Research Article

Effects of Magnesium L-lactate on Metabolic Syndrome Features in a Sample of Iraqi Women

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Received: 25-04-2017; **Revised:** 18-06-2017; **Accepted:** 09-07-2017.

ABSTRACT

Metabolic syndrome (MetS) is a group of the most dangerous risk factors including abdominal obesity, diabetes, high cholesterol, and high blood pressure. It occurs as a mixture of certain risk factors that appear as adverse complications including type 2 diabetes mellitus (T2DM) and cardiovascular disorders (CVD). The current study was designed for evaluation the effect of oral magnesium supplementation on MetS features in a sample of Iraqi women. In this interventional prospective randomized trial, 58 females diagnosed with MetS in accordance with the international diabetic federation (IDF) criteria and were randomly allocated to receive either placebo or magnesium l-lactate 84 mg, twice daily. Magnesium supplement showed significant declines in body weight, waist circumference (WC), and body mass index (BMI). Glycemic state showed a significant reduction in glycated hemoglobin (HbA1c), no significant reduction in fasting serum glucose (FSG), and no significant changes in HOMA-insulin resistance (HOMA-IR) in those patients on magnesium. Significant reduction was seen in the serum levels of total cholesterol, non-high density lipoprotein (non-HDL), and low density lipoprotein (LDL) in comparison with placebo. Significant increment in serum magnesium levels and significant decline in the fractional excretion of magnesium (FE_{Mg}) were observed, especially within hypomagnesaemic patients, while the levels of urine magnesium increased significantly innormomagnesaemic patients on magnesium supplement. From above, one can conclude that oral supplementation of magnesium l-lactate can improve some features of MetS in women.

Keywords: metabolic syndrome, magnesium supplement.

INTRODUCTION

The term of metabolic syndrome (MetS) was first identified by Haller and Hanefeld in 1975[1]. It is characterized as a collection of basic risk factors leading to adverse outcomes, including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and consequently about 1.6 fold increase in mortality rates[2]. Diagnostic criteria for the MetS have been established by the World Health Organization (WHO) in 1998. In 2001, it is identified by the National Cholesterol Education Program's: Adult Treatment Panel III (NCEP: ATP III), and also by the International Diabetes Federation (IDF) in 2005. According to IDF reports, there was one-quarter of the world's adult population has the MetS[3, 4].

The major risk factors for widening of MetS are physical inactivity, diet rich in fats and carbohydrates, leading to the two major clinical features of MetS identified by central obesity and insulin resistance (IR). Obesity is basic to MetS as it appears to participate in developing other MetS risk factors [5, 6].Despite obesity and IR are considered major factors, the causes of MetS are continued to challenge the experts. Genetics, aging, inflammatory processes and hormonal factors may also contribute in causation of the syndrome [7, 8].The MetS is best described by abdominal obesity when an endocrine organ that releases excess amount of free fatty acids (FFA), angiotensin II, and adipokines into blood stream. The increased FFA inhibits the muscle uptake of glucose. Elevated levels of FFA and angiotensin II can cause destruction to the pancreas [9, 10].Metabolic syndrome can be associated with broad complications including CHD, atrial fibrillation, aortic stenosis, heart failure, ischemic stroke, and possibly veno-thromboembolic disease [11, 12]. Lifestyle modification, including regular exercise, is the primary step in the treatment of MetS[13]. From available drugs to reduce IR are metformin and insulin sensitizers such as thiazolidinediones[14]. Different trials found that statins have a role in reducing the risk of CVD events in subjects with MetS[15].

Magnesium plays an essential physiological role in many functions of the body. This role is achieved through two important properties of magnesium; the ability to form chelates with important intracellular anionic ligands, especially ATP, and its ability to compete with calcium for binding sites on proteins and membranes [16].Many situations could lead to hypomagnesaemia and magnesium deficiency, including gastrointestinal causes like reduced intake and reduced absorption, renal loss and renal disease, endocrine causes like diabetes mellitus, and drugs like proton pump inhibitors[17, 18]. Most cases of

Mg deficiency are asymptomatic until levels of serum Mg drop below 1.2 mg/dl. Analysis of different articles about magnesium intake and MetS and others about serum magnesium with or without MetS found that higher magnesium intake was positively associated with lower MetS risk [19]. This study was designed to evaluate the effect of oral magnesium supplementation on MetS features in a sample of Iraqi women.

Patients and Methods

This interventional prospective randomized placebo-controlled trial was carried out on 58 female patients diagnosed with MetS according to the IDF criteria, with BMI of 30-40 kg/m^2, age range of 30-60 years old, and waist circumference of > 80 cm, under supervision of professional endocrinologists, from October2015 to August 2016. The protocol was reviewed and approved by the Scientific and Ethics Committee in the College of Pharmacy/ University of Al-Mustansiriayah, and Alkindi College of Medicine/ University of Baghdad. Patient's oral consent was taken and all participants were advised to take a low carbohydrate and fat dietary regimen and achieving 60 minutes of aerobic exercise per day during their treatment duration.

Certain exclusion criteria were followed to avoid interference with the study design and include: estimated glomerular filtration rate (eGFR) less than 30ml/min, pregnant and lactating women, patients with a newly prescribed and/or added antihypertensive medication (less than one month), patients with a newly prescribed, and/or added antidiabetic or lipid lowering agents (less than 2 month), those suffered thyroid disorders (hypo-or hyper-thyroidism), those on laxatives, diuretics, proton pump inhibitors and alcohols, those on antacids and other preparations or dietary supplements that containing magnesium or calcium in their compositions. Female patients were randomly allocated to either placebo or Mg group. From 58 female patients, only 47 completed this study, the other 11 were excluded (3 from magnesium group and 8 from placebo group) due to poor compliance, violation of the study protocol, or other reasons. Group (A) included 17 female patients taking placebo capsules twice daily for 8 weeks, while group (B) included 30 female patients taking Mg l-lactate tablets (84 mg) twice daily after meal in a sustained release formula for 8 weeks.

At baseline and for all patients, a specially designed questionnaire was filled, recording their medical history and pretreatment characteristics. The demographic and baseline characteristics were evenly distributed for both groups, as summarized in table 1. Parameters of the anthropometry, glycemic status, lipid profile, magnesium status, kidney function and electrolytes levels, serum uric acid, in addition to the oxidative stress and inflammatory markers, were measured at baseline and after 8 weeks for both groups. Adverse effects (if any) were recorded at the end of the study.

Table 1: Baseline characteristics for placebo and magnesium groups.

Baseline characteristics		Placebo group (N= 17)	Magnesium group (N= 30)	*P*-value
Age (years)		50.12 ± 1.671	53.77 ± 1.491	0.127
Weight(kg)		85.705 ± 2.642	86.766 ± 2.473	0.784
Height (cm)		156.76 ± 1.062	157.73 ± 0.905	0.506
BMI (kg/m^2)		34.9506±.90804	34.847 ± 0.908	0.946
Waist circumference (cm)		111.59 ± 3.225	111.63 ± 1.896	0.990
eGFR (ml/min)		67.347 ± 3.759	71.800 ± 2.520	0.315
Serum magnesium (mg/dl)		1.855 ± 0.067	1.914 ± 0.057	0.525
Hypomagnesaemia%		6(35.5%)	11(36.7%)	0.591
FE_{Mg} (%)		2.9820±.37793	3.963 ± 0.771	0.260
Family history	Combined DM+HT	15(88.2%)	28(93.3%)	0.834
	DM only	1(5.9%)	1(3.3%)	
	HT only	1(5.9%)	1(3.3%)	
DM history		15(88.2%)	24(80%)	0.692
Duration of DM (years)		4.0 ± 0.555	3.933 ± 0.452	0.928
Anti-diabetic history		13(76.5%)	22(73.3%)	0.550
HT history		14(82.4%)	27(90%)	0.653
Duration of HT (years)		3.294 ± 0.560	4.066 ± 0.484	0.321
Antihypertensive history		12(70.6%)	21(70.0%)	0.618
Smoking history		0(0%)	1(3.3%)	0.638
Atherosclerotic cardiovascular history		2(11.8%)	3(10%)	0.603
Lipid lowering agents (statins)		9(52.9%)	6(20.0%)	0.027

Data were expressed as mean ± standard error of mean (SEM) or number(%), N= number of patients, BMI=body mass index, eGFR= estimated glomerular filtration rate, FE_{Mg}=Fractional excretion of magnesium DM= diabetes mellitus, HT= hypertension. P-value> 0.05 considered no significant difference.

Ten milliliters of venous blood samples were drawn by vein puncture from all participants as a baseline sample and then after 8 weeks as endline sample. Serum samples were stored frozen at –20°C until analysis was done. Samples of urine were drawn from patients to measure urine Mg and urine creatinine.

The BMI describes relative weight to height according to the following equation: BMI= weight/ height (m^2)[20]. Insulin resistance was calculated by computer program called HOMA Calculator depending on levels of FSG and c-peptide[21]. Serum LDL-c concentration was calculated by using Friedewald*et al* formula: LDL-c =Total cholesterol-[HDL-c + TG (mg/dl)/5], while non-HDL concentration was calculated from the equation: Non-HDL=Total cholesterol – HDL-c[22].

Fractional excretion of magnesium was calculated by the following equation: FE_{Mg} = (urine magnesium × serum creatinine)/[0.7 (serum magnesium × urine creatinine)] × 100 [23]. Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) online calculator from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website using serum creatinine levels[24]. The levels of C-peptide, 8-epi-prostaglandin F2 alpha (8-epi-PGF2α or 8-isoprostane) and high sensitivity C-reactive protein (hs-CRP) were measured by enzyme-linked immunosorbent assay (ELISA) technique according to their manufacturers.

Statistical analysis

The results were presented as mean ± SEM or percentage of difference. All of the statistical analyses were achieved via the statistical package SPSS version 22.0 (SPSS, Inc.). Two sample t-test was applied to compare the means of the baseline characteristics between the two groups and then data were analyzed by using the analysis of covariance (ANCOVA) for this clinical trial [25].The significance level for all tests was taken as *P*-value less than 0.05.

RESULTS

After adjustment of baseline means for placebo and Mg groups according to the analysis of covariance, there was a significant reduction (*P*-value <0.05) in anthropometric parameters (weight, body mass index and waist circumference) (table 2), levels of HbA1c (table 3), serum total cholesterol, LDL-c, non-HDL-c (table 4), serum Mg and FE_{Mg}(table 5),while there was no significant reduction (*P*>0.05) in levels of FSG (table3), serum triglyceride and HDL-c levels(table 4) in patients on Mg supplements compared with those on placebo after 8 weeks of treatment.

Serum uric acid levels show no significant reduction (*P*>0.05)(table 7), whileinsulin resistance (table 3), serum calcium (table 7), 8-isoprostane and hs-CRP levels (table 8) show no significant difference (*P*>0.05).

Table 2: Effect of magnesium supplement on anthropometric parameters.

Parameter	Group	Adjusted baseline mean	Adjusted end line mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Wt (kg)	Placebo (N= 17)	86.383	86.733±0.361	0.35±0.361	0.001	↑0.40%
	Magnesium (N= 30)		85.118±0.272	–1.265±0.272		↓1.48%
BMI (kg/m^2)	Placebo (N= 17)	34.884	35.027±0.147	0.142±0.147	0.001	↑0.40%
	Magnesium (N= 30)		34.378±0.111	–0.506±0.111		↓1.47%
WC (cm)	Placebo (N= 17)	111.62	112.079± 1.258	0.459± 1.258	0.002	↑0.40%
	Magnesium (N= 30)		106.955±0.947	–4.665±0.947		↓4.36%

Data expressed by mean ±SEM and percentage of difference; P<0.05 was considered a significant difference between treatment groups at endline; N= number of patients, SEM = standard error of mean, wt = weight, BMI = body mass index; WC = waist circumference

Table 3: Effect of magnesium supplement on glycemic status levels.

Parameter	Group	Adjusted baseline mean	Adjusted end linemean ±SEM	Outcome mean±SEM	*P*-value	% of difference
FSG (mg/dl)	Placebo (N= 17)	160.832	157.470±8.375	–3.362±8.375	0.209	↓2.13
	Magnesium (N= 30)		144.024±6.411	–16.808±6.411		↓11.67
HbA1c (%)	Placebo (N= 17)	7.577	7.743±0.140	0.166±0.140	0.003	↑2.14
	Magnesium (N= 30)		7.189±0.106	–0.388±0.106		↓5.39
IR (%)	Placebo (N= 17)	3.273	3.007±0.251	–0.266±0.251	0.343	↓8.84
	Magnesium (N= 30)		3.310±0.190	0.036±0.190		↑1.08

Data expressed by mean ±SEM and percentage of difference; P<0.05 was considered a significant difference between treatment groups at endline; N= number of patients, SEM= standard error of mean, FSG= fasting serum glucose; HbA1c= glycocylated hemoglobin, IR= insulin resistance

Table 4: Effect of magnesium supplement on lipid profile levels.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Serum total cholesterol (mg/dl)	Placebo N= 17	193.793	203.080±6.116	9.286±6.116	0.016	↑4.57
	Magnesium N= 30		183.711±4.678	–10.082±4.678		↓5.48
Serum triglyceride (mg/dl)	Placebo N= 17	199.870	216.226±15.078	16.355±15.078	0.173	↑7.56
	Magnesium N= 30		190.035±11.330	–9.835±11.330		↓5.17
Serum LDL-c (mg/dl)	Placebo N= 17	99.288	105.894±5.273	6.605±5.273	0.040	↑6.23
	Magnesium N= 30		91.800±4.034	–7.488±4.034		↓8.15
Serum HDL-c (mg/dl)	Placebo N= 17	54.280	53.882±1.958	–0.398±1.958	0.936	↓0.73
	Magnesium N= 30		53.684±1.471	–0.596±1.471		↓1.09
Serum Non-HDL-c (mg/dl)	Placebo N= 17	139.550	149.035±5.659	9.485±5.659	0.012	↑6.36
	Magnesium N= 30		130.203±4.324	–9.347±4.324		↓7.17

Data expressed by mean ±SEM and percentage of difference; P<0.05 was considered a significant difference between treatment groups at endline; N= number of patients, SEM= standard error of mean, LDL-c= low density lipoprotein cholesterol, HDL-c= high density lipoprotein cholesterol, non-HDL-c= non-high density lipoprotein cholesterol

Table 5: Effect of magnesium supplement on serum magnesium, urine magnesium, and fractional excretion of magnesium.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Serum magnesium (mg/dl)	Placebo N= 17	1.8932	1.845± 0.053	–0.048±0.053	0.001	↓2.60%
	Magnesium N= 30		2.085±0.039	0.191±0.039		↑9.16%
Urine magnesium (mg/dl)	Placebo N= 17	4.8532	3.874±0.579	–0.979±0.579	0.161	↓25.27%
	Magnesium N= 30		4.913±0.434	0.059±0.434		↑1.20%
FE_{Mg} (%)	Placebo N= 17	3.6008	2.834±0.311	–0.766±0.311	0.007	↓27.02%
	Magnesium N= 30		1.725±0.238	–1.875±0.238		↓108.69%

Data expressed by mean ±SEM and percentage of difference; P<0.05 was considered a significant difference between treatment groups at endline; N= number of patients, SEM= standard error of mean, FE_{Mg}= fractional excretion of magnesium

In table 6, and after subgroup analysis according to the initial Mg status, Mg supplement produce significant increase ($P < 0.05$) in serum Mg levels compared with placebo, where the levels reduced after 8 weeks of treatment in cases of hypomagnesaemia and normomagnesaemia. Hypomagnesaemic patients on Mg supplement show no significant increase ($P > 0.05$) in urine Mg levels compared with placebo, while in normomagnesaemic state there was a significant increase ($P < 0.05$) in urine Mg levels among patients on Mg supplement compared with those on placebo where the levels reduced after 8 weeks of treatment. In hypomagnesaemic case, there was a significant reduction ($P < 0.05$) in FE_{Mg} among patients in magnesium group compared with those in placebo group after 8 weeks of treatment. Meanwhile, the FE_{Mg} levels in normomagnesaemic patients decrease not significantly ($P > 0.05$) in magnesium group compared with placebo after the same period of treatment.

Table 6: Effect of magnesium supplement on serum magnesium, urine magnesium, and fractional excretion of magnesium based on initial magnesium status.

Parameter	Initial Magnesium status	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Serum magnesium	Hypo-Mg N=17	P N= 6	1.5988	1.585±0.097	–0.013±0.097	0.022	↓0.82%
		Mg N= 11		1.896±0.072	0.297±0.072		↑15.66%
	Normo-Mg =30	P N= 11	2.0600	1.991±0.062	–0.069±0.062	0.016	↓3.46%
		Mg N= 19		2.193±0.047	0.133±0.047		↑6.06%
Urine magnesium	Hypo-Mg N=17	P N= 6	5.4024	4.597±0.863	–0.8054±0.863	0.419	↓17.51%
		Mg N= 11		3.701±0.635	–1.701±0.635		↓45.96%
	Normo-Mg =30	P N= 11	4.5420	3.532±0.726	–1.01±0.726	0.035	↓28.59%
		Mg N= 19		5.584±0.548	1.042±0.548		↑18.78%
Fractional excretion of magnesium	Hypo-Mg N=17	P N= 6	2.9093	2.842 ±0.349	–0.067±0.349	0.008	↓2.35
		Mg N= 11		1.451 ±0.269	–1.458±0.269		↓100.4
	Normo-Mg =30	P N= 11	3.9696	2.827±0 .450	–1.1426±0.450	0.104	↓40.32
		Mg N= 19		1.871±0.342	–2.0986±0.342		↓111.7

Data expressed by mean ±SEM and percentage of difference; P<0.05 was considered a significant difference between treatment groups at endline
N= number of patients, SEM= standard error of mean

The changes in serum magnesium level for patients on magnesium supplement show a significant negative correlation (*P*<0.05) with baseline serum magnesium level, as indicated in figure2.

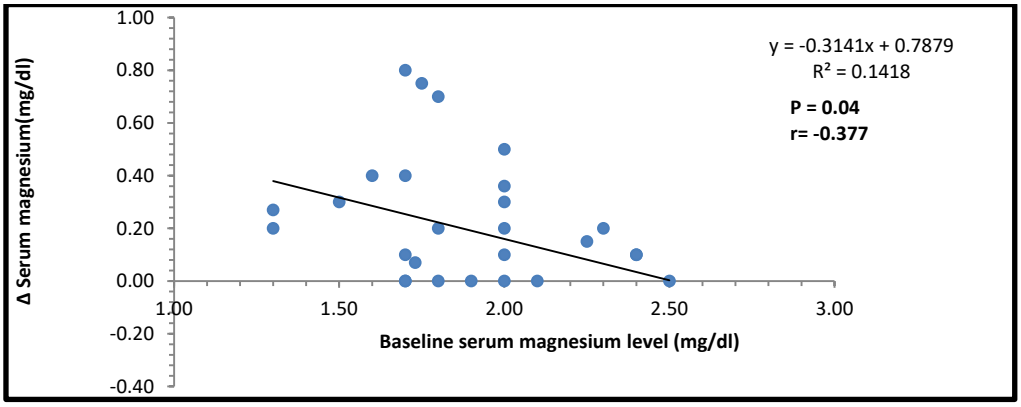

Figure 2: correlation between the changes in serum magnesium level and baseline serum magnesium level among patients on magnesium supplement.

Table 7: Effect of magnesium supplement on serum calcium, serum uric acid and kidney function tests.

Parameter	Group	Adjusted baseline mean	Adjusted endline mean±SEM	Outcome mean±SEM	*P*-value	% of difference
Serum calcium (mg/dl)	Placebo N= 17	9.010	9.137±0.256	0.126±0.256	0.833	↑1.37
	Magnesium N= 30		9.068±0.191	0.057±0.191		↑0.62
Serum uric acid (mg/dl)	Placebo N= 17	4.097	4.348±0.168	0.250±0.168	0.088	↑5.74
	Magnesium N= 30		3.974±0.125	–0.123±0.125		↓3.09
Serum creatinine (mg/dl)	Placebo N= 17	0.966	0.953±0.037	–0.013±0.037	0.999	↓1.36
	Magnesium N= 30		0.953±0.028	–0.013±0.028		↓1.36
eGFR ml/min	Placebo N= 17	70.189	72.460±2.952	2.270±2.952	0.519	↑3.12
	Magnesium N= 30		70.049±2.216	–0.140±2.216		↓0.19

Data expressed by mean ±SEM and percentage of difference; P<0.05 was considered a significant difference between treatment groups at endline;
N= number of patients, SEM= standard error, eGFR= estimated glomerular filtration rate

Table 8: Effect of magnesium supplement on 8-isoprostane and high sensitive c –reactive protein levels.

Parameter	Group	Adjusted baseline mean	Adjusted end line mean±SEM	Outcome mean±SEM	*P*-value	% of difference
8-Isoprostane (pg/ml)	Placebo N= 17	198.430	208.546±15.172	10.116±15.172	0.361	↑4.85
	Magnesium N= 30		226.387±11.783	27.957±11.783		↑12.34
hs-CRP (mg/L)	Placebo N= 17	14.236	13.831±0.629	–0.405±0.629	0.253	↓2.92
	Magnesium N= 30		14.749±0.471	0.513±0.471		↑3.47

Data expressed by mean ±SEM and percentage of difference

P<0.05 was considered a significant difference between treatment groups at endline

N= number of patients, SEM= standard error of mean, hs-CRP= high sensitivity C-reactive protein

DISCUSSION

Abdominal obesity is mostly defined by the IDF. The IDF confirms abdominal obesity as the essential part in MetS[2]. The present study indicated that the patients on magnesium supplement in 84 mg twice a day for 8 weeks showed a significant reduction in weight, BMI, and waist circumference (1.48%, 1.47% and 4.36%, respectively) at the end of study compared with those on placebo twice a day for the same period of treatment (↑0.40%, ↑0.40% and ↑0.40%, respectively) and this agree with Huang *et al*. study that showed a significant reduction in BMI and waist circumference with increasing magnesium intake (*P* <0.001) [26]. Lima de Souza *et al.* study showed that there was no significant difference in body weight, BMI, and waist circumference between intervention and placebo groups after 12 week of treatment with 400 mg of magnesium chloride and this disagree with the results of the present study[27].

The link between magnesium and insulin was studied. Studies showed that magnesium has a role in insulin action, and insulin has a role in regulating of intracellular magnesium accumulation. Use of magnesium supplement chronically can advance insulin action in NIDDM patients[28].In the present study, there was no significant reduction in FSG level (↓11.67%), while no significant changes were observed in IR (↑1.08%) in patients with magnesium supplement compared with those on placebo after 8 weeks of treatment. Meanwhile, HbA1c levels decrease significantly (5.39%) after the same period of treatment (*P*<0.05). The results of Lima de Souza *et al.* study showed that no significant change was shown in IR (*P* =0.928), nor in FBG (*P*= 0.129) between magnesium and placebo groups at the end of the study[27] and this matched with the results of the present study.In Mei Dou *et al.* study, there was a significant decrease from the baseline values in FBG (*p*<0.01) and IR (*P*<0.01) in group taking combination of chromium and magnesium after 12 week of supplementation[29], these results disagree with the results of the present study. Glycemic state measurements also showed decline FSG level in the patients of Mg and placebo group, but the reduction was significant in Mg group compared with placebo (*P*<0.0001), while HbA1c and HOMA-IR showed no significant differences between Mg and placebo group [30].

Hypomagnesaemia and magnesium deficiency play important roles in the pathogenesis of atherosclerosis and ischemic heart disease (IHD) [31]. Oral Mg supplement has a role in reducing of serum total cholesterol, TG, apolipoprotein B, LDL-c, and increasing of HDL-c in patients with IHD [32]. Magnesium acts as a physiological statin when involved in modulation of HMG CoA-reductase that catalyze the rate-limiting step in cholesterol synthesis[33]. In the present study, the levels of serum cholesterol, serum LDL-c and serum non-HDL-c decreased significantly (5.48%, 8.15%, and 7.17%, respectively) in patients taking magnesium supplements compared with those on placebo after 8 weeks of treatment. Meanwhile, serum TG levels decreased not significantly (5.17%) and serum HDL-c levels showed no significant changes (1.09%) in magnesium group compared with placebo. Lipid profile showed no significant changes for serum TG (*P*=0.337), and serum HDL-c (*P*= 0.847) after 12 weeks of magnesium supplementation with 400 mg of magnesium chloride compared with placebo in Lima de Souza *et al.* study on MetS patients without DM and this agree with the results of the present study. Serum total cholesterol didn't change in both magnesium-treated patients (*P*= 0.471) and placebo-treated patients (P= 0.940), LDL-c also showed no significant differences in Mg and placebo groups (P= 0.238 and0.173, respectively) and this was inconsistent with the results of the present study[27]. Solati M *et al.* study found no significant difference in serum total cholesterol and TG levels in magnesium group compared with placebo, but it showed a significant reduction in serum LDL-c levels in Mg group when compared with the placebo (*P*<0.01), also there was a significant reduction in non-HDL-c level among patients on Mg compared with those on placebo (*P*<0.001)[30].

Serum Mg concentration alone has limitations to identify Mg status, since only <1% of total body Mg content is presented in the serum and 99% in intracellular

compartment, so it may not always mirror intracellular Mg status. Though, hypomagnesaemia is an investigative of a systemic Mg deficiency[34]. The value of FE_{Mg} might consider better distinguishable for hypomagnesaemic patients than the urinary magnesium/ creatinine ratio. In subjects with normal renal function, FE_{Mg} is a very useful as a diagnostic approach of hypomagnesaemia. The level >4% is investigative of inappropriate magnesium loss[35]. Results of the present study indicate a significant increase in serum magnesium levels (9.16%) within Mg group compared with placebo, where the levels reduced after 8 weeks of treatment (2.60%). Meanwhile, urine magnesium levels increased but not significantly in magnesium group (1.20%) compared with placebo, where the levels reduced (25.27%) after the same period of treatment. The values of FE_{Mg} reduced significantly in magnesium group (108.69%) when compared with placebo (27.02%) at the end of study. Correction of serum magnesium levels and the values of FE_{Mg} less than 2% give an explanation that hypomagnesaemic status is corrected to reach normal level, and the mean of FE_{Mg} gives an indication that magnesium is shifted to cells to treat magnesium deficiency.Again, in the present study after subgroup analysis according to the initial magnesium status, the increment in serum magnesium level within Mg group stilled significant in both hypomagnesaemic and normomagnesaemic status (15.66% and 6.06%, respectively) but was more evident in hypomanesaemic state. Urinary magnesium level in patients on Mg supplement appears a different picture after subgroup analysis when the increment became significant in patients with normomagnesaemia (18.78%), whereas this increment changed to reduction in patients with hypomagnesaemia (45.96%). This gives an indication that hypomagnesaemia had been corrected with Mg supplementation, while the excess amount of magnesium was excreted in normomagnesaemic subjects. The FE_{Mg} value for Mg group showed a significant reduction in hypomagnesaemic state (100.4%) that is directly proportional with the reduction in urine magnesium, while the reduction was not significant in normomagnesaemic subjects.

The changes in serum magnesium levels showed a significant inverse correlation (P=0.04) with baseline serum magnesium levels, it reduced until became zero when serum magnesium level reached 2.5 mg/dl. This result gives clear explanation about safety of magnesium supplement in patients with MetS when eGFR>30ml/min. One study showed that there was an increment in magnesium group compared with placebo by 0.02 mmol/L (P=0.09) after 24 weeks of oral magnesium citrate treatment and this match with the results of the present study. This study also showed that 24-hr urine magnesium excretion appeared to increase by 2.01 mmol (P <0.001)[36]. Another study concluded that serum magnesium levels showed no significant difference between magnesium and placebo group after 12 weeks of treatment with magnesium sulfate 300 mg once daily [30] and this was inconsistent with the results of the present study. Urinary excretion of magnesium in Sacks FM *et al*. study increased significantly (P<0.01) in the group that received two tablets of magnesium lactate in a dose of 84 mg twice daily as a supplement compared with placebo group[37]. This was compatible with the results of the current study when urine magnesium increased significantly in normomagnesaemic state. Elisaf M*et al.* study focused on FE_{Mg} in normal subjects and hypomagnesaemic patients. Results showed that FE_{Mg} was positively correlated with the urinary magnesium/ creatinine ratio[35]. This was compatible with the results of the present study since patients on Mg supplement with hypomagnesaemic status showed a significant reduction in the mean of FE_{Mg} when urine Mg decreased by 45.96%.

In the present study, the levels of serum calcium and kidney function tests (including serum creatinine and eGFR) showed no significant difference (↑0.62%, ↓1.36% and ↓0.19%, respectively) among patients on magnesium supplement compared with those on placebo after 8 weeks of treatment. Serum uric acid showed no significant reduction (↓3.09%) in Mg group compared with placebo after the same period. Results of kidney function in the current study indicate the safety of magnesium supplement in a dose of 168 mg daily (84 mg twice a day) in patients with eGFR more than 30 ml/min (average of eGFR in the present study for patients on Mg supplement was 70.04 ml/min, that means a mild decrease in kidney function). One study reported that no effect was observed on serum calcium concentration among patients on magnesium supplementation compared with placebo after 24weeks of treatment [36] and this was similar to the results of the present study. Obeidat AA *et al.* showed that serum uric acid was considered as a predictor for MetS in women, but not in men, in their study on 322 women and 308 men diagnosed with MetS according to the IDF criteria in the King Hussein Medical Center [38].

Hypomagnesaemia is occurred with higher levels of oxidative stress[39, 40]. Magnesium has shown its antioxidant benefits in the prevention of hypertension through attenuating the damage of vasculature from oxidative stress and preventing vascular injury[41].Results of many animal studies reported that Mg deficiency causes marked elevation of several pro-inflammatory markers including tumor necrotic factor-alpha (TNF-α), interlukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and other pro-inflammatory markers, in addition to increased circulating inflammatory cells[42]. Ford *et al.* mentioned in their study in children and adolescents that serum hs-CRP levels were correlated to MetS[43]. There was no significant difference in the levels of 8-isoprostane (↑12.34%) and hs-CRP (↑3.47%) among patients on magnesium supplement compared with those on placebo at the end of the present study. Vongpatanasin W *et al*. found in their study that urinary 8-isoprostane level was

significantly reduced within subjects received potassium magnesium citrate powder compared with placebo group(P<0.001) [44]. Cocate PG*et al.* found a negative association between high fruit and vegetable intake and concentrations of oxidative stress markers (P< 0.05) in middle aged men (50.5 ± 5.0 years). The urinary concentrations of 8-iso-PGF2α were lower in men with high magnesium intake from fruit and vegetable (P= 0.018)[45]. In the Women's Health Initiative Observational Study on postmenopausal females, age ranged from 50-79 years, plasma concentrations of hs-CRP and other inflammatory markers were measured at the baseline and at the end of study. Results showed that Mg intake was inversely linked with hs-CRP (P = 0.003) and other inflammatory markers. These results emphasized that magnesium intake has a role in improvement of endothelial dysfunction and inflammation and might have a role in prevention of metabolic syndrome[46]. Magnesium supplementation as magnesium oxide (250 mg daily) appeared to have a significant inverse correlation with hs-CRP levels (P=0.05) in magnesium group compared with placebo in a randomized trial included 74 overweight women[47].

One limitation of this study is unselecting of the patients with hypomagnesaemia as inclusion criteria for the study and this may explain the differences in the results when compare with the results of other previous studies. Another limitation may be the IR, since not all patients included in this study have IR which may affect the final results when compare with other studies their subjects have IR.

From this study, many recommendations can be suggested for future work, including further study with large scale sample and long term duration. Increasing the dose used for magnesium l-lactate tablet, or another formulation could be used such as magnesium chloride. More parameters could be measured for magnesium, like its level within erythrocytes, tissues, and platelets that can give more details about magnesium status and magnesium deficiency.

From above results, one can conclude that oral supplementation of Mg l-lactate can improve some features of MetSin patient women. Further studies are required to clarify other effects and mechanisms by which Mg can reduce the complications and consequent events of MetS.

Acknowledgments: The authors would like to thank Al-Must ansiryiah University (www. uomustansiryiah.edu.iq), and Obesity Research and Therapy unit/ Alkindi College of Medicine, Baghdad- Iraq, for its support in the present work.

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Source of Support: Nil, **Conflict of Interest:** None.