# In Type 2 Diabetes Mellitus: any Link between Diabetic Retinopathy and Magnesium?

### Original Article

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#### **ABSTRACT**

**Background:** Diabetic retinopathy imposes a significant health burden. Recent studies suggest a relation between Magnesium and Diabetic retinopathy.

Aim: In type 2 diabetic patients we aimed to evaluate if there is an association between magnesium and diabetic retinopathy. Methods: We conducted the study on 180 participants who included sixty patients with type 2 diabetes but no diabetic retinopathy, sixty type 2 diabetics having diabetic retinopathy & sixty healthy subjects. All participants were aged above 18. We excluded patients with renal insufficiency, malabsorption, diarrhea and those taking medications that affect magnesium levels. Subjects with chronic alcoholism and pregnant women were also excluded. The levels of Magnesium together with HbA1C, Fasting and 2 hours post prandial plasma glucose, serum creatinine, estimated glomerular filtration rate, full lipid profile and albumin/Creatinine ratio were determined in all participants who also a fundus examination performed. We used post hoc analysis to compare magnesium levels between the 3 groups. We used ROC-curve to determine the optimum level of Magnesium as risk factor for diabetic retinopathy. Multivariate analysis was performed to define the independent predictors that affect retinopathy.

**Results:** Serum magnesium was lower significantly in diabetic retinopathy with a positive predictive value 80 % when less than 1.5 mg/dl, with specificity 88.33% and sensitivity 46.67%. Magnesium was independently linked to retinopathy in patients with diabetes mellitus type 2 after accounting for other confounders.

**Conclusion:** There is a link between magnesium and diabetic retinopathy.

**Key Words:** Magnesium, retinopathy, type 2 diabetes mellitus.

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#### INTRODUCTION

Diabetes mellitus and its complications are growing health problems. Nearly 90% of the cases of diabetes are due to type 2 diabetes mellitus (T2DM) characterized by insulin resistance [1]. Diabetic retinopathy(DR) is one of the major microvascular complications of diabetes that can be reduced by good glycemic control. It threatens vision and is one of the main causes of blindness [2].

Magnesium (Mg) has an important contribution in glucose metabolism <sup>[3]</sup>. It is an abundant intracellular cation that has an important role in phosphorylation reactions of glucose<sup>[4]</sup>. An altered Mg homeostasis has been noted in T2DM<sup>[5]</sup> together with a high prevalence of

hypomagnesemia [6]. Hypomagnesemia was also prevalent among patients with microvascular and macrovascular complications<sup>[7]</sup>.

Kumar et al., 2019 suggests that Mg may be related to DR [4]. Pham et al., 2007 proposed that correction of hypomagnesemia can decrease DR progression [8]. Since hypomagnesemia is a proposed correctable contributing factor for diabetic retinopathy development, we aimed to further investigate the link between Mg and diabetes induced retinopathy

#### AIM OF THE WORK

We targeted studying the relationship of Mg to retinopathy in diabetes mellitus type 2.

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#### PATIENTS AND METHODS

We conducted a study that included 3 groups with 60 patients each with a total of 180 patients. We selected the participants from Ain Shams University hospitals diabetes clinic. The Faculty of Medicine, Ain Shams University research ethics committee approved the study. We obtained an informed written consent from all patients. Group I included patients with T2DM not complicated by DR, Group II T2DM patients complicated by DR and Group III included healthy participants.

We selected participants all aged above 18 and both males and females. Females were not pregnant or lactating. We excluded patients with conditions like renal insufficiency, malabsorption and diarrhea and those taking supplements, multivitamins or antacids that contain magnesium or taking other medications that could affect Mg levels like laxatives diuretics digoxin aminoglycosides diuretics amphotericin B, proton pump inhibitors, cyclosporine and cetuximab. Subjects with chronic alcoholism were also excluded.

For all participants, we took detailed history and completed a thorough clinical examination that included a fundus exam. The degree of retinopathy was classified in accordance with the eye with more severe affection. The levels of Mg together with HbA1C, fasting plasma glucose (FPG), 2 hours post prandial plasma glucose (2-h PG), estimated glomerular filtration rate (eGFR), total cholesterol, Triglycerides, HDL and LDL were also determined.

Statistical Analysis: We collected data, revised and entered them into the Statistical Package for Social Science (IBM SPSS) version 20. We presented the qualitative data as number and percentages and quantitative data as mean, standard deviations and ranges when parametric distribution. On comparing between the groups for qualitative data we used Chi-square test and Unpaired Student T-test for quantitative data. We also used Analysis of Variance (ANOVA) to compare 3 groups then used turkey's test for post hoc analysis to compare all possible pairs of group means. Linear Correlation coefficient was used for detection of correlation between two quantitative variables in one group. Multivariate analysis was done to define the independent predictors that affect retinopathy. Receiver operating characteristic curve (ROC-curve) was used to find out the best cut off value of magnesium Probability (*p-value*) was considered significant if < 0.05.

#### **RESULTS**

#### **Background data**

Among the 60 patients with type 2 diabetes without diabetic retinopathy (Group I) participants included 21 males and 39 females with a mean age of patients  $52.783 \pm 9.491$  years. In the 60 types 2 diabetes patients with diabetic retinopathy (Group II) 26 of the patients were males, and 34 were females and the mean age of the patients was  $(56.933 \pm 10.917)$  years. Among the 60 participants who did not have diabetes (Group III) 33 participants were males and 27 were females and the had a mean age of  $54.433 \pm 15.258$  years. (Table 1)

 Table 1: Comparison between the three studied groups as regards age & Gender.

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				Gr	oups			AN	OVA
	_	Gr	oup I	Gro	oup II	Gro	up III	F	P-value
Age in	Range	29	9-76	22	2-77	21	- 76	1 770	0.172
years	Mean $\pm SD$	52.783	$5 \pm 9.491$	56.933	$\pm\ 10.917$	54.433	$\pm\ 15.258$	1.778	0.172
Chi	i-Square	N	%	N	%	N	%	$X^2$	P-value
Gender	Male	21	35.00	26	43.33	33	55.00	4.005	0.006
	Female	39	65.00	34	56.67	27	45.00	4.905	0.086

On comparing the 3 groups by ANOVA test there was no significant difference as regards age and sex (Table 1) yet There was a significant difference regarding BMI, SBP, DBP, glycemic and lipid profiles together with eGFR. (Tables 2-6).

On comparing diabetic patients with and without retinopathy by post hoc turkey test, patients DR had significantly higher SBP and significantly lower eGFR. There was no significant difference as regards BMI, DBP, glycemic and lipid profiles. (Tables 2-6)

Table 2: Comparison between the three groups as regards BMI.

			Groups			IOVA		TUKEY'S Test	
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
BMI (kg/m <sup>2</sup> )	Range	21.48 -44.92	21.83 -39.73	22.43 -35.2	0.140	<0.001*	0.067	<0.001*	0.177
	Mean ±SD	$31.068 \pm 5.550$	$29.309 \pm 3.996$	$27.905 \pm 2.951$	8.149	<0.001*	0.067	<0.001*	0.177

Table 3: Comparison between the three groups as regards SBP & DBP.

			Groups			OVA	TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
SBP	Range	100 -140	110 -150	100 -120	54.982	<0.001*	<0.001*	<0.001*	<0.001*
mmHg	Mean $\pm SD$	$119.333 \pm 10.555$	$128.500 \pm 10.222$	$109.667 \pm 8.629$					
DBP	Range	70 -90	70 -100	60 -70	56.140	<0.001*	0.782	<0.001*	<0.001*
mmHg	Mean ±SD	$78.667 \pm 7.241$	$79.500 \pm 8.321$	$67.667 \pm 4.265$					

Table 4: Comparison between the three groups regarding glycemic profile.

			Groups		AN	OVA	7	TUKEY'S T	est
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
FPG	Range	74 -432	80 -367	70 -97	30.799	<0.001*	0.997	<0.001*	<0.001*
Mg/dl	$Mean \pm SD$	$163.833 \pm 84.447$	$163.007 \pm 72.592$	$83.400 \pm 8.611$					
2h PG	Range	73 -531	110 -491	97 -123	43.919	<0.001*	0.607	<0.001*	<0.001*
Mg/dl	$Mean \pm SD$	$235.917 \pm 108.322$	$222.137 \pm 83.691$	$112.333 \pm 7.747$					
A1C%	Range	5.6 -14.5	6 -13.1	4.1 -5.6	103.112	<0.001*	0.617	<0.001*	<0.001*
	$Mean \pm SD$	$8.672 \pm 2.042$	$8.425 \pm 1.406$	$5.287 \pm 0.264$					

**Table 5:** Comparison between the three groups as regards lipid profile.

			Groups		AN	OVA	TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
Total	Range	100 -311	58 -412	84 -211	10.791	<0.001*	0.126	0.022*	<0.001*
Cholesterol mg/dl	Mean ±SD	$179.267 \pm 51.164$	$197.117 \pm 62.199$	$154.900 \pm 31.699$					
TGs	Range	80 -380	56 -299	60 -163	8.265	<0.001*	0.857	0.004*	0.001*
mg/dl	$Mean \pm SD$	$135.917 \pm 60.503$	$140.800 \pm 57.689$	$106.133 \pm 26.080$					
HDL	Range	19 -84	20 -100	40 -91	9.937	<0.001*	0.911	0.001*	<0.001*
mg/dl	$Mean \pm SD$	$44.180 \pm 13.633$	$43.182 \pm 14.578$	$53.017 \pm 11.506$					
LDL	Range	13 -233	12.4 -324.2	7.6 -152	14.259	<0.001*	0.093	0.005*	<0.001*
mg/dl	$Mean \pm SD$	$107.903 \pm 49.420$	$125.775 \pm 55.878$	$80.657 \pm 30.858$					

**Table 6:** Comparison between the three groups as regards eGFR.

		Groups			ANOVA		TUKEY'S Test		
		Group I	Group II	Group III	F	P-value	I&II	I&III	II&III
eGFR	Range	49.3 -228	42 -227	67 -262	14.973	<0.001*	0.015*	0.023*	<0.001*
ml/min/ 1.73m <sup>2</sup>	Mean ±SD	$103.065 \pm 31.394$	$86.413 \pm 27.347$	$118.800 \pm 37.678$					

As regards magnesium levels:

On comparing the 3 groups as regards the Mg levels there was a significant difference of p value <0.001. By post hoc turkey test, patients with diabetic retinopathy

(group II) had significantly lower Mg levels ( $1.665\pm0.283$  mg/dl) than diabetic patients without retinopathy (group I) ( $1.827\pm0.297$  mg/dl) (p-value 0.002). Both groups had significantly lower levels of Mg levels than healthy nondiabetic participants (group III) (Table 7).

Table 7: Comparison between the three groups as regards serum Mg levels.

Mg		Groups		AN	OVA	T	TUKEY'S Test		
mg/dl	Group I	Group II	Group III	F	P-value	I&II	I&III	II&III	
Range	1.3 -2.4	1.1 -2.2	1.9 -2.6	12.050	<0.001*	0.002*	<0.001*	<0.001*	
Mean ±SD	$1.827 \pm 0.297$	$1.665 \pm 0.283$	$2.097 \pm 0.176$	43.050	<0.001*	0.002*	<0.001*	<0.001*	

Among patients with DR 56.67% of patients had non proliferative diabetic retinopathy (NPDR), 26.67% proliferative diabetic retinopathy, (PDR), and 16.67%

diabetic macular edema (DME) and no significant difference was found between them in serum Mg levels. (Table 8).

Table 8: Serum Mg levels in patients with different stages of diabetic retinopathy.

Group II			Mg				ANOVA		
		N	Mean	±	SD	F	P-value		
	NPDR	34	1.688	±	0.291				
Fundus examination	PDR	16	1.650	$\pm$	0.280	0.319	0.728		
	DME	10	1.610	$\pm$	0.277				

Also, in patients with DR serum Mg was significantly lower in males (1.577  $\pm$  0.292 mg/dl) compared to females

 $(1.732 \pm 0.260 \text{ mg/dl})$  (p-value 0.034) (Table 9).

Table 9: Comparison between males and females in patients with diabetic retinopathy as regards serum Mg levels.

C II	,		Mg		T-Test		
Group II		N	Mean	±	SD	t	P-value
C1	Male	26	1.577	±	0.292	-2.176	0.034*
Gender	Female	34	1.732	$\pm$	0.260		

Mg was an independent risk factor for DR after confounding for age, systolic blood pressure, eGFR and

cholesterol levels (Table 10).

Table 10: Multivariate analysis of serum Mg levels in diabetic retinopathy patients after adjustment of age, SBP, cholesterol and eGFR.

			Varia	bles in the E	quation				
		D	C.E.	W7-14	De	G:-	E(D)	95% C.I.f	or EXP(B)
		В	S.E.	Wald	Df	Sig.	Exp(B)	Lower	Upper
	Age	.001	.022	.001	1	.980	1.001	.959	1.044
	SBP	.092	.025	13.606	1	.000	1.097	1.044	1.152
	Cholesterol	.008	.004	3.932	1	.047	1.008	1.000	1.017
Step 1 <sup>a</sup>	eGFR by MDRD equation	025	.009	8.149	1	.004	.975	.958	.992
	Mg	-1.722	.778	4.900	1	.027	.179	.039	.821
	Constant	-7.601	3.858	3.882	1	.049	.001		

a. Variable(s) entered on step 1: Age, SBP, Cholesterol, eGFR by MDRD equation, Mg.

ROC curve analysis showed that the best cutoff value of Mg that could predict DR in persons with T2DM was Mg  $\leq$ 1.5 with sensitivity 46.67 % and specificity 88.33 %,

Positive predictive value 80%, negative predictive value 62.4% and accuracy 65% (Table 11)(Figure 1).

Table 11: ROC curve analysis for the cut off value of Magnesium in predicting retinopathy in patients with type 2 diabetes.

ROC curve between Group II and Group I								
	Cutoff	Sens.	Spec.	PPV	NPV	Accuracy		
Mg	≤1.5	46.67	88.33	80.0	62.4	65.1%		

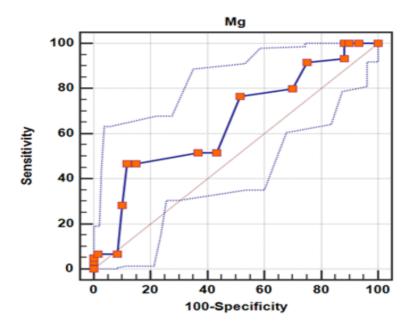


Fig. 1: ROC curve analysis for the cut off value of Magnesium in predicting retinopathy in patients with type 2 diabetes.

Our study showed that mg was negatively correlated with HbA1c in type 2 diabetics with and without DR and

with age in type 2 diabetics with DR. (Table 12)

Table 12: Correlations between serum Mg levels and all other variables in diabetic patients with and without diabetic retinopathy.

		Correlations		'
		M	Ig	
	Gro	oup I	Gro	up II
	r	P-value	r	P-value
Age (years)	0.025	0.850	-0.297	0.021*
Duration (years)	0.053	0.686	0.195	0.134
SBP (mmHg)	-0.105	0.424	-0.159	0.224
DBP (mmHg)	0.001	0.994	0.064	0.625
Weight (kgs)	-0.118	0.369	-0.017	0.898
Height (m)	-0.110	0.404	-0.239	0.066
BMI (kg/m²)	-0.043	0.742	0.131	0.317
FPG (mg/dl)	0.041	0.757	-0.071	0.588
2h-PG (mg/dl)	-0.005	0.968	-0.025	0.849
A1C%	-0.323	0.012*	-0.318	0.013*
Cholesterol (mg/dl)	-0.076	0.562	-0.069	0.600
TGs (mg/dl)	0.131	0.319	-0.123	0.349
HDL (mg/dl)	-0.234	0.071	0.078	0.556
LDL (mg/dl)	-0.046	0.725	-0.072	0.586
S.Cr (mg/dl)	0.101	0.442	-0.006	0.964
eGFR (ml/min/1.73m <sup>2</sup> )	-0.158	0.229	-0.150	0.251

#### **DISCUSSION**

Mg has a significant role in the metabolism of carbohydrates, it contributes to the regulation of rate limiting enzymes important for glucose homeostasis and insulin action [9] and its deficiency can be linked to diabetic retinopathy [4]. We aimed to explore if there is a connection between DR and Mg in T2DM.

Our study showed an association between lower serum Mg levels and type 2 diabetes in agreement with previous studies<sup>[3,10-12]</sup>. Hypomagnesemia can have different underlying causes in patients with T2DM. Resistance to insulin decreases the expression of the renal Mg channel transient receptor potential melastatin 6, which increases Mg loss in urine and affects intracellular magnesium transport<sup>[13]</sup>.

Our study also showed that serum Mg was significantly lower in T2DM patients with retinopathy compared to those without in accordance with previous reports<sup>[12,14,15]</sup>. Hypomagnesemia can aggravate inflammation of the retinal vascular endothelium leading to endothelial dysfunction and increased permeability, Hypomagnesemia can also lead to vasoconstriction and retinal ischemia<sup>[15]</sup>.

Also in our study, the Mg level had no statistical difference between different stages of DR. This can support the hypothesis that once Mg deficiency occurs the sequence of hypoxia and microvascular complication will start with further severity of complication not dependent on how much the level of Mg decreased<sup>[16]</sup>.

In patients with DR serum Mg was significantly lower in males in line with *Khanna et al.* 2020 [10] where males were more likely to have hypomagnesemia. However, this was against *Shivakumar et al.* 2021 where lower levels of serum Mg were associated with female gender. This conflict may be attributed to racial issues<sup>[14]</sup>.

In our study analysis of ROC curve reported Mg  $\leq$ 1.5 mg/dl as a cutoff that could predict retinopathy in type 2 diabetics with 88.33 %specificity and 46.67 % sensitivity, Positive predictive value 80%, negative predictive value 62.4% and accuracy 65% .On the other hand *Xing et al.* 2022 reported an optimum cut-off value of serum Mg in giving the prediction of DR development of 0.875 mmol/L<sup>[17]</sup>.Our study also identified serum magnesium level was an independent risk factor for DR which was in accordance with *Xing et al.* 2022 who also reported that lower Mg levels are related with an increased risk of developing DR <sup>[17]</sup>.

We found that serum Mg was significantly negatively correlated with HbA1c among T2DM patients without and with DR in agreement with *Alekya et al.* 2023 [18]. Also, *Moradiya et al.* 2021, an observational cross-sectional

study of T2DM patients showed that the prevalence of hypomagnesemia in patients with controlled diabetes was less than its prevalence in uncontrolled patients<sup>[11]</sup>. These findings could be due to the increased levels of HbAlc could induce tissue hypoxia by binding to oxygen and thus accelerating angiopathy<sup>[4]</sup>. However, *Saeed et al.* 2018 showed no significant association between HbA1c levels and Serum Mg levels<sup>[19]</sup>.

In our study, in T2DM patients with DR serum Mg levels negatively correlated with age which agrees with Gautam & Khapunj 2021 [20] this may be due to a reduction in dietary intake and intestinal absorption and an increase in renal excretion with the advancement of age.

In our study there was no correlation between serum Mg levels and duration of diabetes mellitus, BMI, lipid profile and eGFR in T2DM patients without and with DR in accordance with *Akyüz et al.* 2020 [21]. Additionally, *Khanna et al.* 2020 reported no significant association between diabetes duration and hypomagnesaemia [10]. Moreover, *Wahid et al.* 2017 demonstrated that patients with hypomagnesaemia did not differ from normomagnesemic diabetics in terms of duration of diabetes, lipid profile and BMI<sup>[11]</sup>.

In summary, our study suggests that hypomagnesemia is associated with DR.

#### **CONCLUSION**

There is a relationship between Mg and DR. This is line with the concern of hypomagnesaemia being linked to development of DR most probably through retinal blood vessels'endothelial dysfunction together with vasoconstriction and decreased blood glow to retina and subsequent ischemia. This favours investigating hypomagnesaemia in persons with retinopathy in T2DM to correct it.

#### RECOMMENDATIONS

For a causal relationship between hypomagnesemia and DR we recommend conducting a RCT to explore effect of correction of hypomagnesaemia on development or progression of DR. We recommend considering screening for hypomagnesaemia in diabetic patients while considering retinopathy besides fundus examination, optical coherence tomography and Fluorescein angiography.

#### **CONFLICT OF INTEREST**

There are no conflicts of interest that need declaration

#### **AUTHORS CONTRIBUTION**

Iman Zaky Ahmed, Meram Mohamed Bekhet and Bahaa Mahmoud Mohammed developed the study question and designed the methodology. Eman Mahmoud Mohamed Ahmed collected and analysed the data. Mahmoud Ahmed Elsamkary and Caroline Adel Girgis Bishay wrote the final manuscript.

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## مستويات المغنيسيوم واعتلال الشبكية لدى مرضى السكري من النوع الثانى

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المقدمة: يفرض اعتلال الشبكية السكري عبئا صحيا كبيرا. تشير الدراسات الحديثة إلى وجود علاقة بين المغنيسيوم واعتلال الشبكية السكري.

الهدف: هدفنا إلى التحقيق في ارتباط مستويات المغنيسيوم واعتلال الشبكية في داء السكري من النوع الثاني.

الأساليب: أجرينا الدراسة على ١٨٠ مشاركا شملهم ٢٠ مريضا بداء السكري من النوع الثاني بدون اعتلال الشبكية السكري، و ٢٠ مريضا بالسكري من النوع الثاني يعانون من اعتلال الشبكية السكري و ٢٠ شخصا من أصحاء. كان جميع المشاركين فوق سن ١٨ عاما. استبعدنا المرضى الذين يعانون من القصور الكلوي وسوء الامتصاص والإسهال وأولئك الذين يتناولون الأدوية التي تؤثر على مستويات المغنيسيوم. كما تم استبعاد الأشخاص الذين يعانون من إدمان الكحول المزمن والنساء الحوامل. تم تحديد مستويات المغنيسيوم بالدم،السكر التراكمي والسكر الصائم و بعد الاكل بساعتين في البلازما، الكرياتينين في الدم، معدل الترشيح الكبيبي المقدر، الكوليسترول الكلي، الدهون الثلاثية، الليبوبروتين عالمي الكثافة و المنخفض الكثافة، نسبة الألبومين / الكرياتينين في البول في جميع المشاركين مع فحص قاع و قد استخدمنا لمقارنة مستويات المغنيسيوم بين المجموعات الثلاث تحليل التباينو تم استخدام منحني المشغل المستقلة التي تؤثر أفضل قيمة قطع للمغنيسيوم كعامل خطر لاعتلال الشبكية السكري. تم إجراء تحليل متعدد المتغيرات لتحديد التنبؤات المستقلة التي تؤثر على اعتلال الشبكية.

النتائج: كانت مستويات المغنيسيوم في الدم أقل بشكل ملحوظ في مرضى السكري من النوع ٢ المصابين باعتلال الشبكية السكري وكان لها قيمة تنبؤية إيجابية لاعتلال الشبكية السكري ٨٠٪ عندما تكون مستوياتهم  $\leq 0.1$  مجم / ديسيلتر، مع حساسية 7.7 % وخصوصية 7.7 % بعد تعديل العمر، ضغط الدم الانقباضي، الكوليسترول ومعدل الترشيح الكبيبي المقدر الاستنتاج ارتبط المغنيسيوم بشكل مستقل بمرض السكري.