Original Paper

Magnesium Replacement Improves the Metabolic Profile in Obese and Pre-Diabetic Patients with Mild-to-Moderate Chronic Kidney Disease: A 3-Month, Randomised, Double-Blind, Placebo-Controlled Study

Omer Toprak[a]*   Huseyin Kurt[b]   Yasin Sarı[b]   Cihat Şarkış[c]   Halil Us[b]
Ali Kırık[b]

[a]Department of Medicine, Division of Nephrology; [b]Department of Medicine, Division of Internal Medicine; [c]Department of Medicine, Division of Gastroenterology, Balikesir University School of Medicine, Balikesir, Turkey

Abstract
Background/Aims: Magnesium is an essential mineral for many metabolic functions. There is very little information on the effect of magnesium supplementation on metabolic profiles of chronic kidney disease (CKD) patients. The aim of this study was to assess the influence of magnesium supplementation on metabolic profiles of pre-diabetic, obese and mild-to-moderate CKD patients with hypomagnesemia. *Methods:* A total of 128 hypomagnesemic, pre-diabetic and obese patients with an estimated glomerular filtration rate between 90 and 30 ml/min/1.73m^2 were enrolled in a randomised, double-blind, placebo-controlled trial. Patients in the magnesium group received 365 mg of oral magnesium (*n* = 57) once daily for 3 months, while patients in the control group received a placebo (*n* = 61), also once daily for 3 months. Hypomagnesemia is defined by a serum magnesium level <1.8 mg/dl in males and <1.9 mg/dl in females; obesity is defined as a body mass index ≥30 kg/m^2; and pre-diabetes is defined as fasting plasma glucose ≥100 but <126 mg/dl. The primary end point of the study was the change in insulin resistance measured by the homeostatic model assessment for insulin resistance (HOMA-IR). *Results:* At the end of follow-up, insulin resistance (-24.5 vs. -8.2%, *P* = 0.007), HOMA-IR index (-31.9 vs. -3.3%, *P* < 0.001), hemoglobin A1c (-6.6 vs. -0.16%, *P* < 0.001), insulin (-29.6 vs. -2.66%, *P* < 0.001), waist circumference (-4.8 vs. 0.55%, *P* < 0.001) and uric acid (-0.8 vs. 2.2%, *P* = 0.004) were significantly decreased in terms of mean changes; albumin (0.91 vs. -2.91%, *P* = 0.007) and magnesium (0.21 ± 0.18 vs. -0.04 ± 0.05 mg/dl, *P* < 0.001) were significantly increased in those taking magnesium compared with a placebo.

Omer Toprak, MD

Balikesir University School of Medicine, Department of Medicine, Division of Nephrology, Çagış Yerleşkesi, Balikesir, 10145 (Turkey), Tel. +90-507-2589585, Fax +90-266-6121023, E-Mail omertoprak@balikesir.edu.tr; info@omertoprak.com

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The decrease in metabolic syndrome (-10.5 vs. -4.9%, P = 0.183), obesity (-15.7 vs. -8.2%, P = 0.131), pre-diabetes (-17.5 vs. -9.8%, P = 0.140), and systolic (-5.0 ± 14.8 vs. 0.22 ± 14.9 mm Hg, P = 0.053) and diastolic (-3.07 ± 9.7 vs. 0.07 ± 9.6 mm Hg, P = 0.071) blood pressure did not achieve to a significant level after study. **Conclusion:** Our data support the argument that magnesium supplementation improves the metabolic status in hypomagnesemic CKD patients with pre-diabetes and obesity.

Introduction

Magnesium is an essential co-factor for biochemical reactions and plays an important role in glucose metabolism [1]. Deficiency of magnesium, which is an inexpensive and non-toxic element, results in diseases that cause incalculable suffering and costs worldwide. Hypomagnesemia has been reported in patients with type 2 diabetes mellitus (DM), pre-DM, metabolic syndrome, insulin resistance, hyperlipidemia, hypertension and CKD (chronic kidney disease) [2-4]. Hypomagnesemia may also be associated with cardiovascular mortality and kidney function decline in CKD patients [4, 5]. The efficacy of magnesium supplementation in improving glycemic control among non-diabetic, pre-diabetic and diabetic individuals has been suggested by some clinical trials [1, 3, 6].

Serum glucose levels that are higher than normal but do not fulfil the definition of DM are classified as pre-DM. Diabetes is a major cause of CKD, and pre-diabetes is accompanied by an increased prevalence of CKD as well. It is reported that 17.7% of people with pre-diabetes have had CKD [7]. Most CKD observed in patients with pre-diabetes is due to macrovascular disease, especially hypertension. A high incidence of obesity and insulin resistance are other risks for developing CKD in pre-diabetics [8]. Magnesium intake reduces the risk of progression from pre-DM to DM [6]: Pre-DM is a reversible state, and magnesium deficiency is also a modifiable risk factor for the decline in kidney function [4, 9]. In the literature, there is no information about the effect of magnesium supplementation in improving glycemic control among hypomagnesemic pre-diabetic or diabetic patients in the early stages of CKD. We hypothesise that magnesium supplementation would improve insulin resistance in hypomagnesemic obese and pre-diabetic patients with CKD. An early optimisation of magnesium may delay or decrease the incidence of DM in pre-diabetic CKD patients and return insulin resistance to normal in study patients. In this study, we examined the effect of 3-month magnesium supplementation on metabolic profiles in hypomagnesemic obese and pre-diabetic patients in stage 2 and 3 of CKD.

Materials and Methods

Study Population

A single-centre, randomised, double-blind, placebo-controlled trial was performed on patients (aged 20 to 70 years) with mild-to-moderate CKD, hypomagnesemia, pre-DM and obesity between July 2014 and April 2015 at Balikesir University School of Medicine, Department of Nephrology. The study was approved by the Ethical Committee of the university (Approval No:2014/43). All patients gave written, informed consent. A total of 128 patients met the inclusion criteria. Patients were randomly allocated to receive either magnesium (magnesium group) or placebo (placebo group) solutions, once a day for 3 months. Individuals in the magnesium group received 100 ml of 613.20 mg of magnesium oxide solution, equivalent to 365 mg of elemental magnesium (Magnorm® tb, Vitalis, Istanbul, Turkey); individuals in the placebo group received 100 ml of placebo solution, which consisted of sodium-free carbonated water. The placebo was the same in colour and appearance to the magnesium solution. Investigator and subject blinding were maintained until data collection was complete. Computer-generated random numbers were used for assigning participants to either the magnesium group or the placebo group. Both groups were advised to consume a special diet (restricted sodium intake, protein intake of 0.8 g/kg body weight per day, total daily caloric intake of 25 kcal/kg/day) and perform physical activity for 30 minutes per day.

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Analytical Methods

Blood samples taken to measure serum glucose, insulin, HbA1c (hemoglobin A1c), creatinine, urea, uric acid, parathyroid hormone, C-reactive protein (CRP), albumin, magnesium, calcium, lipids (triglyceride, high-density lipoprotein cholesterol [HDL-C], total cholesterol, low-density lipoprotein cholesterol [LDL-C]) and hemoglobin were drawn after an 8-hour overnight fasting condition and in a standing position, and follow-up parameters were measured 3 months after the magnesium treatment or placebo. Urine samples taken to measure the urine protein to urine creatinine ratio were calculated at baseline and then again 3 months later. Anthropometric measurements like weight, height, waist circumference and body mass index (BMI) were performed with the subjects wearing light clothing and no shoes. Weight and height were measured using a fixed scale with a stadiometer (Nan DR-MOD-85, Istanbul, Turkey). BMI was calculated as the weight divided by the square of the height in metres. Waist circumference was measured to the nearest 0.1 cm using a flexible metric measuring tape with the subject in a standing position, and the anatomic landmarks used were at the midpoint between the costal margin and the iliac crest in the mid-axillary line. Insulin resistance was estimated by using the homeostatic model assessment for insulin resistance (HOMA-IR: fasting insulin [μU/mL] x fasting glucose [mg/dL]/405) [10]. Glomerular filtration rates were estimated using the Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation [11]. Systolic and diastolic blood pressure were measured according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [12].

Assays

Blood samples were collected from the antecubital vein by venipuncture into vacutainer tubes after an 8-hour overnight fasting, then centrifuged and stored at −80 °C until analysis. Serum magnesium was analysed by the colorimetric method with a clinical chemistry autoanalyser. HbA1c was analysed by a high-performance liquid chromatography method (Menarini/ARKRAY ADAMS A1c HA-8180V analyser). Insulin levels were determined using a commercial ELISA kit. Calcium, urea and urinary protein concentrations were measured via the colorimetric method. Serum creatinine and urinary creatinine concentrations were determined enzymatically on an autoanalyser and with the Jaffé method. Uric acid levels were determined with the uricase–peroxidase method, while glucose levels were calculated via the glucose oxidase method. Albumin and CRP were determined in serum by the nephelometric method. Parathyroid hormones were measured with an enzyme-linked immunosorbent assay. Lipid profiles were analysed by enzymatic methods and with the Beckman Coulter AU680 Analyser (Beckman Coulter, Inc., CA, USA) using commercially available kits.

Clinical Definitions

Hypomagnesemia has been defined by a serum magnesium level <1.8 mg/dl in males and <1.9 mg/dl in females [13, 14] (reference ranges of magnesium in the study laboratory were 1.8–2.6 mg/dl in males and 1.9–2.5 mg/dl in females); obesity has been defined as a BMI ≥30 kg/m^2, while insulin resistance has been defined as a HOMA-IR index ≥3 [15-17]; diabetes has been defined as a fasting plasma glucose level ≥126 mg/dL, which can be confirmed by repeated testing, previous diagnosis of diabetes, or the current use of antidiabetic medications; lastly, pre-DM has been defined as the presence of a fasting plasma glucose level ≥100 but <126 mg/dl [18]. The identification of metabolic syndrome (MS) conformed to the definition used by the National Cholesterol Education Program Adult Treatment Panel III guidelines [19]. Those patients who had 3 or more of the following 5 components were classified as having MS: abdominal obesity, high blood pressure, hypertriglyceridemia, low HDL-C and high fasting glucose. The MS score was defined as the number of constituents of MS. According to the National Kidney Foundation Clinical Practice Guidelines, a cut-off value of ≥60 to <89 ml/min/1.73m^2 in eGFR (estimated glomerular filtration rate) with kidney damage, and ≥30 to <59 ml/min/1.73m^2 in eGFR regardless of kidney damage, were used to define stage 2 and 3 of CKD, respectively [20]. Kidney damage was indicated by a protein to creatinine ratio ≥200 mg/g. The causes of CKD in study patients included hypertension (37.5% vs. 34.3%), glomerulonephritis (18.7% vs. 14.1%), polycystic kidney disease (6.25% vs 3.1%), myeloma (3.1% vs 1.5%), pyelonephritis (9.3% vs. 12.5%) or unknown (28.1% vs 34.3%) in the magnesium group and placebo group, respectively.

Adherence to pharmacological treatment, diet and exercise were assessed every month by personal interviews, tablet counts and measurements of the remaining solution, and independent interviews with individuals in charge of preparing meals for the patients.

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Exclusion Criteria

Exclusion criteria included malabsorption, prior history of inflammatory bowel disease or any severe gastrointestinal disorder, diarrhoeal disease, alcohol abuse, or the concurrent use of magnesium supplements, laxatives, diuretics, corticosteroids, oral contraceptives, bile acid sequestrants, magnesium-containing phosphate binders, proton pump inhibitors, amphotericin B, aminoglycosides, tetracycline or chemotherapy drugs. Also, any prior history of allergy or intolerance to magnesium, inherited renal tubular defects, kidney transplants, or pregnancies were counted as exclusion criteria.

Sample Size

Sample size was estimated based on a statistical power of 80% and an alpha value of 0.05. It was estimated that 61 patients would be required in each group to detect a mean difference in insulin resistance (study endpoint) of at least 25% between the two groups at the end of the treatment period.

Statistical Analysis

The primary study endpoint was the efficacy of magnesium supplementation in reducing insulin resistance. Secondary endpoints included changes (improvement) in pre-diabetic status, obesity, fasting glucose, blood pressure, MS rates, inflammatory markers and proteinuria. Comparisons of continuous variables between groups were performed using a Student's t-test for normally distributed data and the Mann–Whitney U-test for non-normally distributed data. Within-subject comparisons of continuous variables were carried out using a paired t-test or the Wilcoxon signed-rank test for normally and non-normally distributed data, respectively. Categorical variables were analysed using the chi-square test or, alternatively, the Fisher's exact test. All tests were 2-sided, and a p-value of < 0.05 was considered statistically significant. Continuous data are reported as mean ± SD. Categorical data are presented as absolute values and percentages. Analyses were performed using the IBM SPSS Statistics Version 20.0 (IBM Corp., USA).

Results

Screening was performed on 2,335 patients, 2,207 (97.2%) of whom were excluded because they either did not fulfil the inclusion criteria or met the criteria for exclusion. A total of 128 patients were enrolled and randomly allocated to the study groups, although 7 patients from the magnesium group and 3 from the placebo group dropped out. Thus, a total of 118 patients, 57 from the magnesium group and 61 from the placebo group, successfully completed the study (Fig. 1). Magnesium was well tolerated in study patients. Only slight epigastric pain and mild diarrhoea were documented in 3 patients (5.2%) from the magnesium group and 1 patient (1.6%) from the placebo group ($P = 0.104$). The adverse effects did not require treatment and were resolved within 24 hours of ceasing intake of magnesium or the placebo. No significant difference in adherence to treatment (89.1% to 95.3%) and adherence to diet and exercise (96.5% to 96.7%) was found between the magnesium and placebo groups, respectively. Baseline characteristics were not statistically different between the groups in terms of anthropometric and biochemical variables (Table 1). The following baseline parameters were also non-significant between the groups: gender ($P = 0.13$), weight ($P = 0.311$), parathyroid hormones ($P = 0.705$), calcium ($P = 0.120$), hemoglobin ($P = 0.523$), CRP ($P = 0.86$), total cholesterol ($P = 0.94$), LDL-C ($P = 0.613$), MS score ($P = 0.376$), urea ($P = 0.83$) and creatinine ($P = 0.205$). Moreover, the use of calcium supplements because of CKD ($P = 0.780$) and oral antidiabetics because of insulin resistance ($P = 0.650$) were also non-significant between the groups (4 patients in the magnesium group and 5 in the placebo group received either vildagliptin or sitagliptin). Prescriptions for uric acid-lowering drugs, statins and RAS inhibitors were also non-significant between the groups. At the end of the follow-up, waist circumference ($P = 0.036$), systolic ($P = 0.035$) and diastolic ($P = 0.039$) blood pressure, HbA1c ($P = 0.001$), fasting insulin ($P = 0.035$) and HOMA-IR index ($P = 0.018$) had decreased, while magnesium levels had increased ($P < 0.001$) in the magnesium group compared with the placebo group. In addition, when the basal and final conditions in the magnesium group were compared, the following changes were significant: insulin resistance (70.1% to 45.6%, $P < 0.001$), HOMA-IR index (4.67 ± 2.77 to 3.17 ± 1.93, $P < 0.001$), insulin (17.11 ± 10.23 to 12.03 ± 7.31 mmol/l, $P < 0.001$), fasting glucose (110.77 ±

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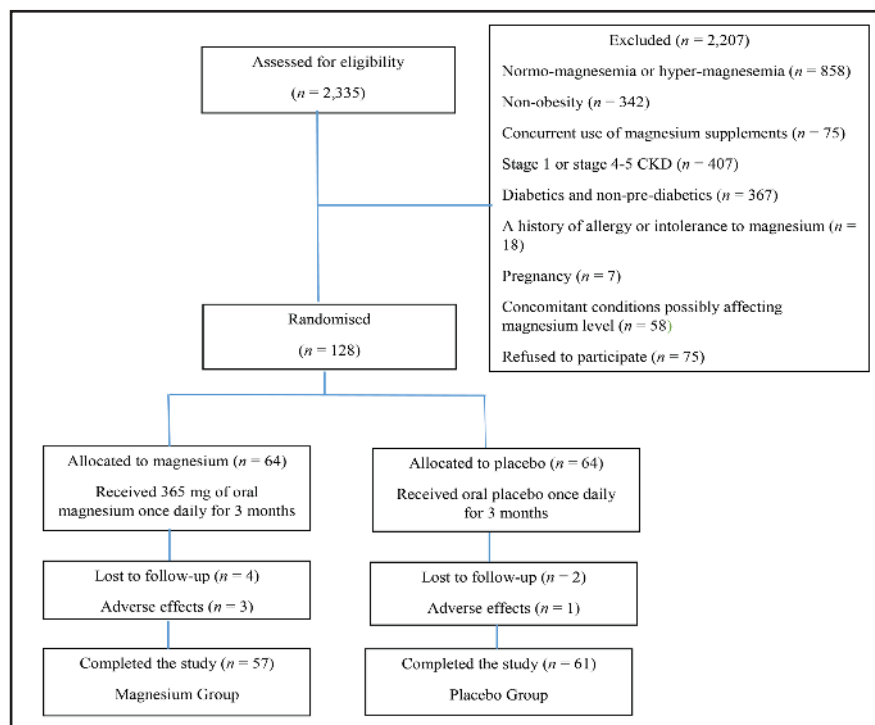**Fig. 1.** Flow diagram of study participants from enrolment to analysis.

Table 1. Study variables in the magnesium and placebo groups before and after intervention Values are expressed as mean ± SD or number (%) of patients. Mg: magnesium; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; P/C: protein/creatinine; BMI: body mass index; WC: waist circumference. *$P < 0.001$, **$P < 0.02$ between the basal and final condition in the magnesium group.

|	Basal			Final		
	Magnesium (n = 57)	Placebo (n = 61)	P value	Magnesium (n = 57)	Placebo (n = 61)	P value
Age, years	55.58 ± 13.75	57.09 ± 12.91	0.528	-	-	-
BMI, kg/m²	33.86 ± 2.81	33.99 ± 2.63	0.794	32.90 ± 3.21	33.88 ± 2.83	0.376
WC, cm	104.54 ± 11.3	103.17 ± 10.98	0.493	99.5 ± 11.07*	103.72 ± 11.01	0.036
SBP, mm Hg	130.7 ± 14.4	131.5 ± 17.7	0.78	125.7 ± 14.6**	131.74 ± 6.78	0.035
DBP, mm Hg	73.42 ± 10.05	74.06 ± 12.64	0.758	70.35 ± 8.6**	74.13 ± 11.21	0.039
Glucose, mg/dl	110.77 ± 5.46	111.32 ± 6.55	0.617	106.9 ± 8.95*	109.8 ± 9.57	0.088
HOMA-IR index	4.67 ± 2.77	4.23 ± 2.42	0.347	3.17 ± 1.93*	4.07 ± 2.21	0.018
Insulin resistance	40 (70.1%)	42 (68.9%)	0.805	26 (45.6%)*	37 (60.6%)	0.089
HbA1c, %	6.05 ± 0.31	5.95 ± 0.35	0.111	5.65 ± 0.47*	5.94 ± 0.50	0.001
Metabolic syndrome	38 (66.6%)	41 (67.2%)	0.407	32 (56.1%)	38 (62.3%)	0.660
Triglyceride, mg/dl	164.1 ± 60.94	169.2 ± 73.2	0.674	152.3 ± 54.2	169.1 ± 91.9	0.228
HDL-C, mg/dl	46.18 ± 11.84	48.29 ± 13.52	0.358	47.51 ± 12.04	48.62 ± 13.72	0.633
Uric acid, mg/dl	6.16 ± 1.82	5.89 ± 1.58	0.385	5.66 ± 1.32**	6.03 ± 1.64	0.164
eGFR, ml/min/1.73m²	55.28 ± 16.15	50.69 ± 12.54	0.075	52.60 ± 16.15	49.75 ± 14.62	0.279
Urine P/C, mg/dl	0.43 ± 0.56	0.54 ± 0.71	0.345	0.36 ± 0.48*	0.56 ± 0.69	0.073
Serum albumin, gr/dl	4.36 ± 0.31	4.46 ± 0.56	0.275	4.41 ± 0.56	4.32 ± 0.41	0.236
Serum magnesium, mg/dl	1.70 ± 0.13	1.72 ± 0.08	0.531	1.91 ± 0.22*	1.69 ± 0.12	< 0.001

5.46 to 106.9 ± 8.95 mg/dl, $P < 0.001$), uric acid (6.16 ± 1.82 to 5.66 ± 1.32 mg/dl, $P < 0.02$), HbA1c (6.05 ± 0.31 to 5.65 ± 0.47%, $P < 0.001$), waist circumference (104.54 ± 11.30 to 99.54 ± 11.07 cm, $P < 0.001$), systolic (130.7 ± 14.4 to 125.7 ± 14.6 mm Hg, $P < 0.02$) and diastolic (73.42 ± 10.05 to 70.35 ± 8.6 mm Hg, $P < 0.02$) blood pressure, urine protein to creatinine ratio (0.43 ± 0.56 to 0.36 ± 0.48 mg/dl, $P < 0.001$) and magnesium levels (1.70 ± 0.13 to 1.91 ± 0.22 mg/dl, $P < 0.001$). No change in any parameter in the placebo group between basal and final conditions was observed (Table 1). In spite of the decrease in systolic and diastolic blood pressure, fasting glucose levels, and urine protein to creatinine ratios in the magnesium group, changes in the compared means after treatment did not show significant differences between the two groups ($P = 0.053$, $P = 0.071$, $P = 0.087$, and $P = 0.075$, respectively) (Table 2). Despite the non-significant increase in albumin levels in the magnesium group, changes in the means after treatment did show a significant increase (0.04 ± 0.18 to -0.13 ± 0.45, $P = 0.007$). A summary of the significant mean changes after treatment by percentage is

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presented in Fig. 2. Levels of triglycerides (-11.84 ± 35.1 mg/dl, P = 0.214), LDL-C (-3.52 ± 20.4 mg/dl, P = 0.257), BMI (-0.96 ± 1.35 kg/m^2, P = 0.146), weight (-2.22 ± 3.09 kg, P = 0.132), MS rates (-10.5%, P = 0.183), MS score (-0.40 ± 0.97, P = 0.166), obesity rates (-15.7%, P = 0.131) and pre-DM status (-17.5%, P = 0.140) were decreased, while HDL-C increased (+1.33 ± 6.7 mg/dl, P = 0.39) in the magnesium group after the magnesium treatment; however, this increase was not significant (Table 2). During the follow-up, there were no changes from pre-DM to DM.

Table 2. Mean changes in magnesium, metabolic and renal parameters after treatment Δ: mean change from baseline to endpoint between the beginning and end of the study.

Parameters	Magnesium	Placebo	P value
Δ Magnesium, mg/dl	0.21 ± 0.18	-0.04 ± 0.05	< 0.001
Δ HbA1c, %	-0.40 ± 0.35	-0.01 ± 0.38	< 0.001
Δ Fasting insulin, mmol/l	-5.07 ± 4.30	-0.41 ± 2.69	< 0.001
Δ HOMA-IR index	-1.49 ± 1.18	-0.16 ± 0.86	< 0.001
Δ Insulin resistance, n (%)	14 (- 24.5%)	5 (- 8.2%)	0.007
Δ Pre-diabetes, n (%)	10 (- 17.5%)	6 (- 9.8%)	0.140
Δ Obesity, n (%)	9 (- 15.7%)	5 (- 8.2%)	0.131
Δ Metabolic syndrome, n (%)	6 (- 10.5%)	3 (- 4.9%)	0.183
Δ Metabolic syndrome score	-0.40 ± 0.97	-0.18 ± 0.75	0.166
Δ Fasting glucose, mg/dl	-3.84 ± 6.4	-1.52 ± 8.2	0.087
Δ Triglycerides, mg/dl	-11.84 ± 35.1	-0.22 ± 62.5	0.214
Δ HDL cholesterol, mg/dl	+1.33 ± 6.7	+0.33 ± 5.5	0.36
Δ LDL cholesterol, mg/dl	-3.52 ± 20.4	+0.07 ± 15.0	0.257
Δ Waist circumference, cm	-5.0 ± 3.01	+0.55 ± 3.19	< 0.001
Δ Body mass index, kg/m²	-0.96 ± 1.35	-0.61 ± 1.35	0.146
Δ Uric acid, mg/dl	-0.05 ± 1.4	0.13 ± 0.9	0.004
Δ Albumin, gr/dl	0.04 ± 0.18	-0.13 ± 0.45	0.007
Renal Parameters			
Δ eGFR, ml/min/1.73m²	-2.68 ± 5.2	-0.96 ± 5.4	0.075
Δ Urine protein to creatinine ratio	-0.07 ± 0.12	0.01 ± 0.34	0.075
Δ Systolic blood pressure, mmHg	-5.0 ± 14.8	+0.22 ± 14.9	0.053
Δ Diastolic blood pressure, mmHg	-3.07 ± 9.7	+0.07 ± 9.6	0.071

Fig. 2. Significant mean changes by percentage in metabolic parameters after treatment in the study groups. HOMA-IR, homeostatic model assessment for insulin resistance, HbA1c, hemoglobin A1c.
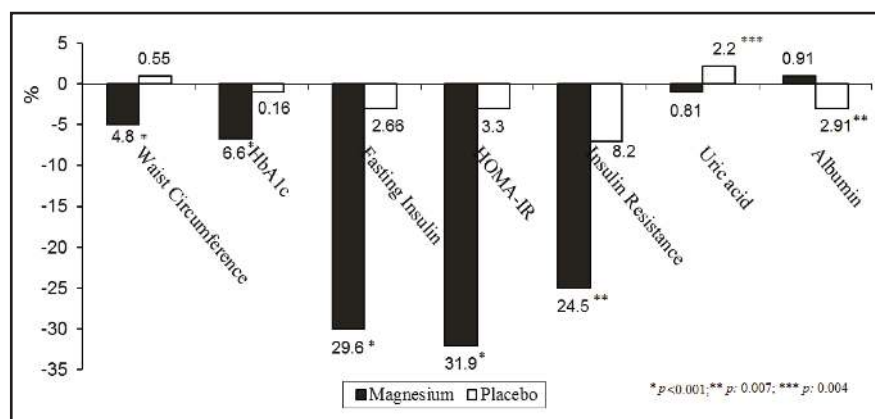
Discussion

In this study, we showed that a 3-month oral administration of magnesium oxide improved the metabolic profile – and especially insulin sensitivity – in pre-diabetic and obese patients with stage 2 and 3 CKD. Although the role of magnesium in glucose metabolism has already been demonstrated in diabetics without CKD [6, 21-23], this study is valuable insofar as it confirms the beneficial effects of magnesium among CKD patients. This is the first study to demonstrate the influence of magnesium on the metabolic profile of hypomagnesemic patients in the early stages of CKD.

Associations between hypomagnesemia and an increased risk for type 2 DM, pre-DM, insulin resistance, obesity, dyslipidemia, hypertension and MS have been shown in various studies [21-29]. All of these conditions have a high incidence of hypomagnesemia as well as increased risk for cardiovascular mortality [24-26]. Our study groups were recruited from these high-risk patients. Magnesium is essential for insulin secretion, post-receptor insulin signalling, and the glycolytic pathway [1]. The efficacy of magnesium supplementation in improving glycemic control among non-diabetics [30, 31], pre-diabetics [32-34] and diabetics [23, 35, 36] has been suggested in some trials. A recent meta-analysis documented that magnesium is effective in decreasing the HOMA-IR index (P = 0.013) but has no effect on glucose, HbA1c or insulin. However, magnesium supplementation for ≥4 months improves

the HOMA-IR index ($P = 0.001$) and glucose levels ($P < 0.001$) in both diabetics and non-diabetics [3]. In agreement with this report, in our study, magnesium significantly reduced the HOMA-IR index but the glucose level was not decreased significantly. If we had increased the duration of magnesium supplementation from 3 months to 4 months, the decrease of glucose would have been significant. A trial of $MgCl_2$ for 16 weeks in patients with type 2 diabetes demonstrated improvement in the HOMA-IR index, fasting glucose levels, and HbA1c [23]. In another trial, it was shown that daily magnesium supplementation in overweight individuals significantly decreased fasting insulin [37]. In one recent study, HOMA-IR indices and glucose levels were decreased in patients with hypomagnesaemia and pre-DM after treatment with magnesium, and 50.8% of the participants in the magnesium group and 7.0% in the placebo group had decreased glucose levels ($P < 0.005$) [32]. The results of that study are compatible with ours: HbA1c, fasting insulin and insulin resistance were all decreased in our study; however, the incidence of improved glucose status (glucose <100 mg/dl after the study) in the magnesium group was only 17.5%, which was not significant. Some negative studies about the effect of magnesium on glucose, HbA1c, insulin and HOMA-IR, and lipid profiles in diabetics also exist [36]. These mixed results may be attributable to amount or the duration of supplementation. Other studies have investigated the effect of magnesium on MS and obesity [15, 38, 39]. In most of them, magnesium has improved the metabolic profile in obese and MS patients. However, Lima et al. demonstrated that magnesium does not reduce insulin resistance or HOMA-IR in MS [39]. In our study, all patients were obese and most had MS. The incidence of MS, MS scores and obesity were not decreased significantly after magnesium supplementation. Perhaps if the dose or duration of magnesium had been increased, the results would have been significant.

Data about the effect of magnesium on waist circumference is scarce. Increased waist circumference plays a role in insulin resistance and is a component of MS. In our study, there was a significant reduction in waist circumference after magnesium treatment, which may be attributable to the significant decrease in insulin resistance. Different results about the effect of magnesium on lipids in diabetic, pre-diabetic or obese patients have been generated. Some studies have documented that magnesium supplementation increases HDL-C levels [32, 40] and decreases levels of triglycerides and LDL-C [35, 40]. In our study, we found no such benefical effect of magnesium on lipids. Although HDL-C was increased, triglycerides, LDL-C and total cholesterol were decreased after magnesium treatment; yet, these changes were not significant. Another study had the same results as ours, demonstrating that magnesium does not improve the lipid profile in patients with MS [39]. Also, Mooren et al. showed that magnesium has no effect on lipids in non-diabetic, overweight or insulin-resistant subjects [31].

Magnesium deficiency is related to a rise in pro-inflammatory cytokines and acute-phase proteins [41, 42]. Elevated serum uric acid is an inflammatory marker and is related to insulin resistance, pre-DM and MS [43, 44]. Albumin is also a nutritional and inflammatory marker. We found no other study that has reported on the effect of magnesium supplementation on albumin and uric acid in hypomagnesemic patients. In our study, we showed that magnesium supplementation decreased uric acid and increased mean albumin. However, the CRP level was not changed. One possible explanation for this is that the decrase in insulin resistance may have helped to decrease uric acid and increase albumin levels. In the literature, it has been shown that magnesium supplementation decreases high-sensitive CRP, tumor necrosis factor-alpha, and interleukin-6 [41, 42]. In our study, we did not measure high-sensitive CRP, which may account for the failure to detect a significant decrease in CRP. Similarly, Simental-Mendía et al. did not show a beneficial effect of magnesium on CRP levels in hypomagnesemic patients [33].

Studies on CKD patients have reported that hypomagnesemia is a predictor for the progression of type 2 diabetic nephropathy to end-stage kidney disease [45] and is associated with incidental kidney disease [5, 46] and accelerated loss of kidney function in renal allografts and transplant recipients [9, 47]. Hemodialysis patients with hypomagnesemia are at high risk for cardiovascular death [24-26]. However, the impact of magnesium on kidney function and metabolic profile in CKD has been poorly investigated thus far. In a trial in hypomagnesemic patients, magnesium improved glycemia after kidney transplantation [48].

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In another study, carotid intima-media thickness was decreased after magnesium treatment in patients on hemodialysis [49]. Other studies have shown that magnesium reduces blood pressure [15, 50]. However, in our study, we did not observe a strong effect of magnesium on blood pressure. Compatible with our results, blood pressure was not significantly decreased in insulin-resistant subjects after magnesium supplementation [31]. Likewise, we found no significant change in renal parameters after magnesium treatment. Although not statistically significant, magnesium supplementation decreased blood pressure levels, urine protein levels, and eGFR. These results may imply that magnesium supplementation alleviates glomerular hyperfiltration via the relationship between magnesium and the renin–angiotensin system [51].

The current study has some limitations. First, the results should be generalised with caution, since the study was conducted at a single centre. Second, the results should also be interpreted with caution because the serum magnesium measured in this study is not a reliable parameter for intracellular magnesium. Most magnesium is found in bones and only ionised, free magnesium is biologically active. Third, we have no information about the causes of hypomagnesemia. Possible causes of hypomagnesmia in our study patients included decreased dietary intake or renal loss; however, we did not measure the renal loss of magnesium.

Conclusion

How can the findings of the present study be adapted to clinical practice? The diagnosis of obesity, pre-DM or CKD is not difficult, and magnesium measurement is an easily available and inexpensive marker. Therefore, checking magnesium levels in metabolically disturbed pre-diabetic and obese patients with stage 2-3 CKD is recommended. If hypomagnesemia is detected, magnesium supplementation can be a useful guide for improving the metabolic status in these patients. In conclusion, oral magnesium administration seems to improve metabolic status in pre-diabetic, obese and stage 2-3 CKD patients with hypomagnesemia.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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