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RESEARCH

The Magnesium and Glucose (MAG) Study: the prevalence and effect of hypomagnesaemia on diabetes control in a regional hospital in KwaZulu-Natal

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Background: Diabetes mellitus (DM) poses a great burden of disease worldwide. The adverse effects of hypomagnesaemia (hypoMg^{2+}) in patients with DM have been well described, with a higher prevalence of hypoMg^{2+} in patients with DM than in the general population (up to 35% vs. up to 15%). No data exist for South Africa (SA).
Objectives: The study aimed to determine the prevalence of hypoMg^{2+} in a cohort of patients visiting a specialised DM clinic and to ascertain whether there is a relationship between hypoMg^{2+} and glycaemic control and hypoMg^{2+} and renal dysfunction.
Methods: Data recorded on standardised clinical sheets from patients who attended a specialised DM clinic at Edendale Hospital, Pietermaritzburg, SA, over a period of one year (July 1, 2015 to June 30, 2016) were collected. Patient demographics, diabetes type, glycaemic control, serum magnesium (Mg^{2+}) and renal function are presented for statistical analysis.
Results: A total of 744 patients were enrolled. Most patients were female (527; 70.8%) and were diagnosed with Type 2 diabetes (DM2) (633; 85.1%) with a mean age of 52.3 (SD 15.6 years). The prevalence of hypoMg^{2+} was found to be 8.44%. HypoMg^{2+} was associated with poor glycaemic control ($r = -0.16$, $p < 0.0001$). A significant relationship was observed between glycaemic control and hypoMg^{2+} in males ($r = -0.21$, $p = 0.0038$), but not females ($r = -0.011$, $p = 0.81$). No significant relationship was evident between hypoMg^{2+} and renal dysfunction ($r = -0.064$, $p = 0.11$).
Conclusion: HypoMg^{2+} in patients with DM was associated with poorer glycaemic control in the male population, potentially increasing the risk of adverse health outcomes. However, the prevalence of hypoMg^{2+} was not higher than in published data, but population-specific controls are required. No association could be found between hypoMg^{2+}and renal dysfunction. The need for routine Mg^{2+} testing and supplementation in our population requires further assessment.

Keywords: Diabetes mellitus, glycaemic control, magnesium, renal function, types 1 and 2

Introduction

The link between magnesium (Mg^{2+}) and diabetes mellitus (DM) has been well established. Mg^{2+} is responsible, both directly and indirectly, for the homeostasis of insulin, and vice versa. Normal levels of Mg^{2+} are required for intracellular signalling, ion channel regulation and other processes that regulate insulin secretion from beta cells within the pancreas.[1] Low serum levels of Mg^{2+} in patients with type 2 diabetes mellitus (DM2) have been well described.[2–8] The prevalence of hypomagnesaemia (hypoMg^{2+}) varies depending on the population studied, and has been found to be 2.5% to 15% in the general population.[9]

Type 1 diabetes mellitus (DM1) and DM2 are major risk factors for cardiovascular disease.[10] It has been reported that hypoMg^{2+} is an independent risk factor for cardiovascular disease in patients with DM, and is also associated with poor glycaemic control in both patients with DM1 and patients with DM2.[11,12] Lin *et al.* demonstrated poor glycaemic control in patients with DM1 and Shaikh *et al.* showed a relationship between serum Mg^{2+} and glycaemic control in patients with DM2.[13,14]

People with diabetes who are hypomagnesaemic are at increased risk of developing microvascular complications.[15,16] Mg^{2+} plays an important role in the energy-dependent transport of calcium and potassium across cell membranes, which in turn regulates, amongst other things, the vasomotor tone. Aberrations in this finely controlled mechanism may lead to the microvascular complications. Antin *et al.* demonstrated that 35% of patients within their observed population of patients with DM2 had hypoMg^{2+}, with a clear correlation between Mg^{2+} and microvascular complications.[17]

Few such data exist within the South African setting, with no recent data available. In 1984 Jialal *et al.* found a relationship between hypoMg^{2+} and microvascular disease in 15 South African patients of Indian descent with DM2.[18] The prevalence, however, remains unknown.

Important interplays between magnesium and renal function (and dysfunction) have been described. Renal handling of magnesium is altered with moderate renal dysfunction and markedly compromised in established chronic kidney disease, which may lead to hypermagnesaemia.[19] HypoMg^{2+} has also been shown to be a predictor of end-stage renal disease in patients with DM2.[20]

This study aimed to determine the prevalence of hypoMg^{2+} within a cohort of South African patients and to determine the relationship between serum Mg^{2+} and glycaemic control as well as renal dysfunction.

Methods

A retrospective, cross-sectional study was performed using data collected from patients who attend a specialised diabetes clinic at Edendale Hospital, Pietermaritzburg, KwaZulu-Natal. Clinicians used a standardised clinic sheet on which patient particulars were recorded.[21] This clinic sheet was approved for use in the clinic by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC)—BCA 194/15. The data for the study included patients who attended the diabetes clinic between July 1, 2015 and June 30, 2016.

Patient demographics, comorbidities, type of diabetes and duration of DM are recorded on the clinic sheet. In addition to

Table 1: Gender, age and type of diabetes of study population after correction for multiple visits

Total (*n*)	**744**
Female	527 (70.8)
Male	209 (28.1)
Unspecified	8 (1.1)
Mean age (years)	52.6 ± 15.5
DM1	102 (13.7)
DM2	633 (85.1)
Unspecified	9 (1.2)

Data expressed as *n* (%) or mean ± SD.

other tests being performed, HbA1c, Mg^{2+} and estimated glomerular filtration rate (eGFR) are documented on the clinic sheet. Missing or incomplete and incorrectly completed data were not considered.

Good glycaemic control was conferred by an HbA1c value of < 7% (or 53 mmol/mol).[22] The National Health Laboratory Service (NHLS) reports the reference range for serum Mg^{2+} for adults (i.e. patients over the age of 18), both males and females, as 0.63–1.05 mmol/l. Serum Mg^{2+} was measured using the Siemens Dimension (Siemens AG, Munich, Germany) clinical chemistry system, which utilises a modified methylthymol blue (MTB) complexometric procedure. HypoMg^{2+} was considered in patients with a Mg^{2+} result of < 0.63 mmol/l. Renal dysfunction was represented by an eGFR (MDRD) of less than 60 ml/min/1.73 m^2.

Statistical analysis

Statistical analysis was performed using the SOFA Statistics software (ver. 1.4.6) (www.sofastatistics.com). Univariate data were assessed and the prevalence of hypoMg^{2+} (overall and grouped data sets) was determined. Bi-/multivariate analysis was performed using Pearson's correlation test, unpaired t-test and ANOVA where applicable. Statistical significance was considered for *p*-values of < 0.05.

Results

A total of 1 450 consecutive patient entries for the period assessed were enrolled. Patients may have visited the clinic more than once, and only the first visit to the clinic was taken into consideration, totalling 744. Of these patients 70.8% (527) were female, 28.1% (209) male and 1.1% (8) unspecified. Of the participants 13.7% (102) had DM1, 85.1% (633) had DM2 and 1.2% (9) were unspecified. The mean age of the participants was 52.6 years (standard deviation 15.5) (Table 1).

Entries containing both Mg^{2+} and HbA1c are reported below (n = 652). This reflects a large discordance between patient entries enrolled and those analysed. Only first visits within the period were considered and the remainder of the excluded entries had incomplete data sheets.

The mean serum Mg^{2+} was 0.78 mmol/l (standard deviation 0.12). The overall prevalence of hypoMg^{2+} was found to be 8.44%.

The mean HbA1c was 9.88% (standard deviation 2.58). The prevalence of poor glycaemic control (as defined above) was 84.82%.

Serum Mg^{2+} and HbA1c were analysed. There was a significant negative linear correlation (Pearson) between the two variables (r = –0.16, p < 0.0001) (Figure 1). When considered separately we failed to show a linear relationship in females (r = –0.011, p = 0.81) as compared with males (r = –0.21, p = 0.0038).

In all, 644 patients had both serum Mg^{2+} and eGFR recorded. Some 170, or 26.40% of, patients had varying degrees of renal dysfunction. A significant linear relationship (Pearson) was not evident between eGFR and Mg^{2+} (r = –0.064, p = 0.11) (Figure 2).

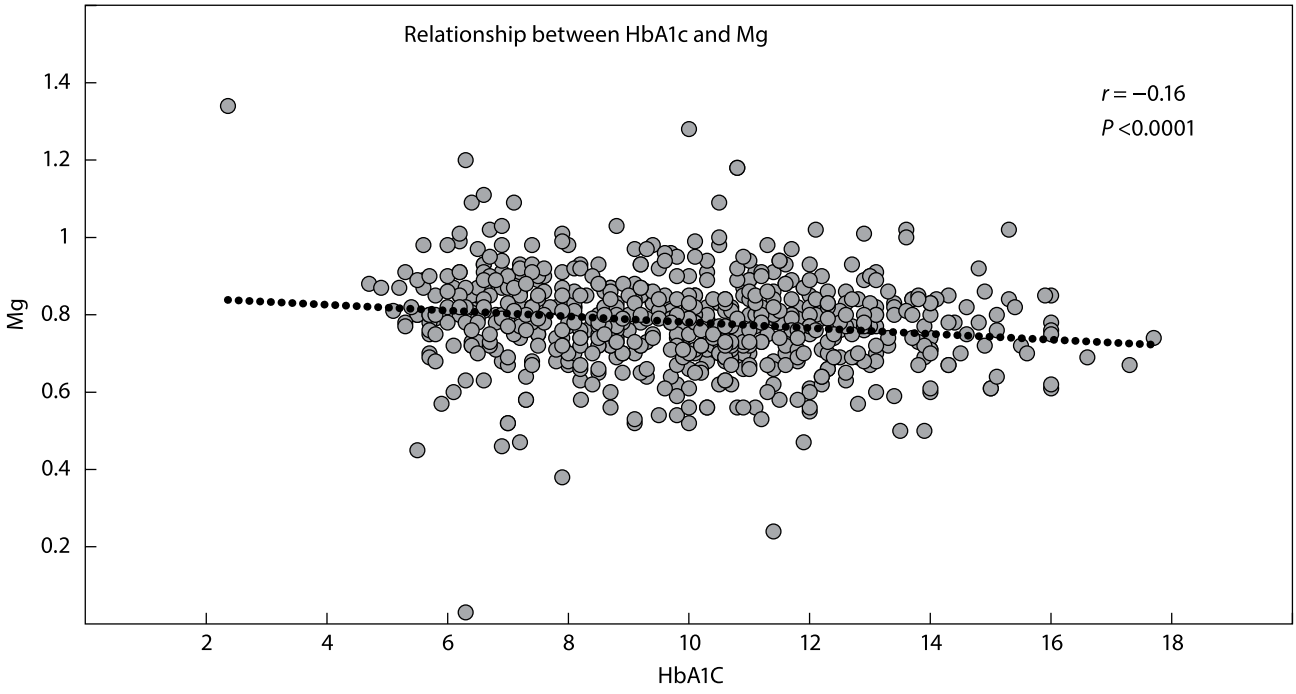

Figure 1: Scatter diagram showing the relationship between magnesium and glycated haemoglobin (superimposed regression line).

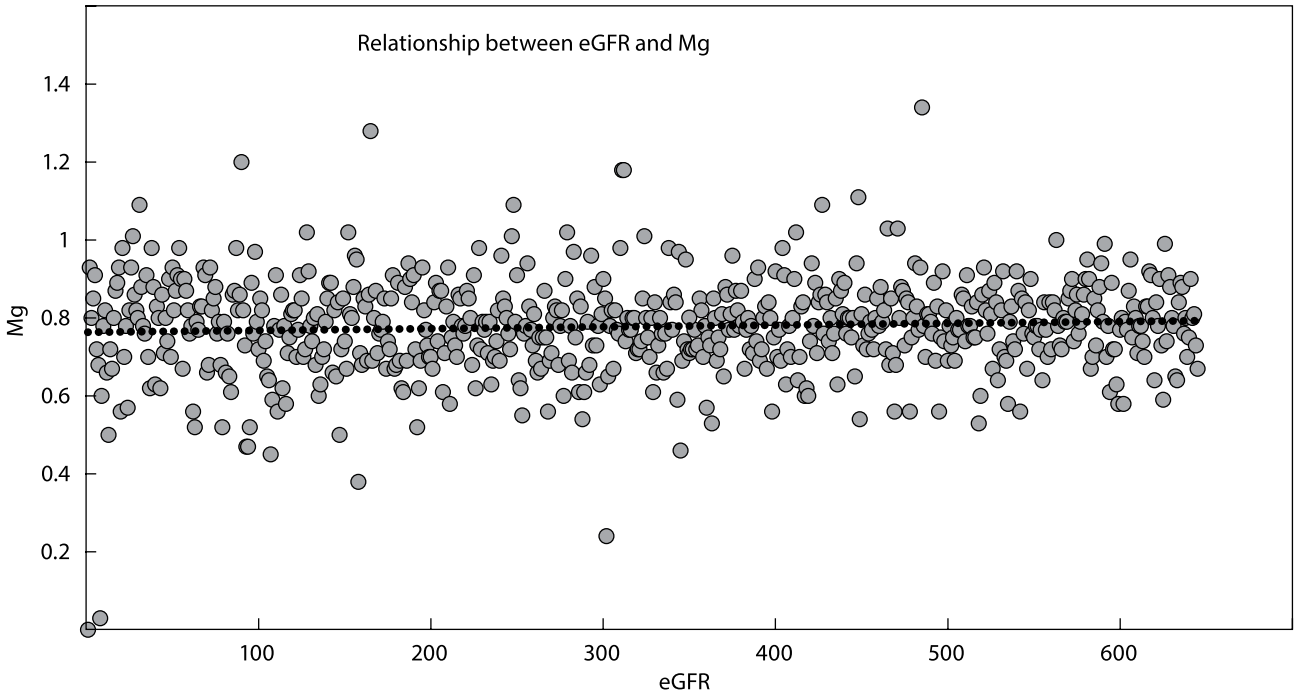

Figure 2: Scatter diagram showing the relationship between magnesium and estimated glomerular filtration rate (superimposed regression line).

Discussion

HypoMg^{2+} was not found to be more prevalent than in that of the general population and a relationship was found between HbA1c and Mg^{2+}.

The prevalence of hypoMg^{2+} amongst patients with DM was shown to be 25% in one study. The findings of this study suggest that the prevalence of hypoMg^{2+} is not higher in our population of patients with DM (8.44%) than that of the general population (up to 15%) as reported by Schimatschek *et al*.[9] This differs greatly from the findings of a study conducted by Seyoum *et al*. in Ethiopia, where hypoMg^{2+} was seen in 65% of their patients.[23] These studies used different cut-offs in determining hypoMg^{2+} amongst their study participants (0.76 mmol/l and 0.70 mmol/l by Schimatschek *et al*. and Seyoum *et al*., respectively). Although no information is available for the assay utilised by Schimatschek *et al*., it was found that Seyoum *et al*. utilised a different assay than was utilised in this study [(Flame Atomic Absorption Spectrophotometer; Perkin-Elmer Company, Waltham, MA, USA) vs. Siemens Dimension clinical chemistry system, which utilises a modified methylthymol blue (MTB) complexometric procedure]. This may explain the differences in prevalence of hypoMg^{2+}.

In addition to these differences in study methods, other reasons may play a role. The recommended daily allowance of Mg^{2+} in adults ranges in values of between 310 mg and 420 mg per day. Wheat- and maize-based food products form part of the staple diet of a large proportion of our population; 100 g of the maize and wheat contain approximately 37 mg and 41 mg of magnesium, respectively.[24] This could form part of the reason for the results obtained. The findings may, in part, be a result of strict food fortification programmes within SA. Regulations were adopted in the early 2000s, focusing on the fortification of foods comprising the staple diet of a majority population, such as wheat flour, maize and margarine. These foods are not fortified with Mg^{2+}, but there appears to be a complex interaction between the naturally occurring Mg^{2+} within these foods and the compounds with which the food is fortified. Margarine, for example, is fortified with vitamin D, which has been shown to increase intestinal Mg^{2+} absorption.[25] Diabetes forms part of a myriad of comorbid diseases (hypertension, dyslipidaemia, etc.) and each of these diseases is managed with various agents. The various diseases and agents could influence magnesium homeostasis.

It is well known that poor glycaemic control can be ascribed to various factors. Early identification and correction of these factors lead to a better health outcome for patients. The study population showed a high prevalence of poor glycaemic control (84.93%). Our study suggests that Mg^{2+}, too, must be closely monitored. A significant relationship between hypoMg^{2+} and poor glycaemic control was evident ($p < 0.0001$) and the clinical significance needs to be established in future studies. Considering sex separately, female sex showed no relationship between HbA1c and hypoMg^{2+}. Male sex, on the other hand, showed a significant relationship. This appears to be a novel finding. Reasons for this are not immediately evident; however, diet, comorbid diseases and alcohol intake could be contributing factors.

Further research is required to establish whether this finding is consistent with what is observed in other populations. The overall relationship between HbA1c and hypoMg^{2+} is in keeping with that found in the literature, suggesting that clinicians within our context, too, must be aware of the importance of recognising hypoMg^{2+} and correcting the deficiency as part of the overall glycaemic control plan.

Literature suggests that glomerular filtration rate appears to be negatively affected by hypoMg^{2+} in patients with DM. Our study could not confirm this in the population studied. Further research, using a wider array of renal function determinants, is required to confirm or refute this finding.

Cross-sectional studies have well-established limitations and our study is no exception. A different time period studied may have

yielded different results. Prevalence-incidence bias (Neyman bias) may skew the results, and human error in recording data (especially paper-based data sets) must also be taken into consideration when interpreting the results. Various other factors that affect serum Mg^{2+} were not recorded, notably diuretic use, body mass indices and alcohol consumption, constituting a limitation.

Diabetes mellitus remains a major burden of disease in both the developed and developing worlds, with an ever-increasing incidence. HypoMg^{2+} has a higher prevalence in patients with DM (up to 35%), has been shown to adversely affect glycaemic control and is associated with complications, including microvascular damage.

We can conclude that a multifaceted approach to diabetic care is of utmost importance. Further research, especially within the developing world, is required to establish the role of routine Mg^{2+} measurement and Mg^{2+} supplementation in patients with DM.

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