Evaluation of Association of Serum Lipid Profile with Serum Magnesium and Microalbuminuria in Type 2 Diabetes

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ABSTRACT

Microalbuminuria (MAU) is considered as an early sign of nephropathic changes in the diabetics. MAU is caused due to generalized endothelial damage. Hypomagnesemia results in reduced insulin sensitivity as well as increased risk of secondary complications. Low levels of Mg may promote endothelial cell dysfunction and risk of thrombogenesis. This study aimed to find any association between serum lipid profile, serum magnesium and microalbuminuria, hypothesizing that early detection and treatment of these parameters can minimize the risk for atherogenic cardiovascular disorder. A total of 100 subjects were selected which included 50 normal healthy individuals and 50 patients of Type-2 diabetes mellitus to interpret the association between lipid profile, serum magnesium and microalbuminuria. Further the statistical analysis depicted a highly-significant negative correlation between serum magnesium and microalbuminuria in type 2 diabetic patients lsupporting the hypothesis that hypomagnesemia may be involved in the pathogenesis of MAU. Microalbuminuria and dyslipidemia were found in patient group but the pathophysiological mechanisms of the association is not well known. The lsignificant correlation between dyslipidemia with microalbumibuira may suggest related pathways for the development of both large and small vessel disease hence categorizing microalbuminuria as a predictor or a possible marker for cardiovascular diseases.

Keywords: Lipid Profile, Microalbuminuria, Magnesium, Nephropathy l

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The worldwide prevalence of diabetes was approximately 2.8% in 2000 and is estimated to grow to 4.4% by 2030.[1] The various complications of diabetes mellitus are: Peripheral neuropathy; Microvascular disease and related abnormalities, which include diabetic nephropathy and diabetic retinopathy; Macrovascular disease with the influence of lipids, which include atherosclerosis, ischemic heart disease and cerebral stroke. The major cause of vascular dysfunction is hyperglycemia. Diabetic patients with poor glycemic control and longer duration of disease are more prone to develop various complications.[2] Injury to the glomerular capillary causes microalbuminuria therefore later may be an indicator of diffuse endothelial dysfunction. Screening of diabetic patients for early nephropathic changes allows better control of progression of nephropathy and cardiovascular events and mortality.[3,4] Magnesium is known to be related to carbohydrate and fat metabolism. Conversion of sugars to ATP (Adenosine triphosphate) in glycolytic cycle requires magnesium as a cofactor. Mg is a cofactor in the glucose transporting mechanisms and various enzymes in carbohydrate oxidation. Magnesium also plays a role in the release and action of insulin. Mg deficiency impairs glucose homeostasis and insulin sensitivity in diabetic patients and results in evolution of complications such as retinopathy, thrombosis and hypertension. Preventing low Mg levels in diabetics may therefore be beneficial in the management of the disease.[5]

A correlation may exist between various complications of diabetes mellitus like microalbuminuria and overt nephropathy, retinopathy, ischemic heart disease, cerebral stroke etc and duration of diabetes and genetic predisposition. The presence of microalbuminuria, which can be detected by a simple, quick and non-invasive test, may be a predictor of vascular complications in patients with diabetes mellitus. Among those with microalbuminuria, ischemic heart disease was more common.[2]

In 2000 Levey et al suggested a 4-variables (4-v MDRD) equation to estimate GFR that does not require albumin and urea with no compromise on accuracy. Taking into consideration patient's age, sex, ethnicity and weight (depending on equation type), 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.[6] Increased urinary albumin excretion (albuminuria) and reduced GFR are risk factors for progressive kidney failure and cardiovascular disease.[7]

We conducted this study to find whether any association exists between serum magnesium, MAU and lipid profile.

MATERIAL AND METHODS

A case control cross-sectional study was conducted done

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by the Department of Biochemistry in collaboration with Department of Medicine, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar with approval of ethical committee of the college. It included 50 cases 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: Selection of subjects were restricted for 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, patients suffering from type-1 DM, serum creatinine > 1.5mg/dl, renal failure and lthose giving positive dip stick test for proteinuria.

Fasting blood sugar (FBS), HbA1C, blood urea, serum creatinine, lipid profile, serum magnesium and microalbuminuria was estimated on the patients and compared with that of normal healthy subjects. Estimation of Serum Magnesium was done by Calmagite method.[8] The principle of this method states that magnesium combines with Calmagite in an alkaline medium and forms a red colored complex. The intensity of the color developed is directly proportional to the amount of magnesium present in the sample. Microalbumin in urine was estimated using Nycocard Reader (Diabetes Care 1997)[9] NycoCard U-Albumin is a solid phase, sandwich-format, immunometric assay. eGFR was estimated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation.[10] lFBS was measured by GOD-POD Method (Trinder 1969).[11] HbA1C by Nycocard Reader (Jeppson 2002)[12] Total Serum Cholesterol was be estimated by CHOD-PAP Method (Allain C.C. et al 1974)[13] Serum Triglyceride was be estimated by GPO-Trinder Method. (McGowan MW et al 1983)[14] Serum High Density Cholesterol (HDL-C) was estimated by Phosphotungstic Acid Method (Gordon T. Et al 1977)[15] Serum creatinine was estimated jaffes kinetic method (Watchtel et al 1995)[16] and its calibrator has been standardized to ID-MS.

RESULTS

Effect of age (p>0.05) and sex distribution (p > 0.05) in the study was non significant. TABLE I compares the FBS, HbA1c, total cholesterol, triglyceride, HDL and MAU levels in cases and controls.

Total cholesterol, triglycerides and HDL-C had no significant correlation with Mg and a highly significant correlation with MAU in type 2 diabetic patients.

There was a highly significant negative (r=-0.57; p <0.001) correlation between Mg and microalbuminuria.

DISCUSSION

Significantly high levels of MAU in type 2 diabetes mellitus when compared to the controls (p<0.001) as seen in present study is supported by other studies.[17],[18] MAU may occur due to the degradation of the glomerular basement membrane. As a result, there is an increased albumin loss in the urine.[19] Highly significant positive correlation between FBS and MAU in was found (p<0.001) and supported by D.A Mutur et al 2010.[19] lAlbumin loss was due to hyperglycaemia which leads to the development of endothelial dysfunction in diabetes[20] A highly significant positive correlation between MAU and HbA1c (p<0.001) is supported by the studies of Padmaja K Rani et al[21] (2011). Prolonged hyperglycaemia in diabetes leads to nonenzymatic glycation of protein. A series of complex molecular rearrangements then forms irreversible advanced glycosylated end-products (AGEs). The role of AGEs in diabetic nephropathy has been established.[21],[22] A (Table II) significant positive correlation of microalbuminuria with total cholesterol and triglycerides however a significant negative correlation with HDL was seen. It is suggested that MAU may be related to insulin resistance in predicting cardiovascular events. Though microalbuminuria is not a direct cause of cardiovascular events but can be a marker for screening those who are at high risk. MAU results due to injury to glomerular capillary hence may be a marker for generalized endothelial dysfunction. Steno hypothesis suggests that albuminuria might indicate a diffuse vascular dysfunction hence albumin and other plasma macromolecules such as low density lipoproteins leakage into the vessel wall leading to inflammatory responses and further start the atherosclerotic process. Early detection allows early intervention and better control of progression of nephropathy and cardiovascular events and mortality. [1]

In this study, patients and controls (p<0.001) presented a highly significant difference in levels of magnesium. Similar observations were found in other studies.[23,24,25]

Parameters	Cases (Mean ± SD)	Controls (Mean ± SD)	P value
Fasting blood sugar	194.38 ± 53.60 (mg/dl)	100.30 ± 12.46 (mg/dl)	< 0.001
HbA1c	8.758 ± 1.83 (%)	5.148 ± 0.51 (%)	< 0.001
Total cholesterol	223.20 ± 45.41(mg/dl)	174.46 ± 33.90 (mg/dl)	< 0.001*
Triglycerides	224.70 ± 76.77 (mg/dl)	161.14 ± 32.42 (mg/dl)	< 0.001*
HDL	40.48 ± 8.18(mg/dl)	55.00 ± 12.04 (mg/dl)	< 0.001*
Magnesium	1.09 ± 0.29 (mEq/L)	2.09 ± 0.29 (mEq/L)	<0.001*
Albumin in urine	35.36 ± 15.36 (mg/L)	18.28 ± 1.47 (mg/L)	<0.001*
Serum creatinine	1.090 ± 0.257 (mg/dl)	1.051 ± 0.318 (mg/dl)	= 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-I: Comparison of various parameters estimated in patients and controls

lSeveral clinical studies have depicted that diabetics with hypomagnesemia have reduced pancreatic β-cell activity. Autophosphorylation of insulin receptor is dependent on intracellular Mg^{2+} concentrations, hence playing a direct role in the development of insulin resistance. On the other hand, insulin is an important regulator of Mg^{2+} homeostasis. In the kidney, insulin activates the renal Mg^{2+} channel melastatin type 6 that determines the final urinary Mg^{2+} excretion. As a result, a vicious circle is created in which hypomagnesemia causes insulin resistance and insulin resistance reduces serum Mg^{2+} concentrations.[26,27,28] Diabetics with hypomagnesemia show a more rapid disease progression and have an increased risk for diabetes complications.[29] Maintaining levels of magnesium (preventing hypomagnesemia) may therefore be considered in the management of the disease.[30] A highly significant positive correlation was seen between FBS, HbA1c and Mg in the present study and lfindings supported by Sharma A et al (2007)[31] and R D Ankush et al (2009).[32] This study depicted a non significant correlation between magnesium and total cholesterol, triglyceride and HDL (Table II) which was supported by Hamid Nasri et al (2008)[33] Absence of any significant correlation between magnesium and lipids profile parameter suggests magnesium being an independent marker for cardiovascular risk factor.

Opposite to this, we found a highly significant negative correlation between serum magnesium and microalbuminuria ($p<0.001$) (TABLE III) which was supported by Khan FA et al 2015.[34] l Hypomagnesemia may promote endothelial cell dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications.[35] Hypomagnesemia may induce proinflammatory and profibrogenic response[36], promote vasoconstriction and hypertension and stimulation of aldosterone among others. In addition to this, Mg being important in DNA synthesis and repair, Mg deficiency may interfere with normal cell growth and regulation of apoptosis.[37] Since microalbuminuria is related to endothelial dysfunction and increased oxidative stress, diabetic atherosclerosis may parallel diabetic glomerulosclerosis and becomes a very powerful risk factor for coronary heart disease and stroke in diabetic persons.[20] l

However, absence of a significant difference in the values of eGFR in cases and control (Table 1) may be justified since microalbuminuria precedes a fall in glomerular filtration rate in patients developing chronic kidney disease.[38,39]

CONCLUSION

Serum Magnesium and microalbuminuria were significantly high in diabetic patients and demonstrated a significant negative correlation ($p<0.001$). Hypomagnesemia might be linked to various micro and macro vascular complications. Detailed understanding of magnesium metabolism and efforts to minimize hypomagnesemia in routine management of diabetes are suggested. Deranged lipid profile was significantly associated with microalbuminuria. Therefore, microalbuminuria may be considered a marker of generalized vascular disease which is related to the formation of atherosclerotic thrombi in arteries. To wind up, in addition to being a marker of incipient diabetic nephropathy, urinary albumin excretion may contribute to development of both large and small vessel disease making microalbuminuria as a possible marker for cardiovascular diseases.

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