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Serum and intracellular magnesium deficiency in patients with metabolic syndrome—Evidences for its relation to insulin resistance

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ABSTRACT

This cross sectional study evaluated serum (SMg) and intramononuclear (MMg) magnesium in patients with metabolic syndrome without diabetes and correlated them with cardiovascular risk factors. 72 patients and 57 controls (blood donors) were studied. Hypomagnesemia (SMg < 1.7 mg/dL) was seen in 23.2% and intracellular depletion in 36.1% of the patients. SMg and MMg means were significantly lower in patients than in controls: 1.80 ± 0.18 mg/dL *vs.* 2.43 ± 0.43 mg/dL and 0.98 ± 0.55 μg/mg *vs.* 1.67 ± 0.64 μg/mg of protein ($P < 0.001$). Inverse correlation was observed between, SMg and MMg with BMI; SMg with systolic blood pressure and waist circumference in women. Patients with acanthosis nigricans had lower SMg (1.75 ± 0.18 mg/dL *vs.* 1.85± 0.18 mg/dL, $P < 0.05$). Non-white people had lower SMg (1.78 ± 0.16 mg/dL *vs.* 1.92 ± 0.24 mg/dL, $P = 0.007$) and MMg (0.95 ± 0.59 μg/mg *vs.* 1.13 ± 0.42 μg/mg, $P = 0.03$). Patients with IR showed lower MgM means (0.84 ± 0.33 μg/mg *vs.* 1.14 ± 0.69 μg/mg, $P < 0.05$). The same occurred in patients with low HDL-c levels (0.92 ± 0.46 μg/mg *vs.* 1.20 ± 0.70 μg/mg, $P = 0.03$), and those with moderate and severe hepatic steatosis (0.77 ± 0.29 μg/mg *vs.* 1.21 ± 0.80 μg/mg, $P < 0.05$). In conclusion, magnesium depletion in serum and mononuclear cells is common in obese people with metabolic syndrome, and it is more evident in non-white people with insulin resistance. This depletion may contribute to a post-receptor insulin resistance.

1. Introduction

Magnesium (Mg) is primarily found within the cell, where it is a metallic cofactor for over 300 enzymatic reactions involved in protein and nucleic acid synthesis and in energy metabolism [1]. It is necessary for glucose transportation between membranes, glucose oxidation, all reactions involving phosphorylation and energy exchange, and it is essential for insulin action, since it is a cofactor of tyrosine kinase activity [2].

Less than 1% of the total body Mg is present in blood, 1/3 binding with protein, and 2/3 in ionized form; thus serum Mg (SMg) does not provide reliable information about total or intracellular magnesium concentration [3].

One of the reasons for magnesium metabolism not becoming routinely investigated is the fact that there is no

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easily available and reproducible measurement of magnesium status. Mg depletion can be seen with normal SMg. Mononuclear cells are probably the compartments which best correlate with muscular magnesium [4].

Magnesium deficiency is present in 10% of patients admitted to general hospitals, and as many as 65% of patients in intensive care units [5].

Hypomagnesemia is a frequent condition in patients with diabetes. It occurs in 25–47% of patients [6,7]. Prospective studies showed an increased risk of diabetes in a population with a low ingestion of the ion [8], and an arm of the Women Health Study showed that the larger the magnesium intake, the lesser the diabetes incidence, especially in obese women [9].

Metabolic syndrome (MS), a complex entity related to metabolic and cardiovascular risk factors including central obesity, dyslipidemia, elevated blood pressure, glucose abnormalities and protrhombotic and proinflammatory states [10] has received increased attention in the past few years. The predominant underlying risk factor for MS appears to be abdominal obesity and insulin resistance [11]. As Mg is essential for insulin action, there is biologic plausibility to associate Mg deficiency to MS, what was found in some papers [12,9]. However, in our knowledge, there is not any study analyzing intracellular magnesium concentrations in patients with MS, which are though to be more reliable as representation of Mg depletion.

The aim of this study was to evaluate the prevalence of magnesium deficiency in serum and in mononuclear cells in patients with metabolic syndrome without diabetes mellitus detected by fasting blood glucose, and to correlate this data with insulin resistance, with each component of the metabolic syndrome, and other cardiovascular risk factors.

2. Material and methods

2.1. Subjects

A cross section study was carried out with seventy-two outpatients seen in the Metabolic Syndrome Clinics of Bahiana School of Medicine, Salvador, Bahia, Brazil.

The inclusion criteria were patients with metabolic syndrome as defined by International Diabetes Federation criteria which requires the presence of abdominal obesity, defined by waist circumference $\geq$90 cm in men and $\geq$80 cm in women, for South American subjects, and two additional criteria, as follows: (1) hypertriglyceridemia: $\geq$150 mg/dL or specific treatment for this lipid abnormality; (2) low HDL-c: $<$40 mg/dL in men and $<$50 mg/dL in women; (3) high blood pressure: systolic pressure $\geq$130 or diastolic pressure $\geq$85 mmHg or treatment of previously diagnosed hypertension; (4) fasting glucose $\geq$100 mg [13]. Excluding criteria used were: use of diuretics or fibrates, persistent diarrhea, alcoholism and patients with confirmed diagnoses of diabetes mellitus.

2.2. Reference population to intramononuclear magnesium

As a reference population for establishing normal serum and intramononuclear magnesium levels, 57 healthy non-obese blood donors (36 males, 21 females), with ages varying between 18 and 54 years (32 ± 8.6 years) were studied. Fasting blood glucose was measured to exclude incident cases of diabetes. The MMg average was 1.69 ± 0.62 μg/mg of protein, with no difference between men and women. The 5th percentile of these normal individuals was used to define the lower level of MMg in this comparing group (0.76 μg/mg of protein).

2.3. Clinical and laboratory evaluation

Patients were initially subjected to a clinical and laboratory evaluation. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. Waist circumference was measured at the middle point between the iliac crest and the last costal arch, at minimal expiration, on orthostasis. Blood pressure was measured twice, and achantosis nigricans or signs of inflammation or infection were described whenever present.

All measurements and blood collection were performed in the morning following a 12 h fast. The laboratory tests performed were: fasting blood glucose, cholesterol, triglycerides, HDL cholesterol, uric acid, AST, ALT, γ-GT by dry chemistry (VITRUS 950–250); LDL cholesterol was calculated based on the Friedwald equation, insulin measured by chemiluminescence's spectroscopy, high sensitivity C protein reactive (CPR) by nephelometry, magnesium in serum and in mononuclear cells by atomic absorption spectrophotometry (VARIAN–220). The homeostasis model assessment (HOMA index) was used as a measure of insulin resistance (HOMA-IR = (insulin (mU/L) $\times$ glucose (mmol/L)/22.5) [14]. When HOMA-IR was higher than 2.7, patients were classified as insulin resistant [15]. Mononuclear cells separation was previously described [7]. The final suspension consisted of a mean of 97.5% lymphocytes, 2.3% monocytes and 0.15% neutrophils. MMg was expressed by cell protein which was measured using the Follin phenol reagent as described by Rodrigues [16].

All patients were sent for an abdominal ultrasound by the same physician, in order to detect non-alcoholic fatty liver disease (SONOACE 6000 color, Madison–USA). Steatosis was graded as 1–3 [17].

2.4. Statistical analysis

Summarized data are shown as mean and standard deviation, and median with interquartile interval. Two-tailed parametric tests were used for comparison of normally distributed variables. Non-parametric tests were used to compare variables when the assumption of normal distribution was not met. Student's independent *t*-test was performed to compare serum magnesium levels between patients and controls. Because of non-normality of intracellular magnesium, GGT and CRP distribution, the Mann–Whitney test was used.

For the categorical variables comparisons, Chi-squared or Fischer Exact test was used. To assess possible relationships between continuous variables, Pearson's or Spearman correlation coefficients were used. Linear Multiple Regression analysis was performed. The model included, the variables

that reached *P*-value <0.1 in the simple linear regression, and age, using MgS and MgM as dependent variables.

The difference between Mg levels for different grades of obesity and race was tested by ANOVA or Kruskal–Wallis. A two-tailed *P*-value ≤0.05 was considered statistically significant.

The SPSS for windows, version 11.1 (Chicago, IL, USA), was used to perform the statistical analysis.

3. Results

Seventy-two patients were enrolled, 91.7% female, with 45.7 ± 11.8 years of age. 87.5% of patients were between 30 and 60 years of age, 3 had less than 30 years of age, and 6 more than 60 years of age. There were no differences on Mg levels according to quartiles of age (Fig. 1). Fourteen patients were white (19.4%) and 58 (80.6%) were non-white. The anthropometric and biochemical measurements of the population studied are shown in Table 1.

All patients had metabolic syndrome: 36 (50.0%) had 3 components of the syndrome, 24 (33.3%) had 4 and 12 (16.7%) had 5 components. Obesity was identified in 52 patients (72.2%), high blood pressure in 56 (77.8%), impaired fasting glucose in 32 (45.1%), hypertriglyceridemia in 26 (36.1%) and low HDL in 45 (62.5%). In addition, hepatic steatosis diagnosed by abdominal ultrasound, achantosis nigricans and hypercholesterolemia were diagnosed in 62.5%, 45.8% and 46.5% of patients respectively. Fifty percent of the 72 patients had insulin resistance defined by HOMA-IR ≥ 2.7. Elevated CRP was present in 40 patients (55.6%).

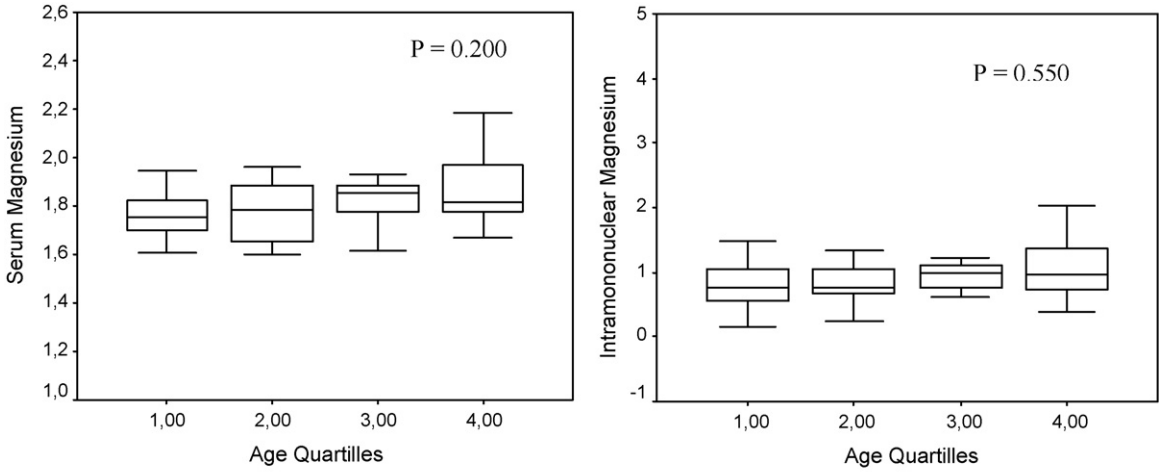
Hypomagnesemia was identified in 23.2% of patients and intracellular depletion in 36.1%, whereas in control group magnesium depletion was seen in 3.3% and 9.8% respectively (Fig. 2). The serum and intramononuclear magnesium concentrations were significantly lower in patients with metabolic syndrome than in subjects of comparing group (SMg: 1.81 ± 0.19 mg/dL *vs.* 2.43 ± 0.43 mg/dL $P < 0.001$; MMg: 0.99 ± 0.56 μg/mg *vs.* 1.67 ± 0.64 μg/mg of proteins, $P < 0.001$).

There was no correlation between serum and intramononuclear magnesium ($r = 0.047$, $P = 0.70$), but a concordance of measures was observed in 59.4% of patients. 49.2% had normal serum and intracellular Mg levels, 10.2% had low SMg and MgM levels. 26.8% had only low MMg concentrations, and 13.4% only low SMg levels

BMI was inversely correlated with SMg ($r = -0.33$, $P = 0.006$) and with MMg ($r = -0.25$, $P = 0.04$) (Fig. 3). After multivariate regression analyses the association between BMI and MgS persisted ($P = 0.019$). An inverse association was met between SMg and systolic blood pressure ($r = -0.24$, $P = 0.04$), and there was a tendency to inverse correlation with diastolic blood pressure ($r = -0.22$, $P = 0.07$), waist circumference in women ($r = -0.24$, $P = 0.058$) and CRP ($r = -0.22$, $P = 0.07$). A tendency to negative correlation was observed with MMg and uric acid ($r = -0.21$, $P = 0.08$) and HOMA-IR ($r = -0.21$, $P = 0.08$) and a positive correlation with HDL cholesterol ($r = 0.220$, $P = 0.07$). The other variables did not show any association with serum or intracellular magnesium.

The levels of serum and intracellular magnesium were progressively lower according to grades of weight excess (Table 2). Patients with insulin resistance (HOMA-IR > 2.7), had lower MMg than patients without insulin resistance (0.84 ± 0.33 μg/mg *vs.* 1.14 ± 0.69 μg/mg of protein, $P < 0.05$), and when acanthosis was present, the SMg was lower (1.75 ± 0.18 mg/dL *vs.* 1.85 ± 0.18 mg/dL, $P < 0.05$). The intracellular Mg levels were lower in patients with steatosis grade 2 and 3, when compared with patients without steatosis suspected by ultrasound: 0.77 ± 0.29 μg/mg *vs.* 1.21 ± 0.80 μg/mg of protein, $P = 0.013$.

Non-white people had lower serum magnesium levels than white people (1.78 ± 0.16 mg/dL *vs.* 1.92 ± 0.24 mg/dL, $P = 0.007$), the same occurs in Intramononuclear levels: 0.95 ± 0.57 μg/mg *vs.* 1.13 ± 0.42 μg/mg of protein ($P = 0.03$).



Quartiles of age : 1: 21– 39 years of age, 2: 40 – 45 years of age, 3 :46 – 54 years of age, 4 : over than 54 years;
P vallue calcullated by ANOVA and Kruskhal-Wallis

Fig. 1 – Serum and intramononuclear magnesium levels according to quartiles of age in the 72 patients studied.

Table 1 – Descriptive analyses of sample characteristics (72 patients with metabolic syndrome).

Variable	Result	Reference value
Age	45.7 ± 11.8	
Weight (kg)	89.7 ± 20.6	
BMI (kg/m^2)	35.3 ± 7.3	
Waist (cm)		
Men	111 ± 20	
Women	108 ± 13	
Systolic blood pressure (mmHg)	134 ± 16	
Diastolic blood pressure (mmHg)	86 ± 9	
Fasting glucose (mg/dL)	101 ± 13	70–99
Insulin (mU/L)	13.5 ± 6.9	1.7–31
HOMA-R	3.3 ± 1.9	≤2.7
Cholesterol (mg/dL)	196 ± 46	<200
Triglycerides (mg/dL)	137 ± 58	<150
HDL cholesterol (mg/dL)	44 ± 10	≥45
LDL cholesterol (mg/dL)	125 ± 41	<130
Uric acid (mg/dL)	5.2 ± 1.3	2.5–7.5
AST (U/L)	27 ± 11	<36
ALT (U/L)	32 ± 14	<52
γ–GT (U/L)	39 ± 40	12–43
CRP (mg/L)	3,4 (1,6–8,8)	<3,0
Serum magnesium (mg/dL)	1.81 ± 0.19	1.7–2.5
Intramononuclear magnesium (μg/mg of total proteins)	0.99 ± 0.56	>0.76

4. Discussion

The results of this cross sectional study demonstrate that patients with metabolic syndrome had lower serum and intramononuclear magnesium concentrations as compared with subjects without the condition. The frequency of hypomagnesaemia was higher than that observed in controls (23.2% *vs.* 3.6%), and even higher than that described in hospitalized patients (10%) [5]. Guerrero-Romero showed hypomagnesemia in 65.6% of 192 patients with metabolic syndrome, compared with 3.9% in a 384 disorder free control group, matched for age and gender [18]. Serum and intramononuclear levels were lower in non-white people, although, only 19% of these individuals were white. This data is similar than those found in American people [8].

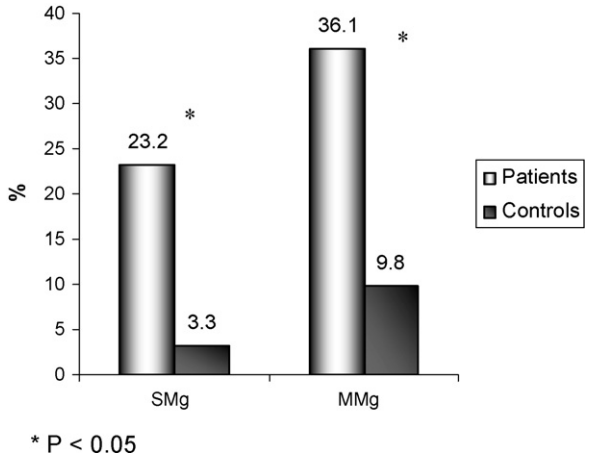


Fig. 2 – Serum and intracellular magnesium depletion in patients and comparing groups.

This study seems to be the first to describe intracellular magnesium concentration in patients with MS. Intramononuclear depletion was found in 36.1% of patients. This finding is well documented in patients with diabetes mellitus, in whom a 30.8% of magnesium depletion in mononuclear cells was found, using the same technique of cell isolation and magnesium measurement [7].

The mechanisms involved in the high prevalence of Mg depletion in patients with MS are probably multifactorial. Consistently with some previous reports, BMI was strongly inversely related to magnesium deficiency in this study [19]. Hypomagnesaemia was described in obese children, and one study suggests that it is a consequence of reduced dietary intake [20]. The wrong nutritional habits of obese people, with low ingestion of whole grains, green leafy vegetables and other foods rich in magnesium may contribute to Mg depletion. Furthermore, the magnesium content of Brazilian soil is poor, and the population ingestion of this mineral is probably less than necessary [21].

The renal loss is other mechanism that may be involved. There are evidences that insulin can induce Mg excretion and

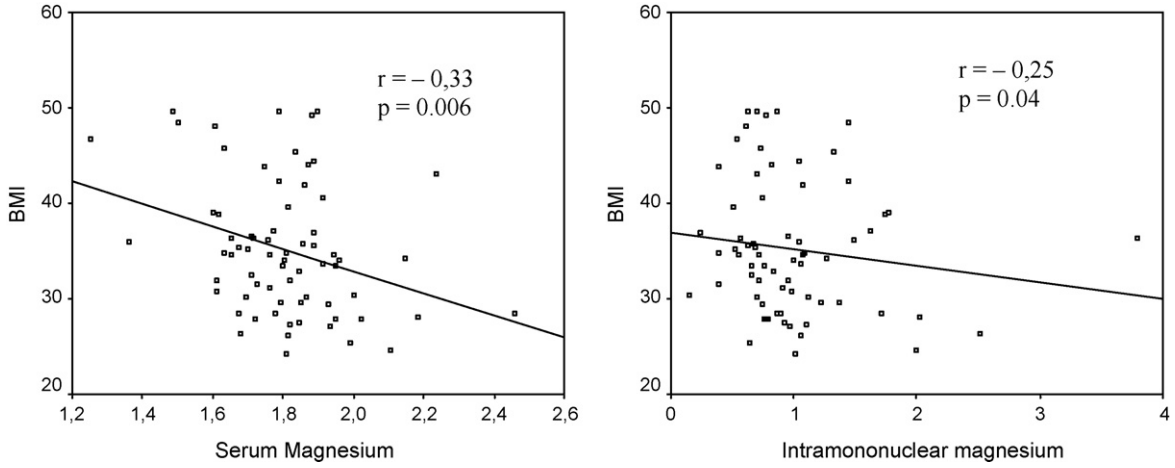


Fig. 3 – Correlation between serum and intracellular magnesium concentration with BMI in patients.

Table 2 – Serum and intramononuclear magnesium according to grades weight excess.

	Normal weight ($n = 2$)	Overweight ($n = 18$)	Obesity ($n = 52$)
Serum magnesium (mg/dL)	1.96 ± 0.20	1.90 ± 0.20	$1.77 \pm 0.16^*$
Intramononuclear magnesium (μg/mg of total protein)	1.49 ± 0.7	1.15 ± 0.53	0.94 ± 0.54

Normal weight: BMI < 25 kg/m^2, overweight: BMI ≥ 25 and < 30 kg/m^2, obesity: BMI ≥ 30 kg/m^2, $P < 0.05$.
The asterisk correspond to P value ($^*P < 0.05$).

lead to hypomagnesemia in patients with hyperinsulinemic states, as found in MS [22].

The prevalence of Mg intramononuclear depletion was greater than that found in serum. MMg levels were lower in patients with insulin resistance (HOMA ≥ 2.7), in patients with achantosis nigricans, an important clinical marker of insulin resistance, lower levels of SMg were found. Insulin resistance may impair the magnesium transport to the cell, once insulin regulates magnesium homeostasis by a mechanism that is not yet definitely established, but probably by ion influxes.

Following ingestion of glucose in non-diabetic subjects, insulin induces a shift of Mg from the extracellular to the intracellular space, producing a significant decline in plasma, and increasing erythrocyte Mg content [23]. This effect can be abolished in platelets by a monoclonal antibody directed toward the insulin receptor, suggesting that intracellular Mg accumulation depends upon activation of the insulin receptor [24].

On the other hand, as magnesium is a critical cofactor for several enzymes in carbohydrate metabolism, important for phosphorylation reactions of tyrosine-kinase in the insulin receptor, and other protein-kinases, necessary to insulin intracellular signalization [12], reduced magnesium levels may contribute for insulin resistance in these patients.

Besides BMI, systolic blood pressure showed inverse association with Mg concentrations, and a tendency for inverse correlation was observed in relation to waist circumference, and diastolic blood pressure. A tendency for positive correlation between MMg with HDL cholesterol was seen, similar to that found by Guerrero-Romero with serum Mg levels [25]. Patients with moderate and severe hepatic steatosis had lower intracellular Mg than patients without this finding. Rodriguez-Hernandez et al. demonstrated hypomagnesemia in patients with insulin resistance and non-alcoholic hepatitis [26]

Epidemiological studies have described an inverse relationship between a magnesium rich food intake and diabetes [8,9], insulin resistance [27], and metabolic syndrome [28]. Experimental evidence suggests that magnesium deficiency combined with a high fructose diet can induce insulin resistance, hypertension, dyslipidemia, endothelial dysfunction and protrombotic changes, with up regulation of markers of inflammation and oxidative stress [29].

In conclusion, serum and intracellular Mg deficiency are common in patients with metabolic syndrome, especially in non-white subjects, with obesity and insulin resistance. The inverse association found between MS components and Mg concentrations, suggests that Mg depletion may contribute for a post-receptor insulin resistance, the link between these cardiovascular risk factors. Further studies are necessary to analyze the potential benefit of long-term magnesium replacement in these patients. Dose and duration of Mg replacement remain to be established.

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Conflict of interest

The authors state that they have no conflict of interest.

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