Magnesium Status in Patients with Type 2 Diabetes (about 170 cases)

Houda Salhi1,2,3, Hanan El Ouahabi1,2,3

1Department of Endocrinology and Diabetology, University Hospital of Fez, 2Faculty of Medicine and Pharmacy, Sidi Mohamed Ben Abdellah University, Fez, Morocco, 3Laboratory of Epidemiology and Research in Health Sciences, Fez, Morocco

Abstract

Magnesium (Mg) is an extremely important mineral. It plays major roles in physiological activities of the body. Lower intake of Mg and low-serum Mg concentrations are associated with metabolic syndrome, insulin resistance, and Type-2 diabetes. Aim: The aim of the study is to evaluate the association between concentration levels of serum Mg and common complications and co-morbidities of diabetes mellitus and other biochemical indices. It is a case control study conducted in our department of endocrinology in Hassan II University Hospital of Fez from January 2015 to 2018. Our patients were classified into two groups. Low Mg (Group 1, n = 85) and normal Mg group (Group 2, n = 85). We evaluated demographics characteristics of our patients; the association between Mg status and clinical, biological parameters; and association between Mg status and degenerative complications. Our study included 170 patients. The research results showed that serum Mg level was strongly related to age, sex, diabetes duration, body mass index, hypertension, and glycosylated hemoglobin. Concerning common complication; we only found a negative correlation between Mg level and the existence of nephropathy. We did not find significant correlation with retinopathy; neuropathy; and macroangiopathy. The study has demonstrated that a low Mg level is correlated with a poor control glycemic; high blood pressure and nephropathy in patients with Type 2 diabetes. However, more research is needed to confirm these effects.

Keywords: Macroangiopathy, magnesium status, microangiopathy, poor glycemic control

Résumé

Le magnésium (Mg) est un minéral extrêmement important. Il joue un rôle majeur dans les activités physiologiques du corps. Une consommation plus faible de Mg ainsi qu’une faible concentration sèrique est associée au syndrome métabolique, la résistance à l’insuline et au diabète de type 2. Le but de notre étude est d’évaluer le lien entre les niveaux de concentration du Mg sèrique et les complications du diabète sucré. C’est une étude cas-témoins menée au service d’Endocrinologie au CHU Hassan II de Fès entre janvier 2015 est 2018. Nos patients ont été classés en deux groupes. Groupe ayant une magnésémie faible (groupe 1, n = 85) et groupe ayant une magnésémie normale (groupe 2, n = 85). Nous avons évalué les données démographiques de nos patients; l’association entre le statut en Mg et les paramètres cliniques et biologiques ainsi que l’association entre le statut de Mg et complications dégénératives. On a inclus 170 patients. Notre étude a montré que le taux sérique de Mg était fortement lié à âge, sexe, durée du diabète, indice de masse corporelle, hypertension et hémoglobine glycosylée. Concernant les complications courantes; nous avons seulement trouvé une corrélation négative entre le niveau de Mg et l’existence d’une néphropathie. Nous n’avons pas trouvé de corrélation significative avec la rétinopathie; neuropathie; et macro angiopathie. Notre étude a démontré qu’un faible niveau de Mg est corrélaté à un mauvais contrôle glycémique; hypertension artérielle et néphropathie chez les patients atteints de diabète de type 2. Cependant, des recherches supplémentaires sont nécessaires pour confirmer ces constations.

Mots clés: Macroangiopathie, statut en Magnésium, microangiopathie, faible contrôle glycémique
**Introduction**

Diabetes is a major public health problem that has attained epidemic proportions globally. According to international diabetes federation, there are 425 million people with diabetes in the world. There will be 629 million people with diabetes in the world in 2045. Type 2 diabetes mellitus is the most common form of diabetes mellitus (DM). Therefore, it is urgent to develop an effective preventive strategy to control this epidemic. Current studies have reported that diet may play important roles in increasing the risk of developing diabetes. Magnesium (Mg) is an extremely important mineral which is found naturally in many foods. It plays major roles in physiological activities of the body including normal nerve and muscle function, cardiac excitability, and insulin metabolism. Furthermore, Mg is an important ion in all living cells being a cofactor of many enzymes involved in glucose metabolism. These enzymes are activated by the MgATP2+ complex which is the essential substrate for their functioning. Lower intake of Mg and low serum Mg concentrations are associated with metabolic syndrome, insulin resistance, and Type-2 diabetes. Several studies have shown that Mg intake in diabetic patients is often below recommended levels. The recommended dietary reference intake is about 301–420 mg/day. The normal serum Mg is about 1.9–2.5 mg/dl. Patients are considered frankly hypomagnesemic with serum Mg concentrations ≤0.61 mmol/L or 1.5 mg/dL. Mg concentrations ≤0.75 mmol/L or 1.8 mg/dL may be considered as preclinical hypomagnesemia. Our study seeks the association between concentration levels of serum Mg and common complications and comorbidities of DM and other biochemical indexes.

**Materials and Methods**

**Study design and patients**

This is a case–control study conducted Department of Endocrinology, Diabetology, and Nutrition at University Hospital Center Hassan II in Fez. Patients with Type 2 diabetes admitted in our department between January 2015 and December 2018 were included in this study. We distinguished two groups. G1: Patients Type 2 diabetics with a normal Mg and G2: Patients Type 2 diabetic with hypomagnesemia. These two groups are matched for age and sex. We excluded from our study: Records without making a full set of biochemical examination, patients with Type 1 diabetes, pregnant and lactating women, those taking diuretics or Mg supplementation or having persistent diarrhea, vomiting, and patients with renal failure.

Basic data were obtained (pathological history, height, weight, body mass index (BMI), waist circumference, and blood pressures), biological evaluation (glycosylated hemoglobin [HbA1c] and the fasting blood glucose were obtained; lipid profile, blood urea, serum creatinine, and 24 h urinary albumin were estimated). Serum Mg was measured by colorimetry and a value of Serum Mg <1.8 mg/dl was considered to be hypomagnesemia. The common complications (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and diabetic macroangiopathy…) were obtained from databases also.

**Statistical analysis**

Statistical analysis was performed using Microsoft Excel 2004 (XML) and d’Epi Info 7 (7.2.2.6 février 2018), Centers for Disease Control and Prevention at United states. The collected information was summarized using the descriptive statistics such as frequency and percentage of qualitative data, mean and standard deviation for quantitative data. Statistical result was considered statistically significant at $P < 0.05$.

**Results**

There were 170 patients evaluated and enrolled. According to the serum level of Mg, patients were classified into two groups: low Mg (Group 1, $n = 85$) and normal Mg group (Group 2, $n = 85$).

Demographics characteristics of our patients are shown in Table 1. Fifty six (33%) were male and One hundred fourteen with a sex-ratio H/F: 0. 49. The mean age of the patients was 61.42 ± 10.89 years (range 29–84 years). The average duration of diabetes was 12.62 ± 8.20 years. Our patients had a higher BMI with an average of 30.15 ± 7.10 kg/m². The mean serum Mg of all the diabetic patients was 19.06 ± 1.31.

**Association between magnesium status and clinical, biological parameters**

Comparing two groups, there was a statistical difference in the sex ($P = 0.029$), ages ($P = 0.009$) and diabetes duration ($P = 0.021$). However; the BMI was higher in patients with hypo Mg. Moreover, among the group with hypomagnesemia; there was more hypertension in comparison with normal Mg group ($P = 0.019$). The serum Mg in the hypomagnesemia group was 16.81 ± 1.33 mg/l while the normal Mg group was 21.32 ± 2.61 mg/l.

In addition, patients with normal Mg had better glycemic control (9.61% ± 1.74% vs. 10.82% ± 2.11%, $P = 0.005$). Concerning dyslipidemia, there was no difference between groups.

**Association between magnesium status and degenerative complications**

There was no difference between the groups for retinopathy and neuropathy ($P = 0.30$ for retinopathy, $P = 0.11$ for neuropathy). However, nephropathy was more common in group with hypomagnesemia ($P = 0.026$) [Table 2].

There was no difference between the groups concerning macroangiopathy ($P = 0.065$ for ischemic cardiomyopathy, $P = 0.14$ for arteriopathy, $P = 0.11$ for diabetic foot) [Table 3].

**Discussion**

Mg is an intracellular ion with an essential role in several biological reactions. Indeed, he has a fundamental role in different biochemical processes such as maintenance of the pancreatic beta cell cycle, release of insulin, regulation of insulin...
action, insulin-mediated glucose uptake, activation of glucose metabolizing enzymes, maintenance of vascular tone, and DNA synthesis.[11] In previous studies, Mg deficiency has been reported in patients with Type 2 diabetes. However, some workers have also reported normal and even high levels.[12] In addition, a low serum Mg level has been shown to induce new diabetes. Besides, it effects on the existing diabetes and its co morbid conditions.[13] The mechanism of Mg deficiency in diabetes is not clearly elucidate but it seems that the most important causes are the reduction of Mg intake and/or augmentation of Mg urinary loss while Mg absorption and retention seem to be maintained.[14]

**Association between magnesium status and clinical, biological parameters**

It seems therefore that plasma Mg concentration is an insensitive, but highly specific indicator of low Mg status.[14] That is why the serum or plasma Mg measurement is the most readily available and widely used test of Mg status. In our study, we assessed the serum Mg. The results of our study showed that serum Mg level was strongly related to age, sex, diabetes duration, BMI, and hypertension. It was similarly in the study of Guerrero-Romero *et al.*, who noted that age, alcohol consumption and use of diuretics were risk factors for low-serum Mg levels in diabetic patients.[15] Mg depletion may cause an insulin-resistant state, poor glycemic control, and disordered lipid metabolism.[16] Mahalle *et al.* have found that diabetes, dyslipidemia, and hypertension were inversely related with serum Mg levels.[15] Besides, Solati *et al.* found that Mg supplementation could significantly decrease both systolic and diastolic blood pressure.[18] It can be explained by the fact that Mg deficiency increases the intracellular Ca/Mg ratio, vascular smooth muscle tone and smooth muscle cell response to external constrictor stimuli increases, which

| Table 1: Demographics characteristics |
|---------------------------------------|
| **Characteristics** | **T2D + normal magnesium** | **T2D + hypomagnesemia** | **Total** | **P** |
| Number of subjects | 85 | 85 | 170 | |
| Age (years) | 61.51±10.36 | 61.34±11.46 | 61.42±10.8 | 0.0009 |
| Sex (H/F) | 36/49 | 20/65 | 56/114 | 0.029 |
| Duration of diabetes (years) | 12.77±8.67 | 12.47±7.73 | 12.62±8.20 | 0.021 |
| Treatment | | | | |
| Oral hypoglycemic | 24 | 38 | 62 | |
| Insulin | 24 | 17 | 41 | |
| Oral hypoglycemic + insulin | 35 | 25 | 60 | |
| Diet | 2 | 5 | 7 | |
| BMI (kg/m²) | 29.72±7.54 | 30.58±6.66 | 30.15±7.10 | 0.032 |
| Waist circumference (cm) | 101.24±22.21 | 102.87±19.75 | 102.05±20.98 | 0.019 |
| Arterial hypertension (n) | 51 | 54 | 105 | 0.019 |
| HbA1c (%) | 9.61±1.74 | 10.82±2.11 | 10.21±1.92 | 0.005 |
| Serum magnesium (mg/l) | 21.32±2.61 | 16.81±1.33 | 19.06±1.31 | |
| Serum calcium (mg/l) | 92.80±15.51 | 93.76±12.5 | 93.28±14.14 | |
| Urea (g/l) | 0.42±0.35 | 0.34±0.25 | 0.38±0.30 | |
| Creatinine (mg/l) | 10.85±11.67 | 9.73±7.97 | 10.29±9.98 | |

**BMI=Body mass index, HbA1c=Glycosylated hemoglobin**

| Table 2: Diabetic microangiopathy |
|----------------------------------|
| **Degenerative complications** | **Number of patients** | **Hypomagnesemia (%)** | **Normomagnesemia (%)** | **P** |
| Retinopathy | 61 | 41 | 30 | 0.30 |
| Nephropathy | 48 | 34 | 22 | 0.026 |
| Neuropathy | 19 | 9.41 | 12.9 | 0.11 |

| Table 3: Diabetic macroangiopathy |
|----------------------------------|
| **Degenerative complications** | **Number of patients** | **Hypomagnesemia (%)** | **Normomagnesemia (%)** | **P** |
| Ischemic cardiomyopathy | 46 | 28.23 | 25.88 | 0.065 |
| Arteriopathy | 11 | 6 | 7 | 0.14 |
| Diabetic ulcer | 8 | 4.7 | 4.7 | 0.11 |
leads to vasoconstriction and as a result elevation of blood pressure. In our study, we noted a statistically significant difference between HbA1c level; existence of hypertension but we did not observe a difference concerning dyslipidemia.

**Association between magnesium status and degenerative complications**

Previous studies have revealed that lower Mg level may lead to the occurrence and development of diabetic microvascular and macroangiopathy complications. Additionally to poor glycemic control, Dasgupta et al. noted that hypomagnesemia is associated with retinopathy, nephropathy, and foot ulcers. In his cohort, Arpací et al., observe that nephropathy was common in the hypomagnesemic group compared to the normomagnesemic group regardless of age and duration of diabetes. Moreover, Coronary Artery Risk Development in young Adults Study showed an inverse relationship between Mg intake and the incidence of diabetes. Similarly, we only found a negative correlation between Mg level and the existence of the nephropathy. However, it is worth to note that our patients with hypomagnesemia and nephropathy had higher BMI and blood pressure. Those two parameters can explain also the increase of nephropathy in our study. In disagreement with this report, we did not note a difference in the presence of retinopathy and macroangiopathy complications. Others studies argued that in diabetics with microalbuminuria, serum Mg might be reduced due to lower serum albumin concentration.

Taking into an account, the increasing prevalence of diabetes and its complications, scientists are trying hard to discover new prevention and treatment methods for diabetes. It appears that Mg supplementation had proven to be effective in improving insulin sensitivity and glucose. On the other hand, researchers think that, one of the principal sites of Mg action can be the muscles. It is possible that Mg can help translocation of glucose transporter number 4 to the cell membrane, to take place. Furthermore, a meta-analysis of 34 trials involving 2028 participants; published by Zhang et al., reported that 368 mg of supplemental Mg daily for 3 months will lower systolic BP by 2 mmHg and diastolic BP by 1.78 mmHg. However, more research is needed to confirm these effects.

The limitations of this study are the relatively small sample size and measurement of serum Mg instead erythrocyte intracellular Mg (As Mg is a predominantly intracellular ion, its serum measurements are not representative of Mg status or intracellular pool). There are still many aspects need further study and exploration.

**Conclusion**

In summary, our study has demonstrated that a low Mg level is correlated to a poor control glycemic; high blood pressure and nephropathy in patients with Type 2 diabetes. Indeed, large-scale clinical trials are needed to determine whether the correction of Mg deficiency could be effective to reduce the incidence and to further elucidate the association between serum Mg and nephropathy. However, we did not find any significant association between retinopathy, neuropathy, macroangiopathy, and low Mg status. It may be prudent in clinical practice to periodically monitor plasma Mg concentrations in diabetic patients.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Atlas du diabète de la FID - 8ème Édition, 2017. Available from: https://www.diabete.qc.ca/fr/comprendre-le-diabete/ressources/documents-utiles/atlas/.
2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin N Engl J Med 2002;346:393-403.
3. Oduson OO, Familoni OB, Odewabi AO, Idowu AO, Adekolade AS. Patterns and correlates of serum magnesium levels in subsets of type 2 diabetes mellitus patients in Nigeria. Indian J Endocrinol Metabol 2017;21:439-42.
4. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Magnesia LA. An update on physiological, clinical and analytical aspects. Clin Chim Acta 2000;294:1-26.
5. Takaya J, Higashino H, Kobayashi Y. Intracellular magnesium and insulin resistance. Magnes Res 2004;17:126-36.
6. Volpe SL. Magnesium, the metabolic syndrome, insulinresistance, and type 2 diabetes mellitus. Crit Rev Food Sci Nutr 2008;48:293-300.
7. Pham PC, Pham PM, Pham PT, Pham SV, Pham PA, Pham PT. The link between lower serum magnesium and kidney function in patients with diabetes mellitus type 2 deserves a closer look. Clin Nephrol 2009;71:375-9.
8. Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. Nutr Rev 2010;68:333-40.
9. Hashizume N, Mori M. An analysis of hypermagnesemia and hypomagnesemia. Jpn J Med 1990;29:368-72.
10. Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia. Requested vs. routine. JAMA 1990;263:3063-4.
11. Pokharel DR, Khadka D, Sigdel M, Yadav NK, Kafle R, Sapkota RM, et al. Association of serum magnesium level with poor glycemic control and renal functions in Nepalese patients with type 2 diabetes mellitus. Diab Metab Syndr 2017;11 Suppl 1:S417-23.
12. Antin SS, Keshavarz M, Dehghani M. Magnesium in type 2 diabetes mellitus. Crit Rev Food Sci Nutr 2008;48:293-300.
13. Grafton G, Baxter MA. The role of magnesium in diabetes mellitus: A possible mechanism for diabetic complications. J Diab Comp 1992;6:143-9.
14. Wälti MK, Zimmermann MB, Spinas GA, Hurrell RF. Low plasma magnesium in type 2 diabetes. Swiss Med Wkly 2003;133:289-92.
15. Guerrero-Romero, F. Rodríguez-Morán M. Complementary therapies for diabetes: The case for chromium, magnesium, and antioxidants. Arch Med Res 2005;36:250-7.
16. Reverter JL, Sentí M, Rubiés-Prat J, Lucas A, Salinas I, Pizarro E, et al. Relationship between lipidoprotein profile and urinary albumin excretion in type II diabetic patients with stable metabolic control. Diab Care 1994;17:189-94.
17. Mahalle N, Kulkarni MV, Naik SS. Is hypomagnesemia a coronary risk factor among Indians with coronary artery disease? J Cardiovasc Dis Res 2012;3:280-6.
18. Solati M, Ouspid E, Hosseini S, Soltani N, Keshavarz M, Dehghani M. Oral magnesium supplementation in type II diabetic patients. Med J Islam Repub Iran 2014;28:67.
19. Dasgupta A1, Sarma D, Saikia UK. Hypomagnesemia in type 2 diabetes mellitus Indian J Endocrinol Metab 2012;16:1000-3.
20. Arpaci D, Tocoglu AG, Ergenc H, Korkmaz S, Ucar A, Tamer A. Associations of serum magnesium levels with diabetes mellitus and diabetic complications. Hippokratia 2015;19:153-7.
21. Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs DR Jr., et al. Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. Diab Care 2010;33:2604-10.
22. Soltanian N, Amini A, Iraj B, Askari GH, Ebneyamin S, Ghias M, et al. Weight status of the first-degree relatives of patients with type 2 diabetes based on the glucose tolerance test. Res Med Sci 2012;17:269-74.
23. Zhang X, Li Y, Del Gobbo LC, Rosanoff A, Wang J, Zhang W, et al. Effects of magnesium supplementation on blood pressure: A meta-analysis of randomize double-blind placebo controlled trials. Hypertension 2016;68:324-33.