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Association of Magnesium Status with Poor Glycemic Control and Microangiopathic Complications (Neuropathy and Nephropathy) in Diabetic Patients in Dakar

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Abstract: Low serum magnesium level has been shown to be associated with diabetes mellitus and its complications. The objective of this study was to determine the magnesium status in our study population and its association with glycemic control and microangiopathic complications particularly neuropathy and nephropathy. This was a cross sectional and prospective study conducted among patients received as part of their follow-up at the Marc Sankalé center of the Abass Ndao hospital in Dakar. For each patient, blood samples and 24h urine collection were performed. Hypomagnesemia was defined for Mg concentrations <17 mg/L and statistical analysis was performed using the XLSTAT 2018 software. A total of 106 diabetic patients were enrolled consisting of 93 type 2 diabetics and 13 type 1 diabetics. Eighty percent of patients had hypomagnesemia compared to 20% who had normal magnesium levels. We found a significantly higher mean HbA1c level in the group of hypomagnesemic patients compared to patients with normal magnesium levels ($p = 0.02$) and significant negative correlation between magnesium and HbA1c ($r = -0.20$, $p = 0.03$). The frequencies of neuropathy and nephropathy were comparable between the two groups with respectively $p = 0.12$ and $p = 0.28$. Our study shows a high frequency of hypomagnesemia in both type 1 and type 2 diabetes and a significant correlation of this hypomagnesemia with poor glycemic control. No association has been found between magnesium and the microangiopathic complications, but it nevertheless alerts clinicians to the possible need for magnesium supplementation in the management of diabetic patients.

Keywords: Diabetes, Magnesium Status, Glycemic Control, Diabetic Neuropathy, Diabetic Nephropathy

1. Introduction

Diabetes is now a real public health problem around the world with more than 422 million people affected [1]. In Senegal, according to the 2014 International Diabetes Federation (IDF) report, 292,000 people are infected in the

age group between 20 and 79 years old [2]. This alarming and growing number over the years with estimates of more than 552 million people in 2030 [3], constantly challenge the scientific community on the possibilities of prevention and improvement of the management of this pathology.

Since the 1940s, a possible relationship between magnesium status and diabetes mellitus has been suggested [4, 5]. Since then, numerous studies have been conducted and have established the high frequency of hypomagnesemia in both type 1 and type 2 diabetic subjects. Indeed, it has been shown that magnesium plays an important role in carbohydrate metabolism and the presence of hypomagnesemia is associated with poor glycemic control and the occurrence of diabetes-related complications, particularly micro and macroangiopathic [6-10]. In our context, no data are available to date regarding the prevalence of hypomagnesemia in diabetic subjects as well as its implication in the occurrence of complications related to this pathology. Thus, we conducted this study to determine the magnesium status in our study population and its association with glycemic control and microangiopathic complications particularly neuropathy and nephropathy.

2. Patients and Methods

2.1. Study Design and Subjects

It was a cross sectional and prospective study conducted over 4 months from June to September 2018.

In all, 93 type 2 diabetic patients and 13 type 1 diabetic patients who were followed up at the Marc Sankalé Center of Abass Ndao Hospital in Dakar were enrolled in the present study.

Non-inclusion criteria included patients with conditions or medications that could interfere with serum magnesium levels and non-consenting patients to participate in the study.

The study was approved by the Scientific Ethics Committee of the Faculty of Medicine, Pharmacy and Odontology of the Cheikh Anta Diop University of Dakar and informed consent was also obtained from patients and / or their tutors.

2.2. Data Collection

Epidemiological and demographic data were collected using a questionnaire and for each patient, blood samples were taken after12h of overnight fasting by venipuncture at the bend of the elbow. A 24h urine collection was also performed for the determination of microalbuminuria.

The blood samples were centrifuged at 3000 revolutions/min for 5 min and were immediately processed or stored at -20°C until use.

All biochemical variables, except HbA1c, were measured using Cobas 6000/c501® analyzer (Roche, Hitachi, Germany) following the protocol provided by the reagent manufacturer and glycated hemoglobin (HbA1c) was measured using D-10® system (BioRad, USA).

Diabetic nephropathy was defined for microalbuminuria concentrations > 30mg/24h and the diagnosis of diabetic neuropathy was established after clinical examination.

2.3. Estimation of Serum Magnesium

The principle of magnesium determination is based on a colorimetric method in which the magnesium ions form a purple complex in an alkaline medium in the presence of xylidyl blue (a diazonium salt). The magnesium concentration directly proportional to the amount of the complex formed is then measured photometrically by decreasing the absorbance of the colored complex at a wavelength of 600 nm. The presence of egtazic acid (EDTA) in the reaction medium, which complexes the calcium ions, makes the reaction specific.

Hypomagnesemia has been defined for magnesium concentrations < 17 mg / L according to the usual laboratory values.

2.4. Statistical Analysis

The statistical analysis was done using the XLSTAT 2018 software. Data are presented as frequencies and percentages for categorical variables and as the mean ± SD for continuous variables. All continuous variables were tested for normal distribution by Shapiro–Wilk test, and the significance of differences between groups was tested with an unpaired t-test and/or Mann–Whitney U-test**.** Categorical variables were compared using the Chi-squared test and the association between the variables was evaluated using the Spearman correlation test. A p value less than 0.05 was considered significant.

3. Results

A total of 106 diabetic patients including 93 type 2 diabetics and 13 type 1 diabetics was enrolled. The study population was characterized by female predominance with 67 women (63%) versus 39 men (37%). Patients were aged between 16 and 87 years with an average of 53.14 years. The mean duration of diabetes was 7.25 ± 6.57 years. Neuropathy and nephropathy were found in 57.5% and 12.2% of patients respectively (Table 1).

Table 1. *General characteristics of the study population.*

	Study population
Included	106
Type 1	13 (12%)
Type 2	93 (88%)
Age (years)	53.14 ± 15.47
Minimum age (years)	16
Maximum age (years)	87
Sex ratio	0.58
Duration of diabetes (years)	7.25 ± 6.57
Neuropathy	61 (57.5%)
Nephropathy	13 (12.2%)

In our study population, 85 patients (80%) had hypomagnesemia whereas 21 (20%) where found to have normal levels of magnesium. This high frequency of

hypomagnesemia was noted in both types of diabetes with 80% and 77%, respectively, in the type 2 diabetic group and the type 1 diabetic group (Figure 1).

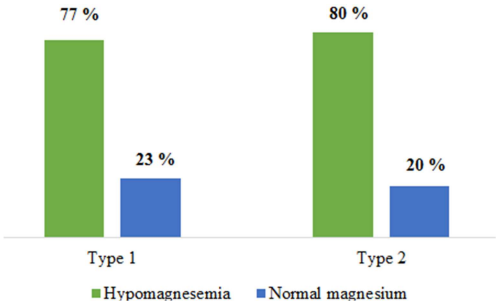

Figure 1. *Magnesium status according to the type of diabetes.*

The mean serum magnesium levels was 15.21 ± 2.17 mg / L. The biological characteristics of the study population are given in Table 2.

Table 2. *Biological parameters of the study population.*

	Means ± standard deviations
Serum magnesium (mg/L)	15.21 ± 2.17
FPG (g/L)	1.68 ± 0.89
HbA1c (%)	8.15 ± 2.30
Microalbuminuria (mg/24h)	15.27 ± 33.70
Urea (g/L)	0.24 ± 0.10
Creatinine (mg/L)	10 ± 2.59
TC (g/L)	2.15 ± 0.51
HDL-C (g/L)	0.70 ± 0.22
TG (g/L)	0.84 ± 0.45
LDL-C (g/l)	1.27 ± 0.45

FPG: Fasting plasma glucose, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol

We then divided the study population into two groups: patients with hypomagnesemia were taken as cases and those with normal magnesium levels were taken as controls. Comparison of the results between the two groups showed a significantly higher average glycated hemoglobin level in the group of hypomagnesemic patients ($p = 0.02$). For the other parameters, no significant difference was found ($p > 0.05$) (Table 3).

Table 3. *Comparison of the results between cases (patients with hypomagnesemia) and controls (patients with normal magnesium levels).*

Variables	Cases (n = 85)	Controls (n = 21)	*p*
Age (years)	53.29 ± 15.37	52.55 ± 16.28	0.94
Duration of diabetes (years)	7.21 ± 6.58	7.43 ± 6.71	0.73
FPG (g/L)	1.70 ± 0.87	1.58 ± 1.01	0.15
HbA1c (%)	8.37 ± 2.24	7.28 ± 2.34	*0.02*
Microalbuminuria (mg/24h)	14.69 ± 35.71	17.56 ± 24.67	0.14
Urea (g/L)	0.24 ± 0.11	0.24 ± 0.07	0.75
Creatinine (mg/L)	10.12 ± 2.74	9.54 ± 1.88	0.28
TC (g/L)	2.12 ± 0.45	2.24 ± 0.71	0.45
HDL-C (g/L)	0.69 ± 0.21	0.75 ± 0.27	0.61
TG (g/L)	0.81 ± 0.44	0.94 ± 0.47	0.23
LDL-C (g/L)	1.27 ± 0.41	1.29 ± 0.60	0.99

FPG: Fasting plasma glucose, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol.

The study of the correlation between serum magnesium levels and the various variables studied revealed a significant negative correlation between serum magnesium and glycated hemoglobin levels ($r = -0.20$; $p = 0.03$). We found no significant correlations for the other parameters ($p > 0.05$) (Table 4).

Table 4. *Correlations between epidemiological and biological characteristics with serum magnesium levels (mg /L).*

Variables	r	*p*
Age (years)	-0.16	0.08
Duration of diabetes (years)	-0.03	0.72
FPG (g/L)	-0.14	0.14
HbA1c (%)	-0.20	0.03
Microalbuminuria (mg/24h)	-0.03	0.72
Urea (g/L)	-0.03	0.71
Creatinine (mg/L)	-0.13	0.15
CT (g/L)	0.19	0.06
HDL-C (g/L)	-0.02	0.83
TG (g/L)	0.19	0.05
LDL-C	0.16	0.08

r: correlation coefficient, FPG: Fasting plasma glucose, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol.

No significant difference was found for the frequencies of neuropathy between hypomagnesemic patient group compared to patients with normal magnesium levels and were 61.2% and 42.8%, respectively ($p = 0.12$) (Figure 2).

There was also no significant difference for nephropathy in both groups with 10.6% for patients with hypomagnesemia vs 19% for patients with normal magnesium levels ($p = 0.28$) (Figure 2).

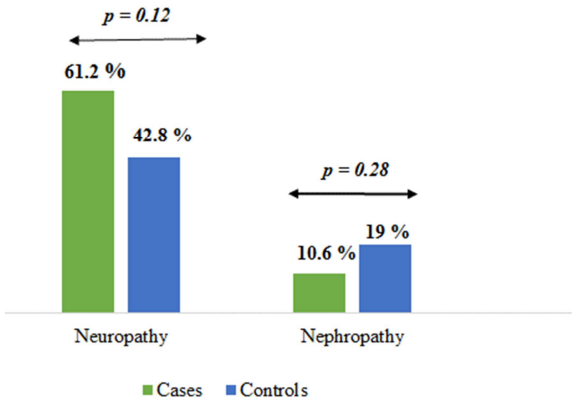

Figure 2. *Comparison of the frequencies of neuropathy and nephropathy between cases and controls.*

4. Discussion

Diabetes mellitus is a chronic disease that causes many metabolic disorders, such as the dysfunction of micronutrient homeostasis including magnesium [11]. The present study reports the frequency of hypomagnesemia among diabetic patients and its association with the glycemic balance and microangiopathic complications related to diabetes, particularly the neuropathy and diabetic nephropathy.

The majority of patients recruited were women (sex ratio =

0.58) with an average age of 53.14 years and extremes of 16 and 87 years. This predominance of women in our study population consisting mainly of type 2 diabetics can be explained by the sedentary lifestyle of women in our society, which constitutes a risk factor for obesity and therefore insulin resistance.

The mean duration of diabetes was 7.25 ± 6.57 years. This long average duration, which indicates a prolonged evolution of the disease, exposes patients more to the occurrence of the complications related to diabetes which constitute the main gravity.

Diabetic neuropathy was found in 57.5% of patients and 12.2% had nephropathy. Higher frequencies have been reported in other studies [12-14] and this difference would probably be related to the size of the populations which was much larger than ours.

Eighty percent of patients had serum magnesium levels below the usual values (< 17 mg/L) with significantly lower mean value in the hypomagnesemic group compared to patients with normal magnesium levels ($p < 0.001$). We found a higher frequency of hypomagnesemia compared to that reported in the literature, which ranged from 13.5% to 47.7% [5, 15].

This wide variation among the reported prevalence is probably due to the heterogeneity of the study subjects and differences in the dietary habits, the definition of hypomagnesaemia and methods for the estimation of serum magnesium.

Seventy-seven percent of patients with type 1 diabetes and 80% of patients with type 2 diabetes had hypomagnesemia. The frequency of hypomagnesemia in diabetes was established in both type 1 and type 2 diabetes. In our study, despite the low proportion of type 1 diabetics, we found a high frequency of hypomagnesemia in these patients. And this result is similar with other studies who found in cohorts composed only of type 1 diabetics a high frequency of hypomagnesemia compared to control subjects with significant differences between the two groups [16-18].

The comparison of the mean values of the different studied parameters between the two groups showed significantly higher HbA1c levels in hypomagnesemic patients. Analogous results have been reported in many studies [19, 20].

We also evaluated the correlation between serum magnesium levels and the different variables and found a significantly negative correlation with HbA1c levels ($r = -0.20, p = 0.03$).

Our findings are in agreement with previous studies that have reported a relationship between hypomagnesemia and poor glycemic control in adults with diabetes [21-23].

In fact, there is a vicious cycle between diabetes mellitus and serum Mg levels. Hypomagnesaemia has been shown as a cause of insulin resistance and higher rates of diabetes type 2 [24]. Insulin increases both glucose and magnesium uptake in pancreatic β cells and cardiomyocytes, suggesting a link between glucose and magnesium homeostasis [25, 26].

It has also been reported that magnesium plays a role in the action of insulin and that, subsequently, insulin stimulates the absorption of magnesium in sensitive tissues [27].

Indeed, hypomagnesaemia is responsible for a deficiency of tyrosine kinase activity which leads to a change in insulin sensitivity by the defective activity of the receptor after binding. And this would be responsible for an alteration of intracellular signaling pathways.

Thus, an intracellular magnesium deficiency can have a direct impact on the development of insulin resistance and alter the availability of glucose in peripheral tissues. Studies have shown that magnesium supplementation improves the cells' sensitivity to insulin and promotes better glycemic control [28-30].

Regarding lipid status parameters, no significant difference was found between the two groups of patients. We also found no significant correlation with magnesium ($p>0.05$).

Other studies have shown that magnesium deficiency is responsible for a disorder in the lipid metabolism of diabetic patients [31].

Pokharel et al. have found in patients with type 2 diabetes, significant negative correlations between magnesium and total cholesterol and LDL cholesterol [20]. And in another study in type 1 diabetics, a positive correlation was found between magnesium and HDL cholesterol and negative correlations with total cholesterol, triglycerides, and LDL cholesterol [16]. It has been shown that low levels of magnesium contribute to the occurrence of dyslipidemia by increasing cholesterol biosynthesis, decreasing the activity of lecithin-cholesterol acetyltransferase as well as lipoprotein lipase. Similarly, hypomagnesemia would promote the oxidation of LDL cholesterol in the subendothelial space [32-34].

The frequencies of diabetic neuropathy were comparable between the groups of hypomagnesemic and patients with normal magnesium levels respectively 61.2% and 42.8% ($p = 0.12$). Similar results have been found in other studies including those of *Arpaci et al.* and *Dasgupta et al*. [12, 13]. Other studies on the contrary have shown a decrease in magnesium levels in diabetic patients with peripheral neuropathy with improved nerve conduction after magnesium supplementation [35]. We also did not find a significant difference between the frequencies of diabetic nephropathy in the two groups with 10.6% and 19%, respectively ($p = 0.28$). The association between microalbuminuria and hypomagnesemia is controversial [23, 36, 37]. In a study in type 1 diabetics, they found that hypomagnesemia was associated with poor glycemic control and urinary excretion of albumin [38]. Another study has shown a negative correlation between magnesium levels and urinary excretion of proteins [13]. On the other hand, other results, such as ours, did not show any association between magnesium and microalbuminuria in both types of diabetes [23, 37].

However, we note a number of limitations in our study, including the small size of the study population and the many other chronic complications related to diabetes that we have not studied such as retinopathy diabetic, diabetic foot and macroangiopathic complications whose occurrence and evolution are also associated with magnesium status in diabetic subjects.

5. Conclusion

In our study, we clearly demonstrated a high frequency of hypomagnesemia in both types of diabetes. In addition, we found a significant correlation of this hypomagnesemia with poor glycemic control. Nevertheless, no association was found between magnesium and microangiopathic complications including neuropathy and diabetic nephropathy. However, this study helps to alert the clinicians to the possible need for magnesium supplementation in the management of diabetic patients.

Further studies are recommended involving much larger cohorts with other complications related to diabetes as well as studies on the effects of magnesium supplementation in the management of diabetic patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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