		3.00 ± 0.24	3.03 ± 0.21	0.03 ± 0.30	0.73	3.07 ± 0.33	2.88 ± 0.29	–0.19 ± 0.26	**0.026**	0.08	0.58	0.20

BP: blood pressure; IL-6: interleukin-6; Mg: magnesium; TG: triglyceride. Values are mean ± standard deviations. Change is defined as the difference between respective values after 12 weeks of supplementation and at the baseline.

significant difference in diastolic BP between Mg and placebo groups ($P < 0.01$).

Other parameters

During the study, no significant body weight changes were recorded.

After 12 weeks of supplementation with Mg citrate or placebo, vitamin D levels increased in both groups. However, the increase was significant only in Mg group ($P < 0.01$). This effect could be explained as study start was in springtime and ended in summer, which must have led to longer sun exposition periods and therefore increased vitamin D levels. Moreover, Mg plays an important role in vitamin D metabolism [28, 29] and Mg supplementation was shown to increase vitamin D concentration [30-32], which could lead to the greater difference in Mg group.

No significant changes occurred in both Mg and placebo groups in following parameters: cholesterol, creatinine, IL-6, and C-reactive protein. Level of TG significantly decreased in placebo group, but there was no significant difference between placebo and Mg group neither on baseline nor at 12 weeks. There were no changes in plasma Ca levels, but as plasma Mg levels increased in Mg group, Ca/Mg ratio showed significant decrease after 12 weeks of Mg supplementation (3.07 ± 0.33 to 2.88 ± 0.29, $P = 0.03$).

Neither of groups showed significant improvement in overall well-being (results quality of life questionnaire [SF-36], data not shown).

There were no adverse effects reported within the Mg or placebo group. One person in the Mg group reported about soft stool, but this effect was transient.

Discussion

The aim of this study was to assess the effect of Mg supplementation in the form of Mg citrate on glycemic control and BP in normomagnesemic subjects with MetS.

To prove the efficacy of Mg supplementation in increasing Mg levels in organism, plasma and blood-ionized Mg concentrations were measured. An easy and simple test to measure body Mg status is still lacking; therefore, serum or plasma Mg concentration is commonly used to assess patients' Mg status, although over 99% of total body Mg is extravascular with only 0.3% in serum [33]. According to the current reference values for plasma and ionized Mg concentrations, all study participants were normomagnesemic [33]. Twelve-week supplementation with 400 mg Mg in the form of Mg citrate led to a significant increase in plasma Mg concentrations after 12 weeks.

The Mg group also showed a significant increase in vitamin D concentration (14.7 ± 6.9 to 19.9 ± 8.3 ng/mL). This effect might be caused by the fact that enzymes involved in vitamin D metabolism are Mg dependent [28, 29]. Mg supplementation increased vitamin D concentration in the blood without any additional vitamin D supplementation [30-32].

Mg supplementation resulted in a significant reduction in HbA1c by 0.28%. The explanation is the importance of Mg for glycemic control. Serum Mg concentration negatively correlates with HbA1c as well as with serum glucose and insulin concentrations [34]. Mg supplementation significantly improved HbA1c, insulin levels, and HOMA-IR (homeostasic model assessment of insulin resistance) in patients with type 2 diabetes [35]. In the review of 12 randomized controlled trials (RCTs), Morais *et al*. showed that the positive effect of Mg supplementation on several parameters, such as HbA1c, fasting insulin and glucose, and HOMA-IR, was more pronounced in hypomagnesemic patients [36]. Only a few studies assessed glycemic control in nondiabetic patients with normal Mg levels, with no clear consensus in results [37-39]. In a RCT by Mooren *et al*. [37], Mg supplementation improved fasting plasma glucose and insulin indices in normomagnesemic, overweight, and nondiabetic subjects. This result could not be replicated in Korean adults by Lee *et al*. [38]. Similarly, no effect of Mg supplementation on HbA1c and HOMA-IR was shown in healthy normomagnesemic young men with family history of MetS [39]. The differences in results probably arise from different study settings (duration of supplementation, dosage and formulation of Mg, ethnic background). A systematic review and meta-analysis of 21 RCTs by Simental-Mendia *et al*. [40] found that Mg supplementation for $\geq$4months improved HOMA-IR and fasting glucose in diabetic and nondiabetic subjects compared to a supplementation period <4 months, but no effect on HbA1c could be found. The effect of Mg supplementation

in MetS was summarized in a review of RCTs by Guerrero-Romero *et al*. [25]. They identified 27 RCTs, focused on the improvement of at least one of the components of MetS. Six studies showed improvement of insulin sensitivity, and 4 out of 12 showed improvement of hyperglycemia upon Mg supplementation. Importantly, out of the nine studies that showed no positive outcome on the MetS, seven were conducted in healthy individuals, or in subjects with normal Mg levels at baseline.

Another parameter of MetS is dyslipidemia, characterized by high plasma TG levels and/or low high-density lipoprotein cholesterol levels. Patients in this study had TG levels of 209 ± 72 mg/dL, which is considered a high value (compared to normal value of <200 mg/dL). After 12 weeks, TG concentration decreased significantly in placebo group (–32 ± 37 mg/dL), whereas there was no change in Mg group, as well as no difference between placebo and Mg groups at any time point. At the beginning of the study, average cholesterol concentration was 202 ± 39 mg/dL (normal value is <200 mg/dL). Mg supplementation had no effect on cholesterol levels, and there was no significant difference between Mg and placebo groups at any time point. Our results correlate well with the data of Lima de Souza *et al*., who showed no significant change in cholesterol and TG levels in women with MetS (76.8% normomagnesemic) upon 12-week Mg treatment [24]. In a review of Guerrero-Romero *et al*., 7 studies out of 11 showed no effect on TG levels and on high-density lipoprotein cholesterol levels [25].

Within the Mg group, there was a significant decrease in systolic and diastolic BP values. At baseline, subjects from the Mg group suffered from isolated systolic hypertension (grade 1 hypertension regarding systolic BP and high normal for diastolic BP values) according to the Guidelines of the European Society of Cardiology and European Society of Hypertension [41]. Systolic BP significantly decreased after 12 weeks of supplementation (from 145.0 ± 10.4 to 120.8 ± 4.6 mmHg, difference of –24.2 mmHg), reaching normal values according to the guidelines. Diastolic BP in Mg supplemented patients displayed decrease from 85.4 ± 3.1 to 78.5 ± 2.8 mmHg (difference of –6.8 mmHg), reaching optimal values. Neither systolic nor diastolic BP was affected in placebo group. We here acknowledge that, despite randomization, there was a significant difference in baseline systolic BP between the two patient groups, which arose after several patients were excluded from the study for not adhering to the treatment protocol. The main reason is probably higher proportion of patients receiving antihypertensive drugs in placebo group (8/11 compared to 5/13 in Mg group). Excluding these patients from analysis removed the difference in systolic BP at the baseline but had no influence on the results on Mg supplementation.

There is an inverse correlation between serum Mg concentration and hypertension [42, 43]. Mg-induced vasodilation through the reduction of intracellular Ca^{2+} concentration within vascular smooth muscle cells seems to be one of the mechanisms how Mg is involved in BP regulation. In addition, extracellular Mg contributes to vasodilation by reducing endothelin-1 expression, directly stimulating prostacyclin, and inhibiting nitric oxide formation [44].

Although not all trials with oral Mg supplementation in hypertension resulted in significant reduction of BP, several meta-analyses confirmed a significant decrease in systolic BP of 3 to 4 mmHg and diastolic BP of 2 to 3 mmHg [45-48]. Zhang *et al*. mentioned that in stratified analyses, a greater reduction in BP tended to be found in trials with high quality or low dropout rate [45]. Moreover, in the meta-analysis of Rosanoff and Plesset [49], studies on patients with high BP (systolic BP > 155 mmHg) reported much stronger effects of oral Mg treatment on systolic BP (–18.7 mmHg) and diastolic BP (–10.9 mmHg) similar to our results. Interestingly, comparable results have also been shown in borderline hypertension [50].

In general, within meta-analyses, the comparison of highly heterogeneous studies regarding Mg dosage, treatment duration, Mg status, sample sizes, trial quality, and participant characteristics may lead to an underestimated potential of Mg in hypertension in some but not all subjects.

It is worth mentioning that systolic and diastolic BPs influence the risk of adverse cardiovascular events independently from each other, although systolic hypertension had a greater effect [51]. Taking this in consideration, Mg supplementation could help reducing both systolic and diastolic BP in people at risk for cardiovascular events.

Several limitations of the study have to be mentioned:
(1) small sample size;
(2) HbA1c as a sole parameter has limited informative value on glycemic control, especially regarding insulin sensitivity/insulin resistance;
(3) and dietary Mg intake was not considered.

Conclusion

In conclusion, oral Mg citrate supplementation reduced HbA1c levels and reduced BP in normomagnesemic persons with MetS. Further interventional studies are required to determine the effect size of Mg supplementation on different parameters of MetS and thus provide optimal alternative strategies to medication.

Disclosure

Financial support: This study was funded by Protina Pharmazeutische GmbH. **Conflict of interest:** The authors Afitska K., Clavel J., and Werner T. are employed at Protina GmbH. The sponsor had no role in the study design and data collection. The authors had full access to all the data in the study.

References

1. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech* 2009; 2 : 231-7.
2. Katsimardou A, Imprialos K, Stavropoulos K, Sachinidis A, Doumas M, Athyros V. Hypertension in metabolic syndrome: novel insights. *Curr Hypertens Rev* 2020; 16 : 12-8.
3. Guerrero-Romero F, Rodríguez-Morán M. Hypomagnesemia, oxidative stress, inflammation and metabolic syndrome. *Diabetes Metab Res Rev* 2006; 22 : 471-6.
4. Samson SL, Garber AJ. Metabolic syndrome. *Endocrinol Metab Clin North Am* 2014; 43 : 1-23.
5. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 2018; 20 : 12.
6. Mottillo S, Filion KB, Genest J, *et al*. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 56 : 1113-32.
7. Zheng Y, Xie Z, Li J, *et al*. Meta-analysis of metabolic syndrome and its individual components with risk of atrial fibrillation in different populations. *BMC Cardiovasc Disord* 2021; 21 : 90.
8. Xu JJ, Song Y, Jiang P, *et al*. Effects of metabolic syndrome on onset age and long-term outcomes in patients with acute coronary syndrome. *World J Emerg Med* 2021; 12 : 36-41.
9. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care* 2012; 35 : 2402-11.
10. Ford ES, Schulze MB, Pischon T, Bergmann MM, Joost HG, Boeing H. Metabolic syndrome and risk of incident diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. *Cardiovasc Diabetol* 2008; 7 : 35.
11. Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. *Arch Biochem Biophys* 2007; 458 : 40-7.
12. Gunther T. The biochemical function of Mg(2)+ in insulin secretion, insulin signal transduction and insulin resistance. *Magnes Res* 2010; 23 : 5-18.
13. Hruby A, Meigs JB, O'Donnell CJ, Jacques PF, McKeown NM. Higher magnesium intake reduces risk of impaired glucose and insulin metabolism and progression from prediabetes to diabetes in middle-aged Americans. *Diabetes Care* 2014; 37 : 419-27.
14. Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. *Nutrients* 2015; 7 : 8199-226.
15. La SA, Lee JY, Kim DH, Song EL, Park JH, Ju SY. Low magnesium levels in adults with metabolic syndrome: a meta-analysis. *Biol Trace Elem Res* 2016; 170 : 33-42.
16. Ghasemi A, Zahediasl S, Syedmoradi L, Azizi F. Low serum magnesium levels in elderly subjects with metabolic syndrome. *Biol Trace Elem Res* 2010; 136 : 18-25.
17. Wang J, Persuitte G, Olendzki BC, *et al*. Dietary magnesium intake improves insulin resistance among non-diabetic individuals with metabolic syndrome participating in a dietary trial. *Nutrients* 2013; 5 : 3910-9.
18. Song Y, Ridker PM, Manson JE, Cook NR, Buring JE, Liu S. Magnesium intake, C-reactive protein and the prevalence of metabolic syndrome in middle-aged and older U. S. women. *Diabetes Care* 2005; 28 : 1438-44.
19. He K, Liu K, Daviglus ML, *et al*. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; 113 : 1675-82.

20. Ford ES, Li C, McGuire LC, Mokdad AH, Liu S. Intake of dietary magnesium and the prevalence of the metabolic syndrome among U.S. adults. *Obesity (Silver Spring)* 2007; 15 : 1139-46.

21. Dibaba DT, Xun P, Fly AD, Yokota K, He K. Dietary magnesium intake and risk of metabolic syndrome: a meta-analysis. *Diabet Med* 2014; 31 : 1301-9.

22. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves the metabolic profile of metabolically obese, normal-weight individuals: a randomized double-blind placebo-controlled trial. *Arch Med Res* 2014; 45 : 388-93.

23. Rodríguez-Morán M, Simental-Mendía LE, Gamboa-Gómez CI, Guerrero-Romero F. Oral magnesium supplementation and metabolic syndrome: a randomized double-blind placebo-controlled clinical trial. *Adv Chronic Kidney Dis* 2018; 25 : 261-6.

24. Lima de Souza ESML, Cruz T, Rodrigues LE, *et al*. Magnesium replacement does not improve insulin resistance in patients with metabolic syndrome: a 12-week randomized double-blind study. *J Clin Med Res* 2014; 6 : 456-62.

25. Guerrero-Romero F, Jaquez-Chairez FO, Rodriguez-Moran M. Magnesium in metabolic syndrome: a review based on randomized, double-blind clinical trials. *Magnes Res* 2016; 29 : 146-53.

26. Werner T, Kolisek M, Vormann J, *et al*. Assessment of bioavailability of Mg from Mg citrate and Mg oxide by measuring urinary excretion in Mg-saturated subjects. *Magnes Res* 2019; 32 : 63-71.

27. Chobanian AV, Bakris GL, Black HR, *et al*. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289 : 2560-72.

28. Risco F, Traba ML. Influence of magnesium on the *in vitro* synthesis of 24,25-dihydroxyvitamin D3 and 1 alpha, 25-dihydroxyvitamin D3. *Magnes Res* 1992; 5 : 5-14.

29. Risco F, Traba ML. Possible involvement of a magnesium dependent mitochondrial alkaline phosphatase in the regulation of the 25-hydroxyvitamin D3-1 alpha-and 25-hydroxyvitamin D3-24R-hydroxylases in LLC-PK1 cells. *Magnes Res* 1994; 7 : 169-78.

30. Kisters K, Kisters L, Werner T, Deutsch A, Westhoff T, Grober U. Increased serum vitamin D concentration under oral magnesium therapy in elderly hypertensives. *Magnes Res* 2021; 33 : 131-2.

31. Vázquez-Lorente H, Herrera-Quintana L, Molina-López J, *et al*. Response of vitamin D after magnesium intervention in a postmenopausal population from the province of Granada, Spain. *Nutrients* 2020; 12 : 2283.

32. Dai Q, Zhu X, Manson JE, *et al*. Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial. *Am J Clin Nutr* 2018; 108 : 1249-58.

33. Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J* 2012; 5 : i3-14.

34. Bertinato J, Wang KC, Hayward S. Serum magnesium concentrations in the Canadian population and associations with diabetes, glycemic regulation and insulin resistance. *Nutrients* 2017; 9 : 296.

35. ELDerawi WA, Naser IA, Taleb MH, Abutair AS. The effects of oral magnesium supplementation on glycemic response among type 2 diabetes patients. *Nutrients* 2018; 11 : 44.

36. Morais JBS, Severo JS, de Alencar GRR, *et al*. Effect of magnesium supplementation on insulin resistance in humans: a systematic review. *Nutrition* 2017; 38 : 54-60.

37. Mooren FC, Kruger K, Volker K, Golf SW, Wadepuhl M, Kraus A. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects - a double-blind, placebo-controlled, randomized trial. *Diabetes Obes Metab* 2011; 13 : 281-4.

38. Lee S, Park HK, Son SP, Lee CW, Kim IJ, Kim HJ. Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normomagnesemic nondiabetic overweight Korean adults. *Nutr Metab Cardiovasc Dis* 2009; 19 : 781-8.

39. Cosaro E, Bonafini S, Montagnana M, *et al*. Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome. *Nutr Metab Cardiovasc Dis* 2014; 24 : 1213-20.

40. Simental-Mendia LE, Sahebkar A, Rodriguez-Moran M, Guerrero-Romero F. A systematic review and meta-analysis of randomized controlled trials on the effects of magnesium supplementation on insulin sensitivity and glucose control. *Pharmacol Res* 2016; 111 : 272-82.

41. Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39 : 3021-104.

42. Han H, Fang X, Wei X, *et al*. Dose-response relationship between dietary magnesium intake, serum magnesium concentration and risk of hypertension: a systematic review and meta-analysis of prospective cohort studies. *Nutr J* 2017; 16 : 26.

43. Sontia B, Touyz RM. Magnesium transport in hypertension. *Pathophysiology* 2007; 14 : 205-11.

44. de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiol Rev* 2015; 95 : 1-46.

45. Zhang X, Li Y, Del Gobbo LC, *et al*. Effects of magnesium supplementation on blood pressure: a meta-analysis of randomized double-blind placebo-controlled trials. *Hypertension* 2016; 68 : 324-33.

46. Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. *Eur J Clin Nutr* 2012; 66 : 411-8.

47. Jee SH, Miller ER 3rd, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *Am J Hypertens* 2002; 15 : 691-6.

48. Dibaba DT, Xun P, Song Y, Rosanoff A, Shechter M, He K. The effect of magnesium supplementation on blood pressure in individuals with insulin resistance, prediabetes, or noncommunicable chronic diseases: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2017; 106 : 921-9.

49. Rosanoff A, Plesset MR. Oral magnesium supplements decrease high blood pressure (SBP>155 mmHg) in hypertensive subjects on anti-hypertensive medications: a targeted meta-analysis. *Magnes Res* 2013; 26 : 93-9.

50. Kisters K. Oral magnesium supplementation improves borderline hypertension. *Magnes Res* 2011; 24 : 17.

51. Flint AC, Conell C, Ren X, *et al*. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019; 381 : 243-51.