SERUM MAGNESIUM IN CHILDREN WITH TYPE 1 DIABETES AND ITS CORRELATION TO GLYCEMIC CONTROL

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ABSTRACT

Background: Type 1 diabetes mellitus (T1DM) is highly prevalent endocrinal disorder. with incidence of around 8/100,000 per year in Egyptian children under the age of 15 years. Evidence indicate that Magnesium (Mg) plays an important role in prevalence of T1DM. and its complications. Thus we aimed to find out the effect of T1DM. on serum Mg level.

Methods: We included 50 Egyptian children with type 1diabetes at Pediatric outpatient clinic, Al-Hussein University Hospital and El-Sahel Teaching Hospital, during the period from May, 2017 to December, 2017, and 25 age- and sex-matched healthy individuals in a case-control study. We measured Serum magnesium, HbA1c, random blood suger, serum urea, and creatinine level and CBC.

Results: Diabetic children had significantly lower serum magnesium level compared to control children (1.91 ± 0.22 mg/dL in diabetic children versus 2.08 ± 0.19 mg/dL in control children). Hypomagnesemia was detected in 26% of diabetic children compared to 8% of control children. Significant negative correlation between serum Mg and HbA1c was detected. ($p=$ 0.000 $r=$ -0.703). also negative correlations between Mg and each of age and duration of DM. ($p=$ 0.016; $r=$ -0.339); ($p=$ 0.000; $r=$ -0.339) respectively.

Conclusion: patients with T1DM more liable to develop hypomagnesemia specially with poor glycemic control.

Recommendations: Proper glycemic control and regular monitoring of serum magnesium in children with T1DM.

Keywords: children, diabetes, magnesium

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most common endocrine and metabolic conditions in childhood. *(El-Ziny et al., 2014)*. Type 1 diabetes is generally thought to be precipitated by an mmune-associated, if not directly immune-mediated, destruction of insulin-

producing pancreatic β cells. *(Todd, 2010)*.

Data from large epidemiologi-al studies worldwide indicate that on an annual basis, the overall increase in the incidence of T1DM is around 3% and about 78,000 children under age 15 years develop T1DM worldwide. The worldwide geographic variation in the incidence of T1DM is striking. Among Eastern Mediterranean and Middle Eastern countries, the largest contribution to the total number of estimated childhood T1DM cases comes from Egypt which accounts for about a quarter of the region's total. The incidence varies between 1/100,000 per year (Pakistan) and 8/100,000 per year (Egypt) in children under the age of 15 years. *(El-Ziny et al., 2014)*.

Mg plays an important role in whole reactions, including cellular energy transfer, glycolysis and phosphorylation, and it prevents free radical generation required to ensure increased glutathione syntheses. *(Salmonowicz et al., 2014)* Moreover, Mg deficiency is involved in the pathogenesis of diabetes complications that inhibit the prostacyclin receptor function and cause increased thrombocyte activation and aggregation. *(Nadler, and Rude, 1995)*.

Numerous causes for low magnesium levels in diabetics can be listed including diets low in magnesium, osmotic diuresis that leads to high renal excretion of magnesium, insensitivity to insulin that affects intracellular magnesium transport and causes increased loss of extracellular magnesium, usage of loop and thiazide diuretics that promote magnesium wasting, diabetic autonomic neuropathies, and reduced tubular reabsorption due to insulin resistance. Additionally, continuous magnesium deficiency correlates to higher levels of TNFα, which may also contribute to post-receptor insulin resistance. *(Dasgupta et al., 2012)*.

PATIENTS AND METHODS

This case control study was carried out on children and adolescents patients at Al-Hussein University Hospital and Al Sahel Teaching Hospital from May, 2017 to December, 2017 according to inclusion and exclusion criteria below. Another group of age- and sex-matched healthy individuals with no obvious medical disorders and not receiving any medication were enrolled as a control group.

Inclusion criteria:
1. Known patient with type 1 diabetes.
2. Age between 1 and 18 years.

3. Duration since time of first diagnosis of DM at least 6 months.

Exclusion criteria:
1. Children who have renal disease detected by serum urea and creatinine test.
2. Children with persistent diarrhea and vomiting.
3. Type 2 diabetes.
4. Patients receiving medication affecting serum Mg level.

Study groups:
1. Patient group: 50 children with type I diabetes.
2. Control group: 25 age- and sex-matched healthy children recruited from Pediatric outpatient clinic, Al-Hussein University Hospital and El-Sahel Teaching Hospital.

Methods:

All children underwent the following:
1. Thorough history taking and complete physical examination.
2. Investigations: complete blood count, renal function tests *(Diamond diagnostics., reference range urea = 15-45 mg/dl., creatinine = 0.5-1.5 mg/dl)*, random blood glucose *(Diamond diagnostics., reference range RBS=60-160mg/dl)*, glycosylated hemoglobin *(kinetic., reference range HbA1c=4.4-6.4%)*, and serum magnesium *(spinreact.,*

reference range Mg=1.7-2.8mg/dl) using Photometer 4040 (ROBERT RIELE GmbH & Co KG., Germany, October 2011)

Ethical consideration:

An informed written consent was obtained from children`s legal guardians before enrollment in the study. This study was approved from the local ethical committee of Al-Azhar University.

No conflict of interest, either financial or commercial.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative variables were presented as number and percentages. The comparison between groups with qualitative data were done by using Chi-square test and Fisher exact test instead of the Chi-square only when the expected count in any cell found less than 5.

The comparison between two groups with quantitative data and parametric distribution were done by using Independent t-test. The comparison between more than two independent groups with

quantitative data and parametric distribution was done by using One Way Analysis of Variance (ANOVA).

Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. Uni-variate and Multi-variate regression analysis was used to assess predictors of Mg level in patients group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

P > 0.05: Non significant

P < 0.05: Significant

P < 0.01: Highly significant.

RESULTS

The study included 50 patients with type 1 diabetes; 24 males and 26 females. They were compared to 25 age- and sex-matched healthy children served as controls. The control group consisted of 13 males and 12 females. The mean age of patients was 9.02 ± 3.06 years (range, 3 – 15 years) while that of controls was 9.60 ± 3.81 years (range, 3 – 15 years). The mean duration of disease in patient group was 4.02 ± 2.03 (range, 1 – 9 years). **Table 1.**

Table (1): Mean age and duration of DM in studied groups.

		Control group	Patients group	Independent t-test	
		No. = 25	No. = 50	t	p-value
Age (yrs)	Mean±SD	9.60 ± 3.81	9.02 ± 3.06	0.712	0.479
	Range	3 – 15	3 – 15		
Duration of DM	Mean±SD	-	4.02 ± 2.03	-	-
	Range	-	1 – 9		

Table 1 shows that, there is no significant difference regarding age in both groups.

Hypomagnesemia was detected in 26% of patient group (13 of 50)., compared to 8% in control group (2 of 25). There was significant difference between the mean Mg level in patient group

1.91 ± 0.22 (range, 1.55 – 2.38), compared to 2.08 ± 0.19 (range, 1.61 – 2.33) in control group. Also, significant difference between the mean HbA1c level in patient group 9.09 ± 1.68 (range, 5.9 – 13.5), compared to 5.72 ± 0.31 (range, 5 – 6.2) in control group was detected. There was significant difference in mean random blood suger in patient group 150.02 ± 44.24 (range, 87 – 271), compared to 119.24 ± 28.81 (range, 79 – 167) in control group. **Table 2**.

**Table (2): Mean Mg level, HbA1c and RBS in studied groups.**

		Control group	Patients group	Independent t-test	
		No. = 25	No. = 50	T	p-value
Mg (N=1.7-2.8mg/dl)	Mean±SD	2.08 ± 0.19	1.91 ± 0.22	3.252	0.002
	Range	1.61 – 2.33	1.55 – 2.38		
HbA1c (N=4.4-6.4%)	Mean±SD	5.72 ± 0.31	9.09 ± 1.68	-9.925	0.000
	Range	5 – 6.2	5.9 – 13.5		
RBS (N=60-160mg/dl)	Mean±SD	119.24 ± 28.81	150.02 ± 44.24	-3.154	0.002
	Range	79 – 167	87 – 271		

Table 2 shows that, there is lower serum Mg level in patient group compared to control group, and higher HbA1c and RBS in patient group. (significant difference)

Table (3): Correlation of Mg level with the other studied parameters in patients group.

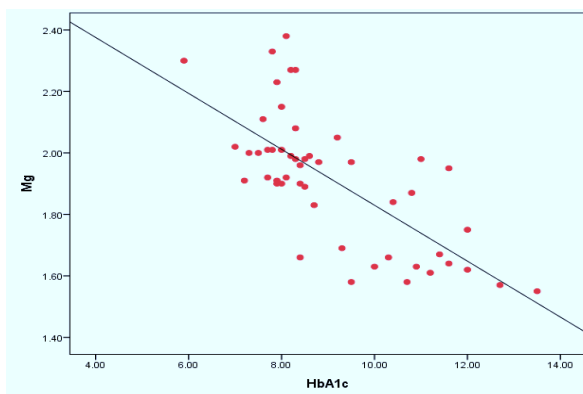|	Mg	
	r	p-value
Age (yrs)	-0.339*	0.016
Duration of DM	-0.501**	0.000
HbA1c	-0.703**	0.000
RBS	-0.338*	0.016
Urea	-0.478**	0.000
Creat	-0.370**	0.008

Table 3 shows that, In patient group, significant negative correlations between Mg and age, duration of DM, HBA1c and RBS were detected.
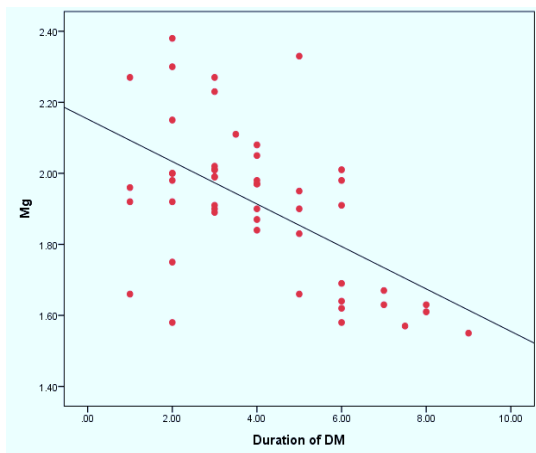
Fig. (1): Negative correlation of Mg level with duration of DM.
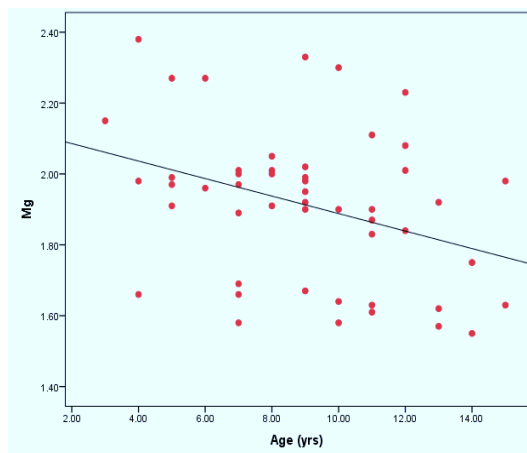
Fig. (2): Negative correlation of Mg level with age.

Fig. (3): Negative correlation of Mg level with HbA1c.

By dividing study group into 4 quartiles based on serum Mg level, First quartile (Q1), serum Mg level < 1.67; Second quartile (Q2), serum Mg level 1.67-1.93; Third quartile (Q3), serum Mg level 1.97-2.02; Fourth quartile (Q4), serum Mg level > 2.02; It was detected that, Q1 (which had lowest Mg level) had longest duration of DM (mean 5.95 ± 2.49), and the highest level of HbA1c (mean 10.98 ± 1.45). highly significant correlation was found. Table 4

Table (4): Comparison of serum magnesium concentration quartiles as regard laboratory findings.

		First quartile	Second quartile	Third quartile	Fourth quartile	One Way ANOVA	
						F	P-value
Age (yrs)	Mean±SD	10.45 ± 3.36	9.71 ± 2.49	8.00 ± 2.80	8.00 ± 3.33	2.105	0.113
	Range	4 – 15	5 – 14	4 – 15	3 – 12		
Duration of DM	Mean±SD	5.95 ± 2.49	3.93 ± 1.73	3.40 ± 1.45	2.95 ± 1.21	6.230	0.001
	Range	1 – 9	1 – 7	1 – 6	1 – 5		
HbA1c	Mean±SD	10.98 ± 1.45	9.02 ± 1.52	8.55 ± 1.29	7.93 ± 0.83	10.929	0.000
	Range	8.4 – 13.5	7.2 – 12	7 – 11.6	5.9 – 9.2		
RBS	Mean±SD	179.45 ± 46.26	144.79 ± 50.11	142.07 ± 40.14	136.90 ± 27.34	2.315	0.088
	Range	97 – 241	93 – 271	89 – 221	87 – 167		
Urea	Mean±SD	37.00 ± 2.90	30.43 ± 2.93	30.40 ± 3.54	29.80 ± 4.37	11.105	0.000
	Range	31 – 40	27 – 37	25 – 36	22 – 38		
Creat	Mean±SD	1.08 ± 0.11	0.88 ± 0.10	0.86 ± 0.12	0.91 ± 0.15	8.403	0.000
	Range	0.9 – 1.2	0.68 – 1	0.65 – 1.05	0.65 – 1.2		

Table 4 shows lower Mg level in patients with longer duration of DM., also lower Mg in patient with higher HbA1c levels

In Uni-variate analysis for predictors of Mg level in patients group, each single variant had independent effect on serum Mg level **Table 5**.

Table (5): Uni-variate analysis for predictors of Mg level in patients group.

	Unstandardized Coefficients		Standardized Coefficients	t	P-value
	B	Std. Error	Beta		
Age (yrs)	-0.025	0.010	-0.349	-2.584	0.013
Duration of DM	-0.060	0.013	-0.562	-4.706	0.000
HbA1c	-0.091	0.013	-0.705	-6.896	0.000
RBS	-0.002	0.001	-0.382	-2.867	0.006
Urea	-0.025	0.006	-0.500	-3.995	0.000
Creat	-0.556	0.204	-0.365	-2.719	0.009

Table 5 shows that, every one of the parameters has its own isolated effect on serum Mg level.

In Multi-variate analysis for predictors of Mg level in patients group, HbA1c had most significant effect on serum Mg level. **Table 6**.

Table (6): Multivariate analysis for predictors of Mg level in patients group.

	Unstandardized Coefficients		Standardized Coefficients	t	P-value
	B	**SE**	**Beta**		
(Constant)	2.854	0.167		17.072	0.000
Age (yrs)	-0.001	0.008	-0.017	-0.144	0.886
Duration of DM	-0.020	0.014	-0.189	-1.399	0.169
HbA1c	**-0.059**	**0.017**	**-0.460**	**-3.391**	**0.002**
RBS	-0.001	0.001	-0.198	-1.761	0.085
Urea	-0.019	0.011	-0.386	-1.678	0.101
Creat	0.477	0.331	0.314	1.441	0.157

Table 6 shows that, HbA1c is the greatest parameter affecting serum Mg level in this study.

DISCUSSION

In this study, we found statistically significant difference in percentage of hypomagnesemia between diabetic patients and control group being higher in diabetic group, as percentage was 26 % in the diabetic group versus 8 % in the control group with lower level of serum magnesium in patients (Mean±SD 1.91 ± 0.22 mg/dL) versus (Mean±SD 2.08 ± 0.19 mg/dL) in control children.

These results are in concordance with ***Khubchandani and Sanghani, 2013,*** on study conducted in Civil Hospital, with 75 subjects (50 patients with diabetes and 25 normal healthy controls), that revealed a lower serum magnesium level in diabetic children compared to control subjects. In an other study on the

patients lived in the Northeast areas of China*, Xu, et al, 2013,* found lower serum magnesium level in diabetic patients compared to control subjects.

Also, *Galli et al., 2014,* In cross-sectional study on 138 children and adolescents with T1DM aged between 1.9 and 20.3 years (61 children, 77 adolescents; 72 boys, 66 girls) who were followed-up in the Outpatient Unit of the 4th Department of Pediatrics, Faculty of Medicine, Aristotle University of Thessaloniki, found 25% of patients had hypomagnesemia.

In our study, we detected significant negative correlation between serum Mg level and HbA1c. By dividing study subjects to 4 quartiles based on the serum magnesium level, we found that Q 1 with the lowest serum magnesium level was associated with longer duration of diabetes, higher HbA1c, and poor glycemic control versus other quartiles with higher serum magnesium. We observed also a negative correlation between serum magnesium level and HbA1c. This agreed with *Galli et al., 2014,* sudy on type I diabetic children that showed a lower Mg level in patients with poor glycemic control with high HbA1c.

Also, *Ramadass et al., 2015,* in study on 50 patients of Diabetes Mellitus type 2 attending the clinics or admitted in the wards of a tertiary care centre in Puducherry, South India., found that Magnesium levels decrease with increase in the duration of Diabetes Mellitus, and revealed a strong negative correlation between Mg and HbA1c.

Inconsistent with our result, *Matthiesen et al., 2004,* study on 81 Danish children with type 1 diabetes, did not show any correlation between serum magnesium level and HbA1c in type 1 diabetic children and adolescents this difference between these studies and ours could be attributed to short duration of DM., the difference in study populations, also to the different methods of evaluating serum magnesium and glycemic control.

CONCLUSION

From this study we conclude that, hypomagnesemia is more common in T1DM patient than healthy control subject, Age , and duration of DM have negative effect on serum Mg level , and there is negative correlation between serum Mg and HbA1c reflecting that "incidence of hypomagnesemia increases with poor glycemic control".

Recommendations

We suggest regular monitoring of serum magnesium in children with type 1 diabetes and correcting hypomagnesemia if present. We need to perform further studies on giving magnesium supplements in diabetic children with hypomagnesemia to observe the effect of correction of serum magnesium on glycemic control, lipid profile, and the risk of diabetic complications.

REFERENCES

1. **Dasgupta A, Sarma D, Saikia UK.:** Hypomagnesemia in type 2 diabetes mellitus. Indian J Endocrinol Metab *2012*;16:1000–3

2. **El-Ziny MA, Salem NA, El-Hawary AK, Chalaby NM, Elsharkawy AA.:** Epidemiology of Childhood Type 1 Diabetes Mellitus in Nile Delta, Northern Egypt - A Retrospective Study. Journal of Clinical Research in Pediatric Endocrinology. *2014*;6(1):9-15.

3. **Galli-Tsinopoulou A, Maggana I, Kyrgios I, Mouzaki K, Grammatikopoulou MG, Stylianou C, Karavanaki K,:** Association between magnesium concentration and HbA1c in children and adolescents with type 1 diabetes mellitus. J Diabetes. *2014*;6:369–377.

4. **Khubchandani AS, and Sanghani H,:** Study of Serum Magnesium and HbA1C in Diabetic Patients along with Changes in their Lipid Profiles Indian Journal of Clinical Practice, April *2013*.Vol. 23, No. 11, 717-719.

5. **Matthiesen G, Olofsson K, Rudnicki M,:** Ionized Magnesium in Danish Children With Type 1 Diabetes. DIABETES CARE, MAY *2004* :27, 5,.1216-1217.

6. **Nadler JL, Rude RK,:** Disorders of magnesium metabolism. Endocrinol Metab Clin North Am. *1995*;24:623–641.

7. **Ramadass S, Basu S, Srinivasan AR.:** Serum magnesium levels as an indicator of status of Diabetes Mellitus type 2. Diabetes Metab Syndr. *2015*;9(1):42-5.

8. **Salmonowicz B, Krzystek-Korpacka M, Noczyńska A.:** Trace elements, magnesium, and the efficacy of antioxidant systems in children with type 1 diabetes mellitus and in their siblings. Adv ClinExp Med. *2014*;23:259–268.

9. **Todd JA.:** Etiology of type 1 diabetes. Immunity. *2010*; 32:457–67.

10. **Xu J, Xu W, Yao H, Sun W, Zhou Q.:** Associations of Serum and Urinary Magnesium with the Pre-Diabetes, Diabetes and Diabetic Complications in the Chinese Northeast Population. PLoS ONE (*2013*) 8(2): e56750.

الملخص العربى

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إن مرض السكري هو مرض مزمن يحدث من خلاله اضطراب فى التمثيل الغذائي ينتج عنه ارتفاع فى مستوى مادة الجلوكوز فى الدم بالإضافة إلى اختلال التمثيل الغذائى لكل من السكريات والبروتينات وكذلك الدهون. ويرجع ذلك إلى عدة أسباب تتعلق باختلال فى إفراز هرمون الأنسولين, أو فاعليته, أو كلاهما.

ويعد مرض السكرى من أكثر الأمراض التى تؤدى إلى كثير من المضاعفات على المدى القريب والبعيد مع اختلال فى كثير من الأجهزة الحيوية فى جسم الإنسان. وتزداد معدلات الإصابة بمرض السكرى على مستوى العالم فى كافة الفئات العمرية, وفى جميع المستويات الاجتماعية, حيث أنه من المتوقع أن يزيد عدد الأفراد المصابين بمرض السكرى الى 592 مليون شخص بحلول عام 2035 م.

هناك الكثير من الأنواع لهذا المرض لكن أغلب المرضى ينتمون إلى النوع الأول أو الثانى. غالبا ما يكتشف النوع الأول فى الأطفال ولكن هذا لا يمنع ظهوره فى أى مرحلة عمرية. أما النوع الثانى يكون ظهوره فى الأشخاص كبار السن غالبا. فى مرض السكرى من النوع الأول يتم تكوين أجسام مضادة للخلايا المختصة بإفراز هرمون الأنسولين, وذلك ناتج لعدة أسباب جينية, و بيئية, و مناعية. إن أعراض المرض متنوعة ولكن غالبا ما تكون فى شكل العطش وكثرة شرب الماء, و كثرة فى إدرار البول, و نقص فى وزن المريض. ويتم تشخيص المرض عن طريق قياس مستوى مادة الجلوكوز فى دم المريض وكذلك نسبة الهيموجلوبين السكرى.

تمثل المضاعفات الحادة مثل الانخفاض الحاد فى مستوى الجلوكوز أو الغيبوبة السكرية اكثر الأسباب المؤدية إلى الوفاة فى مرضى السكرى من النوع الأول. كما أن هناك مضاعفات مزمنة أخرى تحدث على المدى البعيد منها التأثير على الرؤية بسبب اعتلال فى الشبكية, واختلال فى الكلى , والجهاز العصبى, وأمراض القلب والأوعية الدموية.

يعد عنصر الماغنسيوم من أهم العناصر الموجودة فى جسم الإنسان. حيث أنه يساعد فى حدوث أكثر من 300 تفاعل كيميائى داخل الجسم. من هذه التفاعلات ما يسفر عن إنتاج الطاقة على مستوى الخلية ومنها ما هو أساسى لنمو الخلايا وتكوين البروتينات وتكوين المحتوى

الوراثي, وكذلك الحفاظ على توزيع العناصر الكيميائية داخل وخارج الخلية. والحفاظ على مستوى ضغط الدم.

يتم امتصاص الماغنسيوم عن طريق الأمعاء الدقيقة, و يتم إخراجه عن طريق الكلى من خلال البول. يؤثر الماغنسيوم على افراز هرمون الأنسولين وكذلك على مدى فاعليته.

وقد أجريت هذه الدراسة على 50 مريض من الأطفال والمراهقين الذين يعانون من مرض السكرى من النوع الأول (24 من الذكور و 26 من الإناث) من المترددين على مستشفى الحسين الجامعي وكذلك مستشفى الساحل التعليمى. وتم مقارنة المرضى ب 25 من الأطفال الأصحاء المتطابقين فى السن والنو ع (13 من الذكور و 12 من الإناث).

وقد تم أخذ التاريخ المرضي المفصل من جميع المرضى مع التركيز بصفة خاصة على عمر المريض عند ظهور مرض السكري ومدة المرض لديه والعلاج بالإنسولين والمضاعفات المزمنة مثل اعتلال الشبكية، اعتلال الكلى واعتلال الأعصاب وأمراض القلب والأوعية الدموية, وتم أيضا عمل الفحص الطبي الشامل لهم مع التشديد على التقييم الأنثروبومتري لقياسات الجسم وقياس ضغط الدم وفحص كل من الجهاز التنفسى والعصبى والقلب وتم عمل التحاليل الآتية؛ صورة دم كاملة, و ظائف الكلى, و مستوى السكر العشوائى, و نسبة الهيموجلوبين السكرى, ومستوى عنصر الماغنسيوم فى الدم.

وقد لوحظ فى هذه الدراسة وجود انخفاض فى مستوى الماغنسيوم فى 13 شخص من أصل 50 فى مجموعة المرضى (بنسبة 26%) مقارنة بشخصين من أصل 25 فى مجموعة الاصحاء (بنسبة 8%). كما لوحظ ارتفاع فى متوسط مستوى الهيموجلوبين السكرى عند المصابين بنقص عنصر الماغنسيوم عن غيرهم. وكذلك وجدت علاقة عكسية بين مستوى الماغنسيوم وكل من العمر, و مدة المرض, ونسبة الهيموجلوبين السكرى.

وكشف التحليل الإحصائى أن كل من العمر ومدة المرض ونسبة الهيموجلوبين السكرى له تأثير عكسى مستقل على مستوى الماغنسيوم ولكن نسبة الهيموجلوبين هى الأكثر تأثيرا.

وتوصى الدراسة بضرورة المحافظة على مستوى الجلوكوز في الدم ضمن مستوياته الطبيعية وكذلك قياس مستوى الماغنيسوم في الدم بصفة دورية في مرضى السكرى وعلاج نقص الماغنسيوم إن وجد.