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EVALUATION OF ASSOCIATION BETWEEN SERUM MAGNESIUM AND MICROALBUMINURIA IN TYPE 2 DIABETES

Biochemistry

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ABSTRACT

Microalbuminuria (MAU) can be interpreted as an early sign of nephropathic changes in the diabetic patients. MAU occurs because of generalized endothelial damage. Mg depletion reduces insulin sensitivity and may increase risk of secondary complications. Hypomagnesaemia may promote endothelial cell dysfunction and thrombogenesis. Because serum Mg and MAU reflect closely related components of the same disease process, a strong relationship between these two variables may be anticipated. We selected 50 patients of Type-2 diabetes mellitus and 50 normal healthy individuals to evaluate the association between serum magnesium and microalbuminuria. Statistical analysis depicted a highly-significant ($p< 0.001$) negative correlation ($r=-0.57$) between serum magnesium and microalbuminuria in type 2 diabetic patients. This data supports the hypothesis that hypomagnesemia may be involved in the pathogenesis of MAU.

INTRODUCTION: Microalbuminuria, an established marker of diabetic nephropathy, begins insidiously and may precede the diagnosis of type 2 DM. [1] Microalbuminuria is thought to be the consequence of generalized endothelial damage along the vascular tree. [2] There is accumulating evidence that the altered metabolism of some micronutrients in diabetes mellitus might have a specific role in the pathogenesis and complications of the disease. Magnesium deficiency is the most evident disturbance of metal metabolism in insulin-dependent diabetes mellitus. Low Magnesium levels may promote endothelial cell dysfunction and thrombogenesis via increased platelet aggregation and vascular calcification. [3]

The development of formula based calculation of estimated glomerular filtration rate (eGFR) has offered a very practical and easy approach for converting serum creatinine value into GFR result; taking into consideration patient's age, sex, ethnicity and weight (depending on equation type). In 2000 Levey et al subsequently published a 4-variables (4-v MDRD) equation that does not require albumin and urea with no impact on accuracy. [4] Both Increased urinary albumin excretion (albuminuria) and reduced GFR are risk factors for progressive kidney failure and cardiovascular disease. [5]

Because serum magnesium and MAU seems to be closely related component of the same disease process, a strong relationship between these variables may be anticipated.

MATERIALS AND METHODS: The present study was a case control cross-sectional study undertaken in the Department of Biochemistry in collaboration with Department of Medicine, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar after getting approval of ethical committee of the college. A total of 100 subjects willing to participate in the study with informed consent were included in the study. This included 50 patients of poorly controlled Type 2 Non Insulin Dependent Diabetes Mellitus (NIDDM) between 40-65 yrs of age, of either sex whose HbA1c was >7% and 50 healthy, age and sex matched controls from the same population but without any disease and without family history of DM.

EXCLUSION CRITERIA: Patients suffering from type-1 DM, patients with acute complications of DM like Diabetic ketoacidosis, history of acute infections, other ailments like gross congestive heart failure, tuberculosis, gout, rheumatoid arthritis and skeletal muscle injury, serum creatinine > 1.5mg/dl, renal failure and those giving positive dip stick test for proteinuria were not be included in the study.

The patients and controls were screened for fasting blood sugar (FBS), lipid profile, serum magnesium and microalbuminuria and the values were compared with that of normal healthy subjects. Serum Magnesium was estimated by Calmagite method. [6] Magnesium combines with Calmagite in an alkaline medium to form a red colored complex the intensity of which is directly proportional to the amount of magnesium present in the sample. Microalbumin in urine was estimated by Nycocard Reader (Diabetes Care 1997) [7] NycoCard U-Albumin is a solid phase, sandwich-format, immunometric assay. GFR was estimated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. [8] FBS was estimated by GOD-POD Method (Trinder 1969) [9]. HbA1C by Nycocard Reader (Jeppson 2002) [10] Total Serum Cholesterol was be estimated by CHOD-PAP Method (Allain C.C. et al 1974) [11] Serum Triglyceride was be estimated by GPO-Trinder Method. (McGowan MW et al 1983) [12] Serum High Density Cholesterol (HDL-C) was estimated by Phosphotungstic Acid Method (Gordon T. Et al 1977) [13] Serum creatinine was estimated jaffes kinetic method (Watchtel et al 1995) [14] and its calibrator has been standardized to ID-MS.

RESULTS: There was no significant effect of age ($p>0.05$) and sex distribution ($p > 0.05$) in the study. TABLE I shows the FBS, HbA1c, total cholesterol, triglyceride and MAU levels were significantly high while Mg and HDL-C were significantly low in cases as compared to the controls.

TABLE I: Comparison of various parameters estimated in patients and controls

Parameters	Cases (Mean ± SD)	Controls (Mean ± SD)	P value
Fasting blood sugar (mg/dl)	194.38 ± 53.60	100.30 ± 12.46	< 0.001
HbA1c (%)	8.758 ± 1.83	5.148 ± 0.51	< 0.001
Total cholesterol (mg/dl)	223.20 ± 45.41	174.46 ± 33.90	< 0.001*
Triglycerides(mg/dl)	224.70 ± 76.77	161.14 ± 32.42	< 0.001*
HDL(mg/dl)	40.48 ± 8.18	55.00 ± 12.04	< 0.001*
Magnesium (mEq/L)	1.09 ± 0.29	2.09 ± 0.29	<0.001*
Albumin in urine (mg/L)	35.36 ± 15.36	18.28 ± 1.47	<0.001*
Serum creatinine (mg/dl)	1.090 ± 0.257	1.051 ± 0.318	= 0.502**
eGFR (ml/mim/1.73 m^2)	68.28 ± 24.83	68.54 ± 31.87	0.201***

*p <0.001- highly significant
**p>0.05 -non significant
***p>0.05- non significant

Table II shows that FBS and HbA1c were significantly correlated with Mg and MAU in type 2 diabetics. Total cholesterol, triglycerides and HDL-C had no significant correlation with Mg and a highly significant correlation with MAU in type 2 diabetic patients.

TABLE II: Correlation of serum Magnesium and MAU in type 2 Diabetes Mellitus with FBS, HbA1c and lipid profile parameters

Parameters	Magnesium (mEq/L))	MAU (mg/L)		
	R	P	R	P
Fasting blood sugar (mg/dl)	-0.541	0.000*	0.47	<0.001*
HbA1c (%)	-0.320	0.024**	0.60	<0.001*
Total cholesterol (mg/dl)	-1.89	0.189***	0.36	<0.01**
Triglycerides(mg/dl)	- 0.011	0.938***	0.48	<0.001*
HDL(mg/dl)	0.176	0.221***	-0.30	<0.033**

*p<0.001- highly significant
**p<0.05 – significant
***p>0.05- non significant

Table III shows that statistical analysis depicted a highly significant negative (r=-0.57; p <0.001) correlation between Mg and microalbuminuria

TABLE III: Correlation between serum magnesium and microalbumin in urine in patients of type 2 diabetes mellitus (cases)

Parameter	Mean ± SD	R	P
Magnesium (mEq/L)	1.09 ± 0.29	-0.47	0.001*
Microalbumin in urine (mg/L)	35.36 ± 15.36		

*p< 0.001 - highly significant

DISCUSSION:

In our study the MAU levels were significantly high in type 2 diabetes mellitus as compared to the controls (p<0.001) and supported by other studies. [15] [16] MAU may occur due to the degradation of the glomerular basement membrane. As a result, there is an increased albumin loss in the urine. [17] A highly significant positive correlation was found between FBS and MAU in our study (p<0.001) and supported by D.A Mutur et al 2010. [17] Hyperglycaemia contributes to the development of endothelial dysfunction in diabetes and ultimately leads to albumin loss. [18] In our study we found a strong positive correlation between MAU and HbA1c (p<0.001) supported by the studies of Padmaja K Rani et al [19] (2011). In diabetes, prolonged hyperglycaemia results in nonenzymatic protein glycation. A series of further complex molecular rearrangements then yield irreversible advanced glycosylated end-products (AGEs). The role of AGEs in diabetic nephropathy has been established. [19] [20] In our study (Table II) we found a significant positive correlation of microalbuminuria with total cholesterol and triglycerides while a significant negative correlation with HDL. It can be argued that MAU may be related to insulin resistance in the prediction of cardiovascular events.

In our study, a highly significant difference in levels of magnesium were found between patients and controls (p<0.001). Similar observations were found in other studies. [21] [22] [23]. Various clinical studies demonstrated that diabetics with hypomagnesemia showed reduced pancreaticβ-cell activity. Insulin receptor autophosphorylation is dependent on intracellular Mg^2+ concentrations, making Mg^2+ a direct factor in the development of insulin resistance. Conversely, insulin is an important regulator of Mg^2+ homeostasis. In the kidney, insulin activates the renal Mg2+ channel melastatin type 6 that determines the final urinary Mg2+ excretion. Consequently, patients with T2DM and hypomagnesemia enter a vicious circle in which hypomagnesemia causes insulin resistance and insulin resistance reduces serum Mg2+ concentrations. [24] [25] [26] Patients with hypomagnesemia show a more rapid disease progression and have an increased risk for diabetes complications. [27] Preventing hypomagnesemia may therefore be considered in the management of the disease. [28] In our study we found a highly significant positive correlation between FBS, HbA1c and Mg. These findings were supported by Sharma A et al (2007) [29], R D Ankush et al (2009) [30] showed a strong positive correlation (p <0.001). In our study, there existed non significant correlation between magnesium and total cholesterol, triglyceride and HDL (Table II) which was supported by Hamid Nasri et al (2008) [31] No significant correlation between magnesium and lipids profile parameter may suggest that magnesium act as an independent marker for cardiovascular risk factor.

In our study, we found a highly significant negative correlation between serum magnesium and microalbuminuria (p<0.001) (TABLE III). This was supported by Khan FA et al 2015. [32] Low Mg levels may promote endothelial cell dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications. [33] Low Mg levels also may lead to the induction of proinflammatory and profibrogenic response reduction of protective enzymes against oxidative stress [34] , induction or augmentation of vasoconstriction and hypertension and stimulation of aldosterone among others. Moreover, because Mg is crucial in DNA synthesis and repair, it is possible that Mg deficiency may interfere with normal cell growth and regulation of apoptosis. [35] Because microalbuminuria is related to endothelial dysfunction and increased oxidative stress, it is not surprising that diabetic atherosclerosis parallels diabetic glomerulosclerosis and is a very powerful risk factor for coronary heart disease and stroke in diabetic persons. [18]

In our study, no significant difference in the values of eGFR in cases and control was found (Table 1). This may be because the increase Microalbuminuria precedes a fall in glomerular filtration rate in patients developing diabetic chronic kidney disease (CKD). [36][37]

CONCLUSION: A significant negative correlation was found between Magnesium and Microalbuminuria (p<0.001). Magnesium might be linked to various micro and macro vascular complications. A better understanding of magnesium metabolism and efforts to minimize hypomagnesemia in routine management of diabetes are warranted.

References:

1. Isomaa B, Almegren P, Tuomi T, Forsen B, Lathi K, Nissen M. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001. 310:356-360.
2. Kaushik Bhowmick, A.V.M. Kutty and H.V. Shetty. Glycemic control modifies the association between microalbuminuria and C-reactive protein in type 2 diabetes mellitus. IJCB 2007. 22(2):53-59.
3. Maier JAM, Malpuech Brugere C, Zunowska W, Rays-siguier Y, Mazur A. Low Mg promotes endothelial cell dysfunction, Implications for Atherosclerosis inflammatory and thrombosis. Biochem Biophys Acta 2004. 1689; 13-21.
4. Waad-AllahS. Et al. Estimated glomerular filtration rate (eGFR): a serum cretainine-based test for the detection of chronic kidney disease and its impact on clinical practice. Oman Mediacl Journal 2012.27(2):108-113.
5. Toshiharu Ninomiya et al. Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes. J Am Soc Nephrol. 2009 Aug; 20(8): 1813–1821.
6. Grindler E. et al. Calmagite method. Clin Chem 1971. 17:662.
7. Microalbuminuria by Nycocard Reader. Diabetes Care 1997. 20(4):516- 519.
8. Levey AS et al Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–254.
9. Trinder, P.Ann. GOD-POD method. Clin BioChem 1969. 6:24.
10. Jeppson JO et.al., Approved IFCC Reference Method for the Measurement of HbA1C in human Blood. Clin Chem Lab Method 2002. 40(1):78-89.
11. Allian C. C. , Poon L, S. , Chan C. S. G. , Richmond W. and Fu P. , Clin. Chem 1974. 20:47. McGowan MW et al. Clin Chem 1983. 6:24-27.
12. Gordon T. et al. Am. J. Med.1977. 62:707.
13. Wachtel et al, Creation and Verification of Reference Intervals. Laboratory Medicine 14. 1995; 26-593-7.
15. Maduka Ignatius C, Neboh Emeka E, Kwubiri Uchenna N. The Prevalence of Diabetic Nephropathy in Diabetic Patients. European Journal of Scientific Research 2009. 26(2):255-259.
16. Krishnamurthy U., Halyal S.S., Jayaprakash Murthy D.S. Serum sialic acid and microalbuminuria in non insulin dependent diabetes mellitus. Biomedical Research 2011. 22(1):31-34.
17. D A Muttur. Analyzing Anthropometry And Metabolic Variables Associated With Microalbumin And C Reactive Protein As Markers Of Early Glomerular Dysfunction Among Mauritian Patients Suffering From Type II Diabetes. The Internet Journal of Laboratory Medicine 2010. 4:219-226.
18. Hadi AR, Hadi Jassim, Al Suwaidi. Endothelial dysfunction in diabetes mellitus. Vascular Health and Risk Management 2007. 3(6):853–876.
19. Padmaja K Rani, Rajiv Raman, Aditi Gupta, Swakshyar S Pal. Albuminuria and Diabetic Retinopathy in Type 2 Diabetes Mellitus Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study. Diabetology & Metabolic 1.

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Syndrome 2011. 3(9):1-8.
20. M. M. Yassin, H. I. Altibi, A. F. Shanti. Clinical and Biochemical Features of Type 2 Diabetic Patients in Gaza Governorate, Gaza Strip. West African Journal of Medicine 2010. 30(1): 51-56.
21. Barbagallo M et al. Serum ionized magnesium in diabetic older persons. Metabolism 2014; 63(4):502-9.
22. Chutia H, Lynrah KG.Association of Serum Magnesium Deficiency with Insulin Resistance in Type 2 Diabetes Mellitus. J Lab Physicians 2015. Jul-Dec; 7(2):75-8.
23. 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.
24. Lima MdeL, Cruz T, Rodrigues LE, et al. Serum and intracellular magnesium deficiency in patients with metabolic syndrome--evidences for its relation to insulin resistance. Diabetes Res Clin Pract 2009.83:257–262.
25. Gunther T.. The biochemical function of Mg^{2}+ in insulin secretion, insulin signal transduction and insulin resistance. Magnes Res 2010. 23(1):5-18.
26. Lisanne M.M. Gommers, Joost G.J. Hoenderop, René J.M. Bindels and Jeroen H.F. de Baaij. Hypomagnesemia in Type 2 Diabetes: A Vicious Circle? Diabetes Jan 2016; 65(1): 3-13.
27. Dasgupta A
, Sharma D, Saikia UK. Hypomagnesemia in type 2 diabetes mellitus. Indian J Endocrinal Metab 2012. Nov;16(6):1000-3
28. Mooren FC
, Kruger K, Volker K, Golf SW, Wadepuhl M, Kraus A. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects - a double-blind, placebo-controlled, randomized trial. Diabetes Obes Metab 2011. Mar; 13(3):281-4.
29. Sharma A
, Dabla S, Agrawal RP, Barjatya H, Kochar DK, Kothari RP. Serum magnesium: an early predictor of course and complications of diabetes mellitus. J Indian Med Assoc 2007. 105(1):16-20.
30. R.D. Ankush, A N Suryakar and NR Ankush. Hypomagnesemia in type 2 diabetes mellitus patients: A study on the status of oxidative and nitrosative stress. IJCB 2009. 24(2):184-189.
31. Hamid Nasri, Hamid Reza. Lipids in association with serum magnesium in diabetes mellitus patients. Bratisl Lek Listy 2008. 109:302-306.
32. Khan FA et al. Comparative Study of Serum Copper, Iron, Magnesium, and Zinc in Type 2 Diabetes Associated Proteinuria. Biol Trace Elem Res 2015. Dec; 168(2):321-9.
33. Pham PC, Pham PM, Pham PA, Pham SV, Pham HV, Miller JM. Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. Clin. Nephrol 2005. 63: 429–436.
34. Voets T, Nilius B, Hoefs S, Kemp AW, Droogmans G, Bindels RJ, Hoenderop JG. TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+ absorption. J Biol Chem2004. 279:19–25.
35. Pham PCT, Pham PMT, Pham SV, Miller JM, Pham PTT. Hypomagnesemia in patients with type-2 diabetes. Clin J Am Soc Nephrol 2007. 2:366-373.
36. Pradeep Kumar Dabla. Renal function in diabetic nephropathy. World J Diabetes 2010 May 15; 1(2): 48-56
37. Prasannakumar M et al. An observational, cross-sectional study to assess the prevalence of chronic kidney disease in type 2 diabetes patients in India (START - India). Indian J Endocrinol Metab. 2015 Jul-Aug;19(4):520-3