

Association Between Serum Magnesium and Hematological Indices in Type 2 Diabetes Mellitus

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ABSTRACT

Magnesium is involved in immune-inflammatory processes, and hypomagnesemia is associated with type 2 diabetes mellitus (T2DM). Blood cells (BCs) and BCs-derived indices are popular subjects. However, the relationship between magnesium and BCs-derived indices has not been investigated in diabetes. The aim of this study was to compare hypomagnesemic and normomagnesemic patients with T2DM in terms of BCs and BCs-derived indices, and to investigate the correlation of magnesium with these parameters.

The study included 204 patients with T2DM, 62 hypomagnesemic (<1.8 mg/dL) and 142 normomagnesemic (1.8-2.6 mg/dL). Hypomagnesemic and normomagnesemic cases with T2DM were compared in terms of BCs and BCs-derived indices including NLR (Neutrophil/Lymphocyte), MLR (Monocyte/Lymphocyte), PLR (Platelet/Lymphocyte), Systemic immune-inflammatory index, Systemic inflammatory response index, and Aggregate index of systemic inflammation. Also, correlation analysis was performed between serum magnesium and BCs and indices.

There was no significant difference between the groups in terms of demographic and clinical characteristics ($p>0.05$). The two groups were statistically similar with respect to BCs ($p>0.05$), except erythrocytes. Hypomagnesemia group had significantly lower erythrocyte count than normomagnesemia group ($p=0.042$). The groups were not different statistically in terms of BCs-derived indices ($p>0.05$). No significant correlation was found between serum magnesium and BCs and BCs-derived indices ($p>0.05$), except NLR. There was significant negative correlation between serum magnesium and NLR ($r:-0.152$; $p=0.030$).

No overall relationship was found between serum magnesium and BCs-derived indices. The lower erythrocyte count in hypomagnesemics and the negative correlation of magnesium with NLR may be related to hypomagnesemia in T2DM.

Keywords: Blood cells, diabetes mellitus, hematology, inflammation, magnesium

Introduction

Magnesium has important metabolic functions in the human body. This vital mineral plays important roles as cofactor and activator in numerous biochemical processes and enzymatic reactions (1,2). Magnesium regulates immune and inflammatory responses and magnesium deficiency is associated with immune dysfunction with increased inflammatory actions (3,4). Furthermore, magnesium deficiency predisposes to various diseases, including type 2 diabetes mellitus (T2DM) (5,6). Alcoholism, malabsorption and some drugs including proton pump inhibitors (PPI), diuretics and metformin are known to play a role in magnesium deficiency (2,7). As a practical method, measurement of serum magnesium level is the most widely used method to assess magnesium status, despite its limitations in determining total magnesium in the body¹. Despite the abundance of magnesium in nature,

hypomagnesemia is common and despite its clinical importance, underdiagnosis is frequent (5). Therefore, it is important to investigate the potential factors involved in magnesium deficiency.

Blood cells (BCs) and BCs-derived indices, which are considered as immune and inflammatory biomarkers, are given in Table 1, are laboratory-based tests that have attracted much interest and intensive research, because they have important advantages in terms of convenience, cheapness, and accessibility. It has been shown that BCs-derived indices can be used to improve diagnosis (8,9), differential diagnosis (10,11), and prediction of prognosis (12,13), disease severity (14,15), and mortality risk (16,17) in various disorders. Although BCs-derived indices have been studied in many conditions, the relationship between hypomagnesemia and these indices has only been investigated to a very limited extent (18) and has not been investigated in diabetic cases.

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It is well known that hypomagnesemia is associated with T2DM (5,6). In diabetic cases, BCs-derived indices have been shown to be associated with various conditions including proteinuria (19), metabolic syndrome (20) and dry eye disease (21), but such a link between hypomagnesemia and BCs-derived indices in diabetes mellitus has not been investigated. Therefore, we wanted to investigate the potential relationship between serum magnesium and BCs-derived indices in patients with diabetes mellitus. The aim of this study was to compare hypomagnesemia and normomagnesemia in terms of BCs and BCs-derived indices and to examine the correlation of serum magnesium with BCs-derived indices in patients with T2DM.

Materials and Methods

Following ethical approval (number: 106; date: 05 July 2024), a retrospectively analysis was performed on previously collected data. Data from patients admitted between January 2024 and July 2024 were used for the analysis. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Patients selected for the study were determined according to the following inclusion and exclusion criteria. Inclusion criteria were T2DM, age range 30-64 years, use of oral antidiabetics and complete data. Exclusion criteria were type 1 diabetes mellitus, age <30 and ≥65 years, insulin use, missing data, active infection, magnesium use, malignancy, lactation, and pregnancy.

The numbers of BCs were determined in the hospital laboratory and by Mindray BC6800 (Mindray, Chenzhen, China). Based on the relevant studies in the literature (10,11,16), the BCs-derived indices were calculated by deriving from BCs with the formulae given in Table 1.

A total of 204 T2DM patients, 62 hypomagnesemic (<1.8 mg/dL) and 142 normomagnesemic (1.8-2.6 mg/dL), were included in the study. Demographic and clinical characteristics and laboratory results were recorded. BCs-derived indices including NLR (Neutrophil to Lymphocyte ratio), MLR (Monocyte to Lymphocyte ratio), PLR: (Platelet to Lymphocyte ratio), SII (SII: Systemic inflammatory index: Neutrophil×Platelet/Lymphocyte), SIRI (Systemic inflammatory response index: Neutrophil×Monocyte/Lymphocyte), AISI (Aggregate index of systemic inflammation: Neutrophil×Platelet×Monocyte/Lymphocyte)

were calculated by derivation from BCs^{10,11,16}. Hypomagnesemic and normomagnesemic groups were compared statistically in terms of BCs and BCs-derived indices. In addition, statistical correlation analysis was performed between serum magnesium and BCs and BCs-derived indices.

Statistical Analysis: Statistical analyses were conducted in line with established recommendations for reporting statistics in medical literature²². The analyses were performed using IBM SPSS Statistics version 27. The Kolmogorov-Smirnov test assessed the normality of distribution for continuous variables. Normally distributed data were analysed with the independent samples t-test and presented as mean ± standard deviation. For non-normally distributed data, the Mann-Whitney U test was used, with results shown as median (min-max). Categorical variables were summarized using frequencies and percentages [n (%)], and analysed with Fisher's exact test. Furthermore, correlation analyses were applied to explore relationships between continuous variables (n=204). A p-value below 0.05 was considered indicative of statistical significance.

Results

Table 2 presents demographic and clinical characteristics of the groups in the comparative design. No statistically significant difference was found between the two groups in terms of age (p=0.720), gender (p=0.171), weight (p=0.813), height (p=0.059), BMI (p=0.263), diabetes duration (p=0.119), comorbidities (p>0.05), and medications with potential to affect magnesium level (p>0.05) (Table 2).

Table 3 demonstrates the comparison of the groups in terms of BCs and BCs-derived indices. Accordingly, the groups were statistically similar with respect to BCs including leukocytes (p=0.308), platelets (p=0.747), neutrophils (p=0.296), lymphocytes (p=0.494), and monocytes (p=0.418). However, erythrocyte count was significantly lower in the hypomagnesemia group compared to the normomagnesemia group (p=0.042). The two groups were not different statistically in terms of NLR (p=0.114), MLR (p=0.926), PLR (p=0.533), SII (p=0.195), SIRI (p=0.759), and AISI (p=0.684) (Table 3).

Table 4 shows correlations between serum magnesium level and BCs and BCs-derived indices. There was no significant correlation between serum magnesium and BCs and BCs-derived indices (p>0.05), except NLR. There was

Table 1: Derivation of Blood Indices From Blood Cells

NLR	Neutrophil to Lymphocyte ratio
MLR	Monocyte to Lymphocyte ratio
PLR	Platelet to Lymphocyte ratio
SII	(Neutrophil × Platelet) to Lymphocyte ratio
SIRI	(Neutrophil × Monocyte) to Lymphocyte ratio
AISI	(Neutrophil × Platelet × Monocyte) to Lymphocyte ratio

SII: systemic inflammatory index

SIRI: systemic inflammatory response index

AISI: aggregate index of systemic inflammation

Table 2: Clinical Features of Hypomagnesemia and Normomagnesemia Groups

	Hypomagnesaemia (n=62)	Normomagnesaemia (n=142)	p
Age, years	56.0 (13.25)	58.0 (12.0)	0.720*
Female, n (%)	25 (40.32)	73 (51.41)	0.171
Weight, kg	80.0 (16.25)	80.0 (15.0)	0.813*
Height, m	1.67 (0.09)	1.69 (0.08)	0.059*
BMI, kg/m ²	29.49±4.44	28.82±3.69	0.263**
T2DM duration, years	6.0 (9.75)	5.0 (8.0)	0.119*
PPI user, n (%)	26 (41.94)	54 (38.03)	0.641
Metformin user, n (%)	55 (88.71)	120 (84.51)	0.517
Diuretic user, n (%)	16 (25.81)	23 (16.20)	0.123
Hypertension, n (%)	28 (45.16)	61 (42.96)	0.878
Hyperlipidemia, n (%)	15 (24.19)	32 (22.54)	0.857
Coronary artery disease, n (%)	6 (9.68)	17 (11.97)	0.811
Chronic kidney disease, n (%)	11 (17.74)	24 (16.90)	1.0

*: Mann-Whitney U test and median (IQR); T2DM: type 2 diabetes mellitus; PPI: proton pump inhibitor

Table 3: Laboratory Features of Hypomagnesemia and Normomagnesemia Groups

	Hypomagnesemia (n=62)	Normomagnesemia (n=142)	p
Leukocyte, 103/mL	8.35±2.23)	8.04±1.91	0.308
Erythrocyte, 103/mL	4.98±0.48	5.15±0.56	0.042
Platelet, 103/mL	277.50 (97.25)	273.50 (70.75)	0.747*
Neutrophil, 103/mL	4.60 (2.35)	4.42 (1.88)	0.296*
Lymphocyte, 103/mL	2.48 (1.18)	2.55 (0.94)	0.494*
Monocyte, 103/mL	0.44 (0.28)	0.48 (0.21)	0.418*
HbA1c	7.50 (2.52)	7.45 (2.03)	0.324*
Glucose, mg/dL	157.50 (127.0)	140.0 (65.75)	0.174*
Magnesium, mg/dL	1.69 (0.10)	1.98 (0.21)	<0.001*
NLR	2.00 (1.26)	1.79 (0.89)	0.114*
MLR	0.19 (0.11)	0.18 (0.07)	0.926*
PLR	110.53 (50.66)	105.10 (43.56)	0.533*
SII	534.80 (358.95)	472.73 (286.66)	0.195*
SIRI	0.88 (0.89)	0.84 (0.59)	0.759*
AISI	241.06 (239.03)	226.11 (165.36)	0.684*

*: Mann-Whitney U test and median (IQR); NLR: Neutrophil / Lymphocyte; MLR: Monocyte / Lymphocyte; PLR: Platelet / Lymphocyte; SII (Systemic immune-inflammatory index): (Neutrophil × Platelet / Lymphocyte); SIRI (Systemic inflammatory response index): (Neutrophil × Monocyte / Lymphocyte); AISI (Aggregate index of systemic inflammation): (Neutrophil × Platelet × Monocyte / lymphocyte)

Table 4: Statistical correlations between magnesium and BCs and BCs-derived indices

n=204	Leukocyte	Erythrocyte	Platelet	Neutrophil	Lymphocyte	Monocyte
r	-0.058	0.077	0.003	-0.107	0.079	0.099
p	0.411	0.277	0.968	0.127	0.264	0.159
n=204	NLR	MLR	PLR	SII	SIRI	AISI
r	-0.152	0.033	-0.088	-0.133	-0.026	-0.046
p	0.030	0.637	0.209	0.058	0.716	0.513

Spearman test was used in correlation analyses except for platelet and lymphocyte (Pearson test); NLR: Neutrophil / Lymphocyte; MLR: Monocyte / Lymphocyte; PLR: Platelet / Lymphocyte; SII (Systemic immune-inflammatory index): (Neutrophil $\times$ Platelet / Lymphocyte); SIRI (Systemic inflammatory response index): (Neutrophil $\times$ Monocyte / Lymphocyte); AISI (Aggregate index of systemic inflammation): (Neutrophil $\times$ Platelet $\times$ Monocyte / lymphocyte)

a significant negative correlation between serum magnesium and NLR (r : -0.152; p =0.030) (Table 4).

Discussion

This study aimed to investigate the relationship between serum magnesium and blood parameters in T2DM. For this purpose, diabetic cases with and without hypomagnesemia were evaluated and compared in terms of BCs and BCs-derived indices. In addition, correlation analysis was performed between serum magnesium and mentioned parameters. Comparative results revealed that T2DM cases with and without hypomagnesemia were similar in terms of BCs, except erythrocytes. Hypomagnesemics exhibited lower erythrocyte count, indicating the association of magnesium deficiency with reduced erythrocytes. Correlation analysis revealed no significant association between serum magnesium and BCs-derived indices, except NLR. There was significant negative correlation between serum magnesium and NLR, suggesting anti-inflammatory effects of magnesium and the association of magnesium status with NLR in T2DM.

To date, the diagnostic, differential, prognostic, and predictive roles of BCs-derived indices have been studied and shown in numerous conditions such as systemic sclerosis, psoriasis, spondylodiscitis, melanoma, sepsis, calculus cholecystitis, intracerebral hemorrhage, and COVID-19 (8-16). In addition, BCs-derived indices have been shown to be associated with various conditions including cardiovascular outcomes (17), proteinuria (19), metabolic syndrome (20) and dry eye disease (21) in diabetes. However, such a link between hypomagnesemia and BCs-derived indices in diabetes mellitus has not been investigated. Furthermore, the relationship between hypomagnesemia and BCs-

derived indices has only been investigated to a very limited extent (18) and not in diabetic cases. Therefore, we investigated the potential relationship between serum magnesium and BCs-derived indices in patients with T2DM. As a result, hypomagnesemic and normomagnesemic cases were similar in terms of BCs-derived indices in T2DM and there was no correlative relationship between serum magnesium and BCs-derived indices, except NLR. A significant negative correlation was found between serum magnesium and NLR. Therefore, this finding supported the hypothesis that changes in NLR may be associated with changes in magnesium status in patients with T2DM. On the other hand, previous studies have shown that magnesium deficiency is associated with an increase in biomarkers of inflammation such as C-reactive protein, erythrocyte sedimentation rate and pro-inflammatory cytokines (4,24), and also shown that hypomagnesemia is common in diabetes mellitus^{5,6}. Furthermore, the mechanisms and interactions underlying hypomagnesemia in diabetic patients have not been adequately elucidated. In this context, our results suggest that low serum magnesium level in diabetics is associated with changes in only NLR but is not associated with other BCs-derived indices. This may be due to the fact that changes in serum magnesium levels may show short-term fluctuations, whereas changes in BCs-derived indices require a longer period of time.

In our study, the finding that the number of erythrocytes was lower in hypomagnesemia patients compared to normomagnesemics suggests that magnesium has an association with reduced erythrocyte count and magnesium deficiency in diabetic patients is associated with a decrease in erythrocytes. In accordance with this finding, in a previous study, magnesium in lymphocytes was found to be the most sensitive indicator of magnesium deficiency in cases of migraine²⁴.

Moreover, previous studies have demonstrated that magnesium plays a role in the proliferation of hematopoietic cells (25). Therefore, the association between hypomagnesemia and low erythrocyte count may be a result of impaired hematopoiesis due to magnesium deficiency in patients with T2DM.

On the other hand, potential limitations of this study should be noted. Important limitations are related to the retrospective analysis, small sample size and single-centre design. Due to the retrospective analysis, the effects of the drugs taken by the patients on magnesium levels and hemogram parameters were ignored. Another potential limitation is that the measurement method used may not have sufficient power to show total and intracellular magnesium. In addition, this study also includes disadvantages related to the cross-sectional design, which may not have the capacity to reveal a causal relationship. Finally, a discussion comparing data from different studies was not possible due to the lack of specific literature on the topic of this study.

In accordance with the aim of the study, a comparison between hypomagnesemia and hypomagnesemia in terms of BCs and BCs-derived indices, and a correlation between serum magnesium and BCs and BCs-derived indices were performed in T2DM. Accordingly, hypomagnesemics had lower erythrocyte count, indicating an erythropenia activity of magnesium deficiency. Furthermore, there was a significant negative correlation between serum magnesium and NLR, suggesting possible immune-inflammatory effect of hypomagnesemia in diabetes. To our knowledge, the relationship between serum magnesium and BCs-derived indices has not been previously addressed in diabetes mellitus. This is the first study on the subject which needs to be further addressed by new studies.

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