# CASE CONTROL STUDY EVALUATING THE ASSOCIATION OF SERUM MAGNESIUM WITH DIABETES MELLITUS, ITS MICROVASCULAR COMPLICATIONS AND SERUM LIPID PROFILE

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**ABSTRACT**

**BACKGROUND**

We wanted to evaluate the association of serum magnesium with diabetes mellitus and serum lipid profile and its microvascular complications.

**METHODS**

90 participants (30 DM with microvascular complications, 30 DM without microvascular complications and 30 controls) aged 40 to 80 years were enrolled in the present cross-sectional study. Hypertensives, alcoholics, participants with diarrhoea and history of drug use (digoxin, corticosteroids etc.) were excluded. History, physical examination findings, biochemical parameters, ECG findings, nerve conduction study and ophthalmoscopic examination findings were collected. Tests of significance were ANOVA, independent sample 't' test, Kruskal Wallis test, Mann Whitney U test and Chi-square test. $p<0.05$ was considered statistically significant.

**RESULTS**

Significantly lower serum magnesium was observed among participants with neuropathy ($p<0.001$), nephropathy ($p<0.001$) and retinopathy ($p<0.001$) and among diabetics without family history of DM ($p=0.02$). No association of ADA glycaemic goal and serum magnesium was observed. Significant association of serum magnesium with TC ($p<0.001$; OR: 9.5, 95% CI 2.7-33.9), serum LDL ($p<0.001$; OR: 0.01, 95% CI 0.002-0.1), retinopathy ($p=0.03$; OR: 0.2, 95% CI 0.04-0.9), nephropathy ($p=0.001$; OR: 0.1, 95% CI 0.03-0.4) was observed.

**CONCLUSIONS**

There is a linear relationship between duration of DM and serum magnesium, severe hypomagnesaemia among participants with microvascular complications. Participants with hypomagnesaemia had significantly higher blood glucose, urea, serum creatinine, total cholesterol, low density lipoprotein and triglycerides. No association between ADA glycaemic control and serum magnesium was observed. Further studies are required to evaluate the pathophysiological role of magnesium in DM and diabetes dyslipidaemia.

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## BACKGROUND

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by the presence of hyperglycaemia due to impairment of insulin secretion, defective action of insulin or both.[1] Global burden of DM is estimated to be in 415 million adults[2], and India stands tall in the second place in regard with the burden of disease with an overwhelming 69.2 million diabetics and 36.5 million prediabetics.[3] The Indian prevalence of DM ranges from 2.2-9.2% in rural and 5-18.6% in urban population.[4-10] Serum electrolyte disturbances are common in patients with type 2 diabetes mellitus (T2DM) and is attributable to hyperglycaemia induced osmotic fluid shifts or due to the deficit in body fluids due to osmotic diuresis.[11] Serum magnesium has been reported as strong independent predictors of the development of T2DM and its complications.[12,13]

Magnesium is an electrolyte of physiological importance, which is the 4th most abundant cation in human body, 2nd most abundant intracellular ion, and the most abundant intracellular divalent cation.[14] 11-47.7% incidence of hypomagnesaemia has been reported among diabetics[15-19] and an inverse relationship between dietary magnesium consumption and incidence of DM has been reported.[20] Contradicting reports of association of serum lipids and magnesium[21,22] and the role of magnesium in the development of microvascular complications of DM has not been clearly elucidated.[23] Also the association of urine sugar and albumin with serum magnesium requires further exploration. Recent studies have demonstrated that serum magnesium is associated with chronic diabetic

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complications, including cardiovascular diseases,[24,25] diabetic retinopathy[26] and diabetic nephropathy,[27] Hypomagnesaemia is correlated with presence of foot ulcers[28] and diabetic peripheral neuropathy,[29,30] but the relationship between them remains controversial. Hence the present study was conducted to evaluate the association of serum magnesium with DM, microvascular complications of DM, serum lipids, glycosuria and albuminuria.

**METHODS**

Our cross-sectional study enrolled 90 participants aged 40 to 80 years, 30 diabetics with microvascular complications (retinopathy and or nephropathy and or neuropathy), 30 diabetics without evidence of microvascular complications and 30 age and gender matched non diabetic controls presenting to Department of General Medicine, NSCB Medical College and hospital Jabalpur. Diabetes was diagnosed using ADA diagnostic criteria,[31] both type 1 (T1DM) and type 2 diabetes (T2DM) were enrolled in the study. Hypertensives, alcoholics, participants with diarrhoea and history of use of diuretics, digoxin, corticosteroids, penicillamine and cholestyramine were excluded. Data was collected in semi structured case record forms which included history, physical examination findings and biochemical parameters (haemoglobin, fasting plasma glucose (FPG), 2 hour post prandial glucose (2h-PPG), blood urea, serum creatinine, serum magnesium, urine sugar, urine ketones, proteinuria and serum lipid profile), ECG findings, results of nerve conduction study and results of ophthalmoscopic examination. Urine microalbuminuria was detected using Micral test and serum magnesium was estimated using Magnesium estimation kit RANDOX® with the minimum detectable concentration of serum magnesium of 0.68 mg/dL. Lipids were categorized according to ATP III guidelines[32] and serum magnesium < 1.6 mg/dL[33] was considered as low levels. Normality of distribution of parameters were assessed using Shapiro wilk test. Normally distributed nominal parameters are expressed as mean (standard error of mean (SEM)), not normally distributed nominal parameters as median (interquartile range (IQR)) and as frequencies for categorical variables. Values are rounded off to nearest decimal point and analysed using free software R®. Tests of significance for quantitative variables were ANOVA & independent sample't' test (normal distribution), Kruskal Wallis test & Mann Whitney U test (non-normal distribution) and Chi-square test was used for qualitative variables. A $p<0.05$ was considered statistically significant.

**RESULTS**

The median age of diabetic participants were 53.5 (45-60) years. 25 (83.3%) diabetics were females. The median duration of diabetes was 9.5 (5-12) years, median FPG and 2-h PPG were 160 (142.5-183) and 266.5 (237-310) mg/dL respectively. The median blood urea and serum creatinine were 36 (27.3-42) and 1.4 (1.1-1.6) mg/dL respectively. The median total cholesterol (TC), low density lipoprotein (LDL) and serum triglycerides (TG) among diabetic participants were 208.5 (184.3-222), 138.5 (112-151.8) and 138 (128-148) mg/dL respectively and the mean serum HDL among diabetics was 43.3 (0.8) mg/dL. The median serum magnesium among diabetic participants were 1.4 (0.6-1.6) mg/dL. Our study did not detect any association between type of DM and microvascular complications (p=0.2). Among controls, 2 (6.7%) participants had prediabetes. Baseline parameters of the study participants are demonstrated in table 1 and comparison of baseline parameters between groups is demonstrated in table 2.

| Characteristic | N=90 |
|---|---|
| Median Age (IQR)- yrs. | 54 (45-60) |
| Female Sex- no. (%) | 35 (39.9) |
| Median Duration of Diabetes (IQR)- yrs. | 5 (0-11) |
| Median FPG (IQR)- mg/dL | 143 (94-168) |
| Median 2-h PPG (IQR)- mg/dL | 238 (128-286) |
| Median Blood Urea (IQR)- mg/dL | 29 (24-37) |
| Median Serum Creatinine (IQR)- mg/dL | 1.2 (0.8-1.4) |
| Median Serum TG (IQR)- mg/dL | 129.5 (119.5-142) |
| Mean Serum HDL (SEM)- mg/dL | 44.7 (0.6) |
| Median Serum LDL (IQR)- mg/dL | 117.5 (106-147) |
| Median Serum TC (IQR)- mg/dL | 186 (173.5-216.3) |
| Median Serum Magnesium- mg/dL | 1.6 (0.9-1.9) |

***Table 1. Baseline Parameters of Study Participants***

Among the participants with microvascular complications, all had nephropathy (100%), 19 (63.3%) had retinopathy and 12 (40%) had neuropathy. Comparison of baseline parameters between participants with and without hypomagnesaemia is demonstrated in table 3. No association between serum magnesium and type of DM was observed (p=0.1).

| Characteristics | Group 1 (N=30) | Group 2 (N=30) | Control (N=30) | p |
|---|---|---|---|---|
| Median Age (IQR)- yrs. | 55 (40-70) | 52.5 (35.5-69.5) | 55.5 (41.5-69.5) | 0.6 |
| Female Sex- no. (%) | 12 (40) | 13 (43.3) | 10 (33.3) | 0.7 |
| Median Duration of Diabetes (IQR)- yrs. | 12 (8-16) | 5 (2-8) | - | <0.001* |
| Median FPG (IQR)- mg/Dl | 169 (113-225) | 149 (121-177) | 92 (81-103) | <0.001*† |
| Median 2-h PPG (IQR)- mg/dL | 280 (207-353) | 254 (184-324) | 115 (90-140) | <0.001† |
| Median Blood Urea (IQR)- mg/dL | 42 (25-59) | 28 (18-38) | 24 (18-30) | <0.001*† |
| Median Serum Creatinine (IQR)- mg/dL | 1.4 (0.68-2.12) | 1.34 (0.96-1.72) | 0.76 (0.43-1.09) | <0.001† |
| Median Serum TG (IQR)- mg/dL | 140 (122-158) | 137 (113-161) | 112 (91-133) | <0.001† |

| | | | | |
|---|---|---|---|---|
| Mean Serum HDL (SEM)- mg/dL | 43.3 (1) | 43.2 (1.2) | 47.5 (1) | 0.004‡ |
| Median Serum LDL (IQR)- mg/dL | 151.5 (138.5-164.5) | 113 (88-138) | 105 (90-120) | <0.001*† |
| Median Serum TC (IQR)- mg/dL | 220.5 (205.5-235.5) | 185.5 (158.5-212.5) | 171 (154-188) | <0.001*† |
| Median Serum Magnesium (mg/dL) | 0.62 (0.3-0.95) | 1.6 (1.4-1.8) | 2.2 (1.6-2.8) | <0.001*† |

***Table 2. Comparison of Baseline Parameters Between Groups***

*indicates significant difference between diabetics with and without microvascular complications using Mann Whitney U test, † indicates significant difference between groups using Kruskal-Wallis test, ‡ indicates significant difference between diabetics and controls using one-way ANOVA.

| Characteristic | Hypomagnesaemia (N=42) | Normal Serum Mg (N=48) | p |
|---|---|---|---|
| Median Age (IQR)- yrs. | 53 (38-68) | 54.5 (40.5-68.5) | 0.4 |
| Median Duration of Diabetes (IQR)- yrs. | 10.5 (3.5-17.5) | 6 (2-10) | 0.001* |
| Female Sex- no (%) | 17 (40.5) | 18 (37.5) | 0.8 |
| Median FPG (IQR)- mg/dL | 155 (111-199) | 96 (30-162) | <0.001* |
| Median PPG (IQR)- mg/dL | 274 (199-349) | 129.5 (0-262.5) | <0.001* |
| Median Serum Urea (IQR)- mg/dL | 36 (17-55) | 26.5 (17.5-35.5) | <0.001* |
| Median Serum Creatinine (IQR)- mg/dL | 1.4 (0.8-2) | 0.9 (0.4-1.4) | <0.001* |
| Median Serum TG (IQR)- mg/dL | 141 (121-161) | 120 (93-147) | <0.001* |
| Mean Serum HDL (SEM)- mg/dL | 44.4 (0.9) | 44.9 (0.9) | 0.7 |
| Median Serum LDL (IQR)- mg/dL | 147 (124-170) | 108 (92-124) | <0.001* |
| Mean Serum TC (IQR)- mg/dL | 215.5 (190.5-240.5) | 175 (154-196) | <0.001* |

***Table 3. Comparison of Parameters Between Participants Based on Serum Magnesium***

* indicates significant difference between groups using Mann Whitney-U test.

| Characteristic | | N | Serum Magnesium (mg/dL) | p |
|---|---|---|---|---|
| Retinopathy | Yes | 19 | 0.7 (0.6-0.9) | <0.001* |
| | No | 71 | 1.7 (1.5-2.1) | |
| Nephropathy | Yes | 30 | 0.6 (0.5-0.9) | <0.001* |
| | No | 60 | 1.8 (1.6-2.2) | |
| Neuropathy | Yes | 12 | 0.8 (0.6-1) | <0.001* |
| | No | 78 | 1.7 (1.4-2) | |
| Family History of DM Among Diabetics | Yes | 31 | 1.5 (0.8-1.6) | 0.02* |
| | No | 29 | 0.9 (0.6-1.5) | |
| Type of DM | T1DM | 10 | 0.9 (0.6-1.5) | <0.001† |
| | T2DM | 50 | 1.4 (0.7-1.6) | |
| | Non-Diabetic | 30 | 2.2 (1.6-2.8) | |

***Table 4. Comparison of Serum Magnesium Levels Between Groups***

*indicates significant difference between groups using Mann Whitney U test, †indicates significant difference between groups using Kruskal Wallis test probably indicating difference with controls since no significant difference was observed between T1DM and T2DM (p=0.2).

| ADA Glycaemic Goal Among Diabetics | | N | Serum Magnesium (mg/dL) | P |
|---|---|---|---|---|
| FPG < 130 mg/dL | Yes | 5 | 0.8 (0.6-1.6) | 0.5 |
| | No | 55 | 1.4 (0.6-1.6) | |
| PPG < 180 mg/dL | Yes | 0 | - | -* |
| | No | 60 | 1.4 (0.6-1.6) | |
| FPG <130 & PPG <180 mg/dL | Yes | 0 | - | -* |
| | No | 78 | 1.4 (0.6-1.6) | |

***Table 5. Comparison of Serum Magnesium in Participants Attaining ADA Glycaemic Control***

* Mann Whitney U test could not be performed since none of the diabetic participants attained post prandial glycaemic control and both fasting and postprandial glycaemic control.

The median duration of DM was 9.5 (5-12 years) and significantly higher duration of DM was observed among participants with microvascular complications (p<0.001). Significantly higher proportion of participants with microvascular complications had symptoms associated with diabetes such as visual disturbance (p=0.001), oedema (p<0.001), tingling, numbness and hyperesthesia (p=0.005). Significant association of serum LDL with the study groups (p<0.001) was observed probably indicating higher proportion of diabetics with microvascular complications with elevated serum LDL or higher proportion of controls with normal serum LDL. Significant association of serum HDL with the study groups observed (p=0.01) probably indicating the higher proportion of diabetics without microvascular complication with reduced serum HDL. Significant association of serum TG with the study

groups was observed (p<0.001) probably indicating higher proportion of diabetics with microvascular complications with elevated serum TG. Significant association of serum TC and the study groups was observed (p<0.001) probably indicating that none of the controls had elevated serum TC.

No association of serum magnesium with serum HDL (p=0.5), serum TG (p=0.8), family history of DM (p=0.1), gender (p=0.8) and urine ketones (p=0.09) was observed. No association between serum magnesium and serum LDL among diabetics was observed (p=0.5).

Significant association between serum magnesium and TC was observed among study participants (p<0.001; OR: 31.5, 95% CI 9.7-103) and among diabetics (Table 6). No association of serum magnesium with neuropathy (p=0.07) and type of DM was observed. Association of serum magnesium with serum LDL, retinopathy, nephropathy, urine sugar and urine albumin are demonstrated in table 7-11 respectively.

| Serum TC | Hypomagnesaemia (N=42) | Normal serum Magnesium (N=18) |
|---|---|---|
| Elevated (N=38) | 33 | 5 |
| Normal (N=22) | 9 | 13 |

***Table 6. Association of Serum TC with Serum Magnesium Among Diabetics***

Significant association was observed between groups (p<0.001; OR: 9.5, 95% CI 2.7-33.9) indicating 9.5 Odds of encountering elevated serum TC among participants with hypomagnesaemia.

| Serum LDL | Hypomagnesaemia (N=42) | Normal serum Magnesium (N=48) |
|---|---|---|
| Normal (N=32) | 1 | 31 |
| Elevated (N=58) | 41 | 17 |

***Table 7. Association of Serum LDL with Serum Magnesium Among Study Participants***

Significant association was observed between groups (p<0.001; OR: 0.01, 95% CI 0.002-0.1) indicating 0.01 Odds of encountering normal serum LDL among participants with hypomagnesaemia.

| Retinopathy | Hypomagnesaemia (N=42) | Normal serum Magnesium (N=18) |
|---|---|---|
| No (N=41) | 25 | 16 |
| Yes (N=19) | 17 | 2 |

***Table 8. Association of Retinopathy with Serum Magnesium Among Diabetics***

Significant association was observed between groups (p=0.03; OR: 0.2, 95% CI 0.04-0.9) indicating 0.2 Odds of encountering participants without retinopathy among participants with hypomagnesaemia.

| Nephropathy | Hypomagnesaemia (N=42) | Normal Serum Magnesium (N=18) |
|---|---|---|
| No (N=30) | 15 | 15 |
| Yes (N=30) | 27 | 3 |

***Table 9. Association of Nephropathy with Serum Magnesium Among diabetics***

Significant association was observed between groups (p=0.001; OR: 0.1, 95% CI 0.03-0.4) indicating 0.1 Odds of encountering participants without nephropathy among participants with hypomagnesaemia.

| Urine Sugar | Hypomagnesaemia (N=42) | Normal Serum Magnesium (N=48) |
|---|---|---|
| Nil (N=32) | 2 | 30 |
| 1+ (N=14) | 10 | 4 |
| 2+ (N=30) | 21 | 9 |
| 3+ (N=14) | 9 | 5 |

***Table 10. Association of Urine Sugars with Serum Magnesium Among Study Participants***

Significant association was observed between groups (p=0.001) probably indicating the higher proportion of participants without urine sugar with normal serum magnesium.

| Urine Albumin | Hypomagnesaemia (N=42) | Normal Serum Magnesium (N=48) |
|---|---|---|
| Nil (N=60) | 15 | 45 |
| 1+ (N=5) | 4 | 1 |
| 2+ (N=1) | 1 | 0 |
| Microalbuminuria (N=24) | 22 | 2 |

***Table 11. Association of Urine Albumin with Serum Magnesium Among Study Participants***

Significant association was observed between groups (p<0.001) probably indicating the higher proportion of participants with hypomagnesaemia with microalbuminuria.

**DISCUSSION**

30 diabetics with microvascular complications, 30 diabetics without microvascular complications and 30 non diabetic participants were enrolled in our cross-sectional study. The median age of study participants and diabetics were similar

(~54 years), which is reasonably higher compared to the recent literature suggesting an increasing trend of detecting DM among younger individuals.[34] This could be explained on the basis of the time period this study was conducted in (2005-2008) which was during the early phase of the diabetic epidemic. This could also be due to the lower awareness, stigma, religious practices and deficiencies in health care sector causing delay in detection of DM. ~ 60% of diabetics were males which contradicts previous reports from North India.[35,36] Though a linear relationship between gender and DM has not been observed, males are at higher risk of developing DM due to a complex interplay between environmental, social and genetic factors.[37] The median age of microvascular complications was 55 years which is self-explanatory since microvascular complications are strongly linked to the duration of hyperglycemia,[38] which could also explain the longer duration of DM among participants with microvascular complications.

The FPG among participants with microvascular complications was significantly higher than participants without microvascular complications and controls. As DM progresses, the glycaemic control reduces due to the pancreatic β cell failure and subsequent apoptosis[39] results in development of microvascular complications which explains the finding. Participants with microvascular complications had significantly higher serum urea compared to other groups, which could be due to higher proportion of participants with pre-existing nephropathy in group 1 or could be due to unidirectional association of blood urea nitrogen and incident DM.[40] Serum creatinine was significantly higher among diabetics which could be due to the microvascular damage among diabetics due to reduced cellular growth, reduction in growth factors, extracellular matrix production and elevated nephrotoxic substances (e.g. transforming growth factor –β).[41] Serum TG were significantly higher among diabetics, which has been described as a typical finding of diabetes dyslipidemia[42] due to the reduced activity of lipoprotein lipase in muscles and adipocytes reducing catabolism of TG[43] coupled with increased lipolysis cause increased synthesis of TG by liver caused by the high circulating levels of non-esterified free fatty acids. Reduction in catabolism of very low density lipoprotein (VLDL) and loss of inhibitory effect of insulin on VLDL secretion results in secretion of triglyceride rich VLDL.[42] Significantly higher HDL was observed among non-diabetics which is an explainable finding since diabetes dyslipidaemia cause reduced HD due to augmentation of activity of HDL catabolizing enzymes coupled with increased levels of serum TG.[42,44] Serum LDL and TC were significantly higher among participants with microvascular complications which is probably due to the reduction in LDL receptors due to reduced plasma insulin leading to reduced catabolism.[45-47] The elevations in serum LDL and TG cause an elevation in TC.[48]

Serum magnesium was significantly low among diabetics compared to non-diabetic controls and was lower in participants with microvascular complications. Magnesium act as a calcium antagonist and reduction in magnesium increases the levels of intracellular calcium causing reduced response of skeletal muscles and adipocytes to insulin causing insulin resistance.[21] Intracellular magnesium exerts a regulatory role in insulin action and insulin-dependent glucose uptake. Reduction in intracellular magnesium reduces tyrosine-kinase activity subsequently causing insulin resistance.[21] Insulin deficiency and resistance can effect tubular reabsorption of magnesium.[21] Other pathogenic mechanisms to be evaluated include the role of oxidative stress and antioxidant effects of magnesium and the influence of magnesium on $Na^+/K^+$-ATPase and its role in microangiopathy. Our study also demonstrated a linear relationship between hypomagnesaemia and duration of diabetes. Significantly higher FPG and 2-h PPG among participants with hypomagnesaemia was observed in our study which could also be explained on the basis of the previously described pathophysiology. We observed a significantly lower serum magnesium among participants with microvascular complications. Hypomagnesaemia has been reported as a predictor in development and progression of retinopathy,[49] diabetic peripheral neuropathy[50] and end stage renal disease associated with T2DM[51] though clarity of the direction of association still remains unclear. Diabetics with family history of DM were having significantly higher serum magnesium which requires further evaluation on larger samples. Significantly lower serum magnesium was observed among participants with T1DM which is contrary to previous findings that describe hypomagnesaemia to be associated with T2DM.[15] Studies demonstrating association between T1DM and hypomagnesaemia are scarce since T1DM is associated with better glycaemic control and at a lower risk of developing hypomagnesaemia.[21] The exact relationship of serum magnesium and T1DM needs to be evaluated in larger samples. No significant difference in serum magnesium among participants who attained and did not attain ADA glycaemic goal for FPG was observed questioning the relationship between glycaemic control and serum magnesium.[52]

Significant association of serum magnesium with serum LDL and TC was observed with lower Odds of encountering hypomagnesaemia among participants with normal serum LDL and higher Odds of encountering hypomagnesaemia among participants with elevated TC. Magnesium supplementation in diet reduces TC, LDL-C and elevates serum HDL-C[53] but the association of serum magnesium with HDL-C was not observed. Significant association of serum magnesium with nephropathy and retinopathy with lower Odds of encountering hypomagnesaemia among participants without nephropathy and retinopathy was observed. Hypomagnesaemia has been previously described as a predictor for end stage renal disease and progression of retinopathy.[51] Significant association between urine sugar and hypomagnesaemia was observed probably indicating higher proportion (93%) of participants without glycosuria with normal serum magnesium. Significant association between urine albumin and serum magnesium was observed

indicating higher proportion of participants with 2+ urine proteins and micro albuminuria who had hypomagnesaemia.

**CONCLUSIONS**

Our study demonstrated a linear relationship between duration of DM and serum magnesium. Participants with hypomagnesaemia had significantly higher FPG, 2-h PPG, blood urea, serum creatinine, TC, LDL, and TG. Participants with microvascular complications had significantly lower serum magnesium. No association between ADA glycaemic control and serum magnesium was observed. Further studies are required to evaluate the pathophysiological role of magnesium in DM and diabetes dyslipidaemia.

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