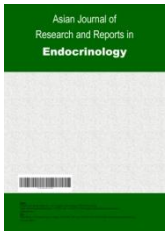

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Assessment of Magnesium Status in Type 2 Diabetes: Relation with Glycemic Control and Chronic Complications

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background and Aim: Magnesium (Mg) deficiency has been frequently associated with type 2 diabetes mellitus (T2DM). The purpose of this study was to evaluate Mg status in patients with T2DM using an intravenous Mg load test and to determine a correlation between Mg deficiency, glycemic control, and the occurrence of chronic complications.
Methods: A descriptive study conducted between 2020 and 2021 in the department of Endocrinology of the Hedi Chaker Universitary Hospital of Sfax, Tunisia, including adults aged over 18 years. The Mg deficiency was defined by a Mg retention rate over 50% after Mg load test.
Results: Thirty patients were included in the study, 53% of whom were women. The average age was 57.3 ± 10 years old. The prevalence of hypomagnesemia was 17%. Patients were divided into 2 groups: 57% had a confirmed Mg deficiency (G1) and 43% had a normal Mg status (G2). G1 patients had a more unbalanced diabetes than G2 patients but insulin resistance was observed with a higher frequency among the latter. Both microvascular (retinopathy, microalbuminuria, diabetic neuropathy) and macrovascular (coronary heart disease, stroke, lower limb arteriopathy) complications of diabetes were observed more frequently in G1 but without statistical significance. Risk assessment using univariate and multivariate models showed that age over 55 years is associated with Mg deficiency in diabetic patients.

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Conclusion: Mg deficiency is more prevalent among T2DM patients, with age over 55 years as a major risk factor. Mg deficiency is associated with a poorly balanced diabetes and the occurrence of macro and micro-vascular complications.

Keywords: Magnesium deficiency; type 2 diabetes mellitus; magnesium load test.

1. INTRODUCTION

Magnesium (Mg) is the fourth most abundant mineral in the body with essential roles in many physiological functions [1]. There is poor correlation between serum Mg and tissue pools of Mg [2]. In fact, Mg deficiency can exist despite normal serum Mg levels [2], reflecting intracellular and systemic Mg depletion involving many tissues. The magnesium load test (MLT) seems to be fairly reproducible and is adequate for clinical use [1,3], contrary to other invasive and expensive techniques such as tissue biopsies and intracellular Mg analysis. Hypomagnesaemia has been reported in 14-48% of patients with type 2 diabetes mellitus (T2DM) versus 2.5-15% in their counterparts without diabetes [4]. The relationship between insulin resistance (IR), T2DM and Mg deficiency has been widely described [5-7,4,8]. The aim of the study is to evaluate the prevalence of Mg deficiency in T2DM and its impact on glycemic control and the occurrence of diabetes' chronic complications.

2. SUBJECTS AND METHODS

A descriptive study was conducted between February 2020 and June 2021 at the department of Endocrinology of the Hedi Chaker Universitary Hospital including thirty T2DM adults aged over 18 years. An informed consent was obtained from each patient. Exclusion criteria were as follows: impaired renal function (clearance of serum creatinine<60ml/min), intake of drugs interfering with Mg status, magnesium supplements, history of thyroid, parathyroid or adrenal disease, diarrhea, atrioventricular block, heart rate ≤ 60 beats min-1, blood pressure ≤110/70mmHg, intestinal malabsorption, malnutrition, alcoholism, important physical activity, chronic respiratory diseases, pregnancy, pancreatic insufficiency or pancreatitis, family hypomagnesemia.

The Mg status was assessed using an intravenous MLT. The test was performed between 8:00 and 10:00 AM. After emptying the urinary bladder, 0.1 mmol /kilogram of bodyweight of the Mg aspartate hydrochloride in 250 mL isotonic saline were infused over 2 hours. Blood samples were drawn without stasis 60 min after starting infusion to measure the peak serum Mg produced by the load. Blood pressure and electrocardiograms were recorded twice during the infusion. Urine was collected in plastic bottles containing 15 mL of 10% hydrochloric acid (HCL) to avoid the precipitation of Mg salts at alkaline pH, from the start of the infusion for 24 h. Subjects were informed of Mg rich foods that were to be avoided during the collection period. Mg retention was calculated from 24-h urinary Mg excretion and expressed as a percentage of the amount of the Mg test dose according to the formula [9]:

$$\% \text{ Mg retained} = 1 - \left(\frac{\text{post infusion urine Mg} - \text{pre infusion urine Mg}}{\text{total elemental Mg infused}}\right) \times 100$$

Serum Mg levels < 0.7 mmol/L defined hypomagnesemia. Mg deficiency is objectified when the percentage of Mg retention exceeds 50%.

The calculated parameters:

$$\text{Urinary excretion fraction of Mg (FE Mg) [9]} = \frac{\text{Mg urinary } (\frac{\text{mmol}}{\text{L}}) \times \text{ plasma creatinine} (\frac{\mu\text{mol}}{\text{L}})}{\text{serum Mg} (\frac{\text{mmol}}{\text{L}}) \times \text{urinary creatinine} (\frac{\mu\text{mol}}{\text{L}}) \times 0.7}$$

Insulin resistance (IR) was estimated using 2 indexes:

➔ HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) [5]

$$\text{HOMA-IR} = \frac{\text{fasting plasma glucose } (\frac{\text{mmol}}{\text{L}}) \times \text{ fasting plasma insulin} (\frac{\mu\text{UI}}{\text{mL}})}{22.5}$$

➔ McAuley index [6]: $\exp^{\left[2.63 - 0.28 \ln\left(\text{fasting plasma insulin}\left(\frac{\mu\text{IU}}{\text{mL}}\right)\right) - 0.31 \ln\left(\text{TG}\left(\frac{\text{mmol}}{\text{L}}\right)\right)\right]}$

Insulin sensitivity (IS) was estimated using QUICKI (Quantitative Insulinsensivity Check Index) [7]

$$\text{QUICKI} = 1/ [\log \text{Fasting plasma insulin } (\frac{\mu\text{UI}}{\text{mL}}) + \log \text{Fasting plasma glucose} (\frac{\text{mg}}{\text{dL}})]$$

The reference values for assessing insulin resistance are: fasting plasma insulin≥12μUI/mL; HOMA-IR ≥ 2.6; QUICKI ≤0.33 and McAuley ≤5.8.

Blood samples were taken at 8AM in fasted patients for 12 hours on an ethylene diamine tetra-acetic acid (EDTA) tube for glycated hemoglobin (HbA1c) and lithium heparinate tube for the other biochemical parameters.

Mg concentrations in serum and urine were measured using an automated calmagite method.

The determination of HbA1c was performed using high performance liquid chromatography method. Insulin concentration was determined by chemiluminescence. The other parameters were determined on the multiparameter automate.

Date were analyzed using Statistical Package for Social Science SPSS 19.0. Descriptive and inferential statistical analyses have been carried out in the present study. Results on continuous measurements are presented as Mean ± SD and results on categorical measurements are presented as Number (%). Comparisons of 2 means in independent series were performed by the t-Student test. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The links between 2 quantitative variables were studied by Spearman's rank correlation coefficient. In order to identify risk factors independently related to the event, we conducted a multivariate logistic regression stepwise analysis. Multivariate analysis allowed the calculation of adjusted odds ratios (OR). In all statistical tests, Significance is assessed at 5% level of significance.

3. RESULTS

3.1 Description of the Population

The average age of our patients was 57.3 ± 10 years. The study population was composed of 14 men (47%) and 16 women (53%), giving a sex ratio (M/F) of 0.87. Forty-seven percent of our patients had hypertension while seventeen subjects had dyslipidemia. The average weight of our patients was 72.3 ± 19.4 kg. The average BMI was 27.5± 4.9kg/m2. Overweight was found in 47% of our patients and obesity in 30% of cases. An android distribution of fat was found in 43% of males and 56.3% of females. The main reasons for hospitalization were, in decreasing order of frequency, poorly balanced diabetes in 83% of cases, primary diabetes in 10% of cases and diabetic ketosis in 7% of cases. Epidemiological and clinical characteristics of our study population are summarized in Table 1.

3.2 Prevalence of Magnesium Deficit and Exploration of Magnesium Status

Mean serum magnesium before the test was 0.7 ± 0.06 mmol/l. Hypomagnesaemia was found in 17% of cases. The Mg deficiency was confirmed by the Mg intravenous load test in 57% of cases. Patients in our study were divided into two groups: G1 including 17 patients with Mg deficiency (percentage of Mg retention>50%) and G2 including 13 patients with normal Mg status (percentage of Mg retention<50%).

Plasma Mg determined one hour after the start of intravenous Mg loading was lower in G1 subjects compared to G2 subjects, but the difference was not significant (0.3 ± 0.5 mmol/l versus 0.7 ± 0.4 mmol/l; p=0.07). The determination of 24-hour urine Mg 24 hours after load test made it possible to conclude that the subjects of the G1 group retained the infused magnesium more strongly (89.8% versus -6.2%; p <0.001). The results of MLT are summarized in Table 4.

Patients in the G1 group were significantly older (60.4 ± 7.5 years versus 53.1 ± 11.6 years; p=0.01). Also, they were predominantly female (M/F sex ratio = 0.54) while those in the G2 group were mostly men (M/F sex ratio= 1.6). Physical examination data showed higher weight, BMI, waist circumference, and systolic blood pressure in patients in the G2 group but without significant difference, except for diastolic blood pressure which was lower in G1 patients (72 ± 1mmHg versus 80 ± 5mmHg; p=0.03). The demographic characteristics, personal history, anthropometric and physical data of the two groups are summarized in Table 2.

Age over 55 was the only factor independently associated with Mg deficiency (OR=12.6; p=0.01). A duration of diabetes> 10 years as well as smoking were associated with Mg deficiency in the univariate model (OR=10.7; p=0.02 and OR=10; p=0.02 respectively) but this association was not found in the multivariate model (Table 3).

In our study, mean Mg intake was 236.8 ± 110.07 mg/d. Ninety percent of our patients did not reach the recommended values of daily Mg intake. The mean Mg intake of patients with Mg

deficiency was lower than that of patients with normal Mg status (251.1 ± 73.2 mg/d versus 278.5 ± 143.4 mg/d; p = 0.4). No correlation was found between daily Mg intake and the percentage of urinary retention of Mg (r = -0.004; p = 0.4).

Clinical signs of Mg deficiency were found only in 30% of patients with Mg deficiency. They were asthenia in 77.8% of these patients and tremor in 22.2%.

3.3 Study of the Relationship between the Deficit in Magnesium and Glycemic Balance, Insulin Resistance and Insulin Secretion (Fig. 1) (Table 5)

Patients in G1 had higher HbA1C levels (11% versus 10%) but the difference was not significant and there was no correlation between HbA1C levels and urinary retention of Mg (p=0.3; r=0.1).

Patients in G2 tended to show a higher tissular insulin resistance (IR). In fact, they had higher mean fasting insulinemia and HOMA-IR and lower mean McAuley index and QUICKI but without statistical significance (Table 5). The prevalence of fasting insulinemia ≥12 µIU/ml was comparable between G1 and G2 (38.5% versus 40% ; p=0.9) . An index of QUICKI ≤ 0.33 was observed in 73.3% versus 84.6% of cases respectively in G1 and in G2 (p=0.4). A HOMA-IR index ≥2.60 was observed in 73.3% versus 84.6% of cases respectively in G1 and in G2 (p=0.4). A McAuley index ≤5.8 was noted in 28.6% versus 41.7% of cases respectively for G1 and G2 (p=0.3). Additionally, no correlation with urinary Mg was found.

3.4 Mg Deficiency and Duration of Diabetes

Diabetes was older in patients with Mg deficiency (G1): the median values were 10 years in G1 (range 1 to 30 years) and 6 years in G2 (range 1 to 17 years). This difference was statistically significant (p=0.03). However, we found no correlation between Mg retention and the duration of diabetes (r = 0.3, p = 0.06).

3.5 Impact of the Magnesium Deficit on the Appearance of Chronic Complications of Diabetes (Table 6)

Diabetic Retinopathy (DR), Diabetic Neuropathy (DN) and Autonomic Neuropathy (AN) were observed in 37%, 30% and 10% of cases respectively in the study population. These complications were more frequent among G1 subjects, but without a statistically significant difference (p=0.4 for DR, p=0.3 for DN, p=0.6 for AN). 24-hour microalbuminuria was found in 10% of cases. It was higher in G1 patients without statistical difference (15% versus 6%, p=0.5). Coronary Heart Disease (CHD) was objectified in 17% of cases. Arteriopathy of the Lower Limbs (ALL) was objectified in 3% of cases, all were present in G1 patients. CHD and history of stroke were more common among G1 subjects but without significant differences (p=0.6 for each).

4. DISCUSSION

4.1 Assessment of Magnesium Status

The determination of serum Mg is the most widely used biochemical test for evaluating Mg status. It is a quick, inexpensive and routine test. However, serum Mg levels are poor indicator of Mg deficiency and may not necessarily reflect true total body Mg content since extracellular Mg accounts for only 1% of total body Mg [1,3]. In addition, many factors may interfere with the interpretation of magnesemia (protein concentration, hemolysis, hyperlipemia, hyperphosphatemia) [4].

Mild and moderate Mg deficiencies (subclinical Mg deficiency) can exist despite the presentation of a normal serum magnesium status [10]. As a result, subclinical Mg deficiency, which is not uncommon in some chronic conditions such as diabetes and hypertension, has not been routinely recognized. If the serum Mg level is normal, other more sensitive tests should be performed.

The determination of free ionized Mg seems interesting since it represents the physiologically active fraction. However, it is not common practice because of the need for expensive specialized methods [1].

The intra-erythrocyte Mg concentration reflects the Mg status during the previous 120 days. However, it is a poor indicator of body content in Mg [8]. Mg concentration in mononuclear cells appears to be a better predictor of Mg content in skeletal and cardiac muscle but it remains difficult to perform because of the large inter-individual variability of Mg in mononuclear cells [1].

The MLT has been considered the best tool to evaluate Mg deficiency [1,2]. However, this test is not standardized. The MLT exposes to the risk of poor cardiac, neurological and vascular tolerance and requires strict monitoring. The MLT was used to determine the prevalence of Mg deficiency in certain conditions such as type 1 diabetes, acute pancreatitis, chronic alcoholism, migraine and angina pectoris. No studies based on this test were described in T2DM [11–13].

4.2 Prevalence of Magnesium Deficiency

The prevalence of hypomagnesaemia observed in our study is similar to that reported in the literature (16–22). Safi et al. found hypomagnesemia in 20% of subjects [14]. McNair et al found that hypomagnesemia was observed in 38.6% T2DM patients [15]. Nevertheless, other studies have shown lower prevalence of hypomagnesaemia [16,17,18]. The wide range in the reported incidence of hypomagnesemia most likely reflects the difference in the definition of hypomagnesemia, techniques in Mg measurements, and the heterogeneity of the selected patient cohort.

4.3 Mechanisms of the Magnesium Deficiency

Several hypotheses have been proposed to better understand the mechanisms of Mg deficiency in diabetic patients:

- Inadequate food intake: the increase in the consumption of "fast-food" at the expense of vegetables and whole grain cereals [19]. Furthermore, the use of fertilizers as well as the growing environmental pollution, have led to an acidification of agricultural soils, leading to a depletion of their Mg content [20]. In our study, ninety percent of patients did not reach the recommended values of daily Mg intake, with the latter being lower in patients with Mg deficiency. These results are close to those found by Schmidt et al., in a population including 50 T2DM patients.
- Gastrointestinal causes: Certain autonomic neuropathies may decrease oral and gastrointestinal absorption and / or increase gastrointestinal losses of Mg [19].
- An increase in the urinary loss of Mg: Hyperglycemia leads to glomerular hyperfiltration and an increase in renal urinary flow. Mg reabsorption is decreased in the ascending limb of Henle when local urine flow increases [21]. In the distal convoluted tubule (TCD), insulin regulates the expression and activity of TRPM6 (transient receptor potential cation channel subfamily M member 6) by increasing its insertion on the basal membrane which provides active transport of Mg [19,22]. In the presence of hypomagnesemia, a urinary excretion greater than 1 mmol/ 24 hours in Mg indicates a urinary magnesium leak. In our series, urinary hyper excretion of Mg was demonstrated in 60% of cases. It was slightly elevated in patients with Mg deficiency, but without significant difference (47.1% versus 46.2%; p = 0.9). Similarly, Sjögren et al. observed a higher urinary excretion of Mg in T2D subjects compared to healthy controls (5 ± 2.68 mmol/ 24H versus 3.62 ± 1.47mmol/ 24H; p <0.05) [23].
- Iatrogenic causes: The frequent use of diuretics in T2DM results in urinary leakage of Mg [22].

4.4 Impact of Magnesium Deficiency on Glycemic Control

In our population, mean fasting glucose was comparable between G1 and G2. HbA1C measurements showed that G1 patients had more unbalanced diabetes (HbA1c> 7%) than those in G2 (94.1% versus 83.3%; p = 0.3). However, we did not find a correlation between the percentage of urinary retention of Mg and fasting glucose (r=0.01 and p=0.9) on the one hand, and the percentage of urinary retention of Mg and HbA1c levels (r=0.1; p=0.3) on the other hand.

Our results are similar to those of Chutia et al, who observed no correlation between urinary retention percentage of Mg and fasting glucose or glycated hemoglobin [24]. In contrast, Arpaci et al, Ramadass et al. and Dasgupta et al. in studies including 673, 50 and 73 T2DM patients respectively, found negative correlation between serum Mg and HbA1c [18,25,16].

4.5 Impact of Magnesium Deficiency on Insulin Secretion and Insulin Resistance

In our series, patients with normal Mg status were more likely to show insulin resistance. In fact, they had higher fasting insulinemia and HOMA-IR index and lower McAuley and QUICKI indexes. None of the evaluated parameters was correlated to urinary retention of Mg.

Similarly to our results, Lima et al. did not note any correlation between intracellular Mg of mononuclear blood cells and HOMA-IR index [26]. Conversely, Bertinato et al. showed that a cohort of South Asian women, with a serum Mg <0.75 mmol/L, had higher insulinemia, HOMA-IR, QUICKI index and lower McAuley index [27]. Similarly, Kim et al. found a negative correlation between serum Mg levels and the HOMA-IR index [28]. They also found a positive correlation between magnesaemia and the QUICKI index, meaning that patients with higher serum Mg tended to be less insulin resistant [24].

Mg deficiency could be a consequence of diabetes but could also contribute to the development of T2DM [29]. Mg deficiency has been involved in both insulin secretion and IR. In fact, Mg is essential for the autophosphorylation of β subunits of the insulin receptor. It binds to the tyrosine kinase domain and increases its affinity for ATP. The Mg deficiency may therefore be responsible of a defective phosphorylation of the insulin receptor [30]. Additionally, there is evidence that Mg increase the expression of glucose transporters GLUT4 in the muscular cell. Thus, Mg deficiency would decrease the uptake of glucose by the muscle [30]. In the liver, Mg is essential for the activity of enzymes, especially glucose-6-phosphatase (G6P) and phosphoenol-pyruvate-carboxykinase (PEPCK), which are essential in gluconeogenesis. In adipose tissue, inflammation is a contributing factor to IR by decreasing the activity of GLUT4 and inhibiting the action of IRS-1 (Insulin-receptor-substrate). Mg is an anti-inflammatory molecule which decreases the secretion of proinflammatory mediators secreted by adipocytes of obese T2DM subject [31].

The role of Mg in insulin secretion could be explained by various mechanisms. In fact, magnesium is a glucokinase cofactor that transforms glucose into glucose-6-phosphate (G6P) in the pancreatic β cell [30]. Mg deficiency affects insulin secretion by decreasing glucokinase activity. The release of insulin depends on the ratio Ca2 + / Mg2 + which initiates exocytosis. A Mg deficiency causes a change in this ratio and decreases the secretion of insulin [31].

4.6 Impact of Magnesium Deficiency on Chronic Complications of Diabetes

In our population, diabetic retinopathy (DR) was more prevalent in patients with Mg deficiency but the difference was not significant between the two groups (p=0.4). Patients with DR had higher magnesemia and higher percentage of urinary retention of Mg (0.74 ± 0.08 mmol/L versus 0.72 ± 0.06 mmol/L (p=0.4) and 54.4 ± 55% versus 52.2 ± 49.3% (p=0.6) respectively). Similarly, patients with Mg deficiency were more prone to diabetic neuropathy (DN). Urinary retention of Mg was more prevalent in the DN group but the difference was not significant (p=0.2). 24-hour microalbuminuria was also more frequent in patients with Mg deficiency (15% versus 6%; p=0,5), and microalbuminuria was associated with a higher urinary retention of Mg.

Similar to our results, Lima et al observed that there was no significant difference in the mean intracellular Mg level of mononuclear cells between patients with RD and patients without RD. However, the mean intracellular Mg was significantly lower in diabetics with ND [26]. Lu et al. and Hatwal et al. found that patients with RD had significantly lower mean serum Mg values [5,32]. Dasgupta et al. found a similar prevalence of ND between the normal and hypomagnesemic groups. In contrast, the prevalence of microalbuminuria and macroalbuminuria were significantly higher in T2DM patients with hypomagnesemia [16]. Chu et al. reported that in patients with magnesium <0.85 mmol/L, the amplitude of nerve conduction was slower indicating axonal degeneration [33]. Similarly, Beherwani et al, in a comparative study including 100 T2DM patients, observed that there was a significantly higher prevalence of hypomagnesaemia (52%) in patients with diabetic nephropathy. Serum magnesium levels were significantly inversely correlated with serum creatinine, and positively correlated with glomerular filtration rate (GFR) [34].

Regarding macrovascular complications, lower limb arteriopathy was found only in patients with Mg deficiency with a frequency of 6%. Stroke and CHD were noted more frequently in T2DM subjects with magnesium deficiency compared to T2DM patients with normal Mg status: 18% versus 15%; p=0.6 and 12% versus 8%; p=0.6 respectively. Urinary retention of Mg was more important in patients with CHD and history of stroke without a significant difference (p=0.05 and p=0.3 respectively). Our results are similar to those of Dasgupta et al. who, in a study including 24 T2DM aged less than 50 years, noted a higher frequency of coronary artery disease in subjects with hypomagnesemia compared to those with normal magnesemia (27% versus 25%; p = 0.796) [16].

Table 1. Summary of demographic characteristics, lifestyle, reasons for hospitalization, personal history, anthropometric and physical data of the study population

	Mean (± standard deviation) / Frequency	Median	Extreme (Min-Max)
Demographic characteristics			
Age (years)	57,3 ± 10	58,5	31-73
Female gender (%)	53		
Reasons for hospitalization			
Poorly balanced diabetes (%)	83		
Newly-discovered diabetes mellitus (%)	10		
Ketosis (%)	7		
Life habits			
Smoking (%)	20		
Personal history			
Hypertension (%)	47		
Dyslipidemia (%)	57		
Menopause (%)	81		
Anthropometric data			
Weight (Kg)	72,3 ± 19,4	67	43 – 116
Body Mass Index (Kg / m2)	27,5 ± 4,9	26,5	16 – 37
Waist circumference (cm)	99,2 ± 13,5	100	91 - 124

Table 2. Summary table of demographic characteristics, physical data, personal pathological antecedents and anthropometric data of patients of G1 and G2

	G1 (n= 17)	G2 (n=13)	P
Age (years)	60.4 ± 7.5	53.1 ± 11.6	0.01*
Sex ratio (M/F)	0.54	1.6	0.1
Personal history			
Hypertension (%)	59	31	0.1
Dyslipidemia (%)	47	69	0.2
Physical data			
Weight (Kg)	67.5 ± 16.7	78.7 ± 21.5	0.2
BMI (Kg/m2)	26.6 ± 4.8	28.8 ± 4.9	0.2
WS (cm)	96.8 ± 17.1	101.6 ± 8.7	0.3
SBP (mmHg)	126 ± 18	133 ± 1	0.2
DBP (mmHg)	72 ± 1	8 ± 5	0.03*
Lipid profil results			
TC (mmol/L)	4.2 ± 1.1	4.7 ± 0.8	0.3
LDLc(mmol/L)	2.5 ± 1.1	2.7 ± 1.1	0.9
HDLc(mmol/L)	1.1 ± 0.3	1.1 ± 0.4	0.9
TG(mmol/L)	1.3 ± 0.9	2.2 ± 2.07	0.09

*SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; LDLc: Low Density Lipoprotein Cholesterol; HDLc: High Density Lipoprotein Cholesterol; TG: Triglycerides; BMI: Body Mass Index; WS: Waist Size; G1:Group1; G2:Group2; *: statistically significant difference p <0.05; **: statistically significant correlation*

The role of Mg in the development of chronic complications of diabetes could be explained by its action as a cofactor for the Na+/K+ ATP pump. Mg deficiency is responsible for impaired conduction of nerve impulses predisposing to ND and coronary artery disease [35]. Moreover, Mg deficiency would cause an increase in plasma concentrations of CHT, LDLc and TG and a decrease in HDLc [36]. Mg also has anti-thrombotic activity via its anti-calcium action. Intracellular Mg deficiency, observed in T2DM, is responsible for an increase in intracellular calcium and, consequently, for platelet hypercoagulability [36-40]. In smooth muscle, Mg

binds to calcium sites, reduces intracellular calcium and causes vasodilation. Therefore, Mg deficiency increases vascular tone and peripheral vascular resistance that may involving the development of cardiovascular diseases [4,41-43].

Table 3. Risk factors associated with the occurrence of magnesium deficiency

	Univariate model 95% Confidence Interval				Multivariate model 95% Confidence Interval			
	OR	**Low**	**high**	**P**	**OR**	**Low**	**High**	**P**
Age>55 years	16,8	2,5	111,5	0,001	12,6	1,7	90,4	0,01
Duration of diabetes > 10 years	10,7	1,1	101,3	0,02	6,5	0,5	79	0,1
Gender	0,3	0,08	1,5	0,1	2,1	0,1	35,2	0,6
Smoking	10	1	100,6	0,02	4,6	0,3	67	0,2

*OR: odds ratio ; *: Statistically significant difference*

Table 4. Results of baseline plasma Mg and one hour after MLT

	Total (n=30)	**G1 (n= 17)**	**G2 (n=13)**	**P**
Baseline plasma magnesium(mmol/l)	0.7 ± 0.06	0.7 ± 0.07	0,7 ± 0,04	0.8
24H urinary magnesium before loading test (mmol/24h)	3 [0.9 ; 10]	3 [0.9 ; 10]	2 [1 ; 6]	0.07
24H Mg EF (%)	5.1 [1.8 ; 19]	4 [1.8 ; 19]	4 [1.8 ; 10]	0.4
24H Mg EF > 4% (%)	60	47.1	46.2	0.9
Plasma magnesium one hour after loading test (mmol/l)	0.5 ± 0.5	0.3± 0.5	0.7± 0.4	0.07
24H urinary magnesium after loading test (mmol/24h)	7.1 [1.5 ; 21]	5.1 [1.5 ; 21]	8.5 [4.4 ; 13.1]	0.4
Magnesium urinary retention percentage (%)	60.5 [-61 ; 115]	89.8 [51 ; 115]	-6.2 [-61 ; 49]	<0.001*

*Mg: Magnesium, EF MG: Magnesium Excretion Fraction of Magnesium; G1:Group1; G2:Group2; *: Statistically significant difference*

Table 5. Glycemic balance, insulin resistance and insulin sensitivity

Groupes/Number	**Total (n=30)**	**G1 (n= 17)**	**G2 (n=13)**	**P**
Glycemic balance				
HbA1c (%)	11 [6 ; 17]	11 [6 ; 17]	10 [6 ; 12]	0.3
Fasting glucose (mmol/L)	10 [5.7 ; 18]	9 [5.7 ; 17]	10 [6 ; 18]	0.9
Insulin Resistance				
Fasting insulinemia (µUI/ml)	12.35 [3.6 ; 43.8]	9 [3.6 ; 43.8]	12.4 [4.2 ; 29.8]	0.8
HOMA-IR	5.4 [1.3 ; 25.1]	5.6 [1.3 ; 25.1]	5.7 [2.2 ; 10]	0.08
McAuley index	6.1 [3.6 ; 11.3]	7.7 [4.1 ; 11.3]	6 [3.6 ; 9.2]	0.2
Insulinsensitivity				
QUICKI	0.29 [0.24 ; 0.36]	0.29 [0.24 ; 0.36]	0.28 [0.27 ; 0.33]	0.5

*HbA1c: glycated hemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; QUICKI: Quantitative Insulin Sensitivity Check Index; G1:Group1; G2:Group2; *: Statistically significant difference*

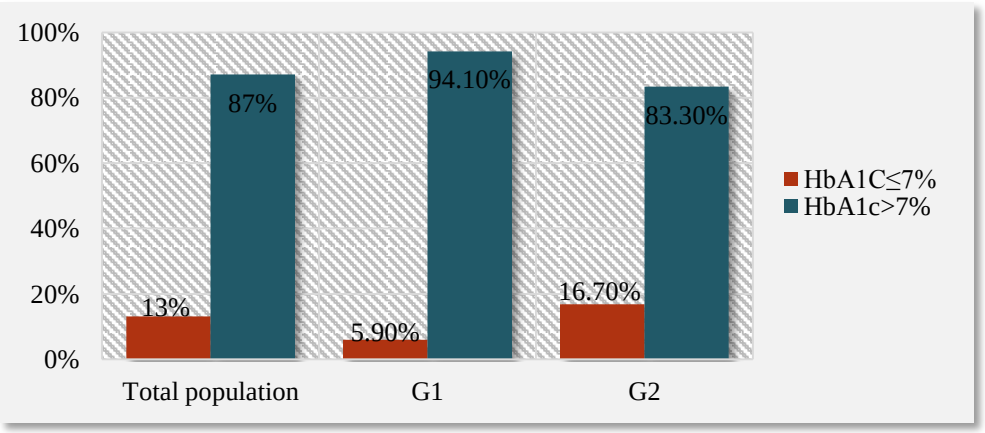

Fig. 1. Distribution of the population according to glycemic balance

Table 6. Distribution of chronic complications of diabetes

	Population N=30	G1 (N=17)	G2 (N=13)	P
Coronary heart disease	17%	18%	15%	0.6
Lower limb arteriopathy	3%	6%	0%	0.6
Stroke	11%	12%	8%	0.6
Diabetic neuropathy	30%	35%	23%	0.3
Diabetic retinopathy	37%	41%	31%	0.4
microalbuminuria	10%	15%	6%	0.5

*G1:Group1; G2:Group2; *: Statistically significant difference*

Table 7. Distribution of the percentage of magnesium retention according to the presence or absence of chronic complications

Complication	Percentage of magnesium retention ± standard deviation	P
DR+	54,4 ± 55,1%	0.6
DR-	52,2 ± 49,3%	
DN+	68 ± 37,7%	0.2
DN-	49,2 ± 55,2%	
Microalbuminuria+	71,7% ± 37,3%	0,4
Microalbuminuria-	52,2 ± 52,%	
CHD+	70,5 ± 24%	0,05
CHD-	51,7 ± 54,3%	
Stroke+	72,5 ± 73,3%	0,3
Stroke-	54,1 ± 49,6%	
LLA+	67,6%	0,8
LLA-	54,4 ± 51,5%	

*DR: diabetic retinopathy ; DN: diabetic neuropathy ; CHD: coronary heart disease ; LLA: lower limb disease; *: Statistically significant difference*

5. CONCLUSION

Magnesium is a major ion in the body. Its involvement in energy and protein metabolism testifies to its crucial importance for the proper functioning of the human body. The magnesium load test is the best indicator of body magnesium status.

The objectives of our work were to assess the Mg status in T2DMs and to find a correlation between the Mg status and glycemic control, on the one hand, and the occurrence of microvascular and macrovascular complications, on the other hand.

Through this study we were able to highlight a higher prevalence of magnesium deficiency in

diabetics, with age, duration of diabetes and smoking as risk factors collected in monovariate analysis. T2DM patients with magnesium deficiency had poorer diabetes control and higher prevalence of macrovascular and microvascular complications of diabetes.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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