

Biochemical Variations of Serum Magnesium with Lipid Analytes in Different Clinical Groups of Type 1 and Type 2 Diabetes Mellitus: A Hospital-based Cross-sectional Study

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ABSTRACT

Objective: Hypomagnesemia associated with dyslipidemia in type 2 diabetes mellitus (T2DM) has been well documented globally by various researchers, as there found a paucity in related data for type 1 diabetes mellitus (T1DM), present observational hospital-based cross-sectional study was planned to estimate, correlate serum magnesium with lipid analytes in different clinical groups of both T1DM and T2DM, and validate its diagnostic significance.

Materials and methods: The study comprised 250 subjects with random inclusion of 200 of both T1DM, T2DM, and 50 normoglycemic healthy controls. Based on medical history and clinical records of 52 T1DM and 148 T2DM clinical cases, they were subgrouped into group I—newly diagnosed, group II—stabilized controlled, and group III—with long course, uncontrolled with associated complications. Biochemical analyses of plasma glucose, serum total magnesium, total cholesterol, and triacylglycerol were analyzed, compared, and correlated statistically with each group and healthy controls.

Results: Comparison and correlations of studied analytes in T1DM and T2DM groups of subgroups with healthy controls, clearly depicted biochemical variations of hypomagnesemia in overt hyperglycemic-hyperlipidemic clinical cases. Hypomagnesemia was inversely correlated with hypertriacylglycerolemia and hypercholesterolemia in hyperglycemic of both T1DM and T2DM with varied statistical significances in different clinical groups with ($p < 0.001$) in group III, ($p < 0.01$) in group I, and ($p > 0.05$) non-significant in group II. However, no statistical significance ($p > 0.05$) for analytes was noted between type 1 and type 2 of all subgroups.

Conclusion: As biochemical variations of hypomagnesemia in overt hyperglycemic-hyperlipidemic type 1 and type 2 clinical cases of diabetes mellitus was depicted and correlated, it is recommended for clinicians to prescribe serum magnesium as a routine investigation of diabetes diagnostic profile for early screening, periodic monitoring, and better management with its supplementation to prevent long-standing critical diabetes complications.

Keywords: Hypercholesterolemia, Hypertriacylglycerolemia, Hypomagnesemia, Type 1 and type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) a chronic, endocrine-metabolic-clinical syndrome characterized by overt hyperglycemia, due to an insufficiency or inefficiency of insulin with increased morbidity and mortality is currently a serious pandemic. The prevalence of type 2 diabetes mellitus (T2DM) is higher than type 1 diabetes mellitus (T1DM).¹ World Health Organization states the prevalence of T2DM has raised dramatically up to 422 million people worldwide in conjunction with an increased westernization of the population's lifestyle in all income levels.² Diabetes mellitus is considered a giant killer disease of the 21st century with the largest number of subjects predicted to be suffered in India, China, and the USA by 2030, where India, is already known as the "Diabetes Capital" of the world.^{3,4}

In DM, the overall metabolism of biomolecules gets deranged along with disturbances in minerals and electrolytes.⁵ Magnesium is a fourth-most-abundant, nutritionally essential macromineral, ingested through common foods of plant and animal origin. It is a free divalent cation of cells deeply and intrinsically woven into cellular metabolism involved with various structural and metabolic functions of the human body. It mainly serves as an inorganic cofactor for most of the enzyme systems that regulate diverse biochemical reactions of carbohydrate, lipid, and protein metabolism for energy production through oxidative

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phosphorylation.⁶ It is indirectly associated with the structural development of bones, DNA, RNA biosynthesis, the antioxidant activity of glutathione, and homeostasis of plasma glucose and blood pressure. Magnesium predominates in the active transport of potassium and calcium ions as a signaling molecule for conduction of nerve impulse, contraction of muscle, and generate normal heart

rhythm. Severe hypomagnesemia frequently causes muscle spasms, associated with anxiety disorders, migraines, osteoporosis, high blood pressure, cardiovascular disease, and infarction. There is a complex interaction between insulin resistance and magnesium. Magnesium is well documented to have an important role in the pathogenesis of diabetes and its complications with derangements in the heart, blood vessels, eyes, kidneys, and nerves.⁷ Regulated magnesium levels have received considerable attention for its potency to improve insulin sensitivity in DM with cardiovascular complications.⁸ Magnesium deficit showed clinical consequences of chronic post-receptor insulin resistance that reduces glucose utilization in cells, aggravating decreased insulin sensitivity in T2DM.⁹ Diabetes mellitus can induce hypomagnesemia, which is a risk factor for its various complications.¹⁰⁻¹³ A negative impact of hypomagnesemia on glucose homeostasis and insulin sensitivity in patients with T2DM was depicted with the evolution of DM complications, such as, arterial atherosclerosis, retinopathy, and nephropathy.^{14,15} Hypomagnesemia in patients with type 2 diabetes was associated with several chronic diseases, such as Alzheimer's disease, hypertension, cardiovascular disease, stroke, migraine headaches, and attention deficit hyperactivity disorder.¹⁶ Myocardial magnesium depletion was interlinked with an influx of Na⁺ and Ca²⁺ into mitochondria that may lead to myocardial cell death and increase the risk of secondary complications.¹⁷

Dyslipidemia a frequent feature of insulin resistance syndrome is another risk factor for pathogenesis in T2DM. Hypomagnesemia has a role in the perturbation of lipid metabolism in DM.¹⁸ It was demonstrated that subjects with hypertension have a marked increase in the prevalence of hypercholesterolemia, DM, hypomagnesemia, and hypertriglyceridemia.¹⁹ A literature search of previous epidemiological studies showed serum magnesium was associated and correlated with various biochemical analytes mostly in T2DM with a paucity of evidence in T1DM. In consideration of all reviewed facts, a present observational, hospital-based cross-sectional study was planned at an Indian government hospital to identify biochemical variations of fasting plasma glucose, serum magnesium, and major lipid analytes serum total cholesterol and triacylglycerol in different clinical groups of both T1DM and T2DM to be compared and correlated with apparently normoglycemic without features of DM as healthy controls.

MATERIALS AND METHODS

The objectives of the present observational hospital-based cross-sectional study were to estimate and correlate serum magnesium with lipid analytes in different clinical groups of both T1DM and T2DM and validate its diagnostic significance. The study was conducted in the department of biochemistry with the collaboration of the medicine department at an Indian government hospital setup. The study comprised a conventional time-bound sample size in 18 months with a total of 250 study subjects. Among these study subjects, there included 200 clinical cases of DM who attended outpatient and inpatient medicine units and 50 normoglycemic healthy controls, by a random sampling technique. The study subjects included both sexes with an age ranged from 10 to 60 years. The study was initiated after an institutional ethical clearance and obtained informed consent from all study participants. Based on inclusion criteria of the study, clinical notes, the clinical state of disease recorded in detailed predesigned patient proforma filled with sociodemographic details, previous medical history of diseases, physical-clinical examinations,

duration, treating drug compliances, clinical and relevant diagnostic records with special reference to DM and its complications, subjects were selected randomly and mainly grouped as T1DM or T2DM and further subgrouped in group I, II, and III. Non-diabetes cases with major comorbid conditions like altered renal, respiratory and gastrointestinal functions, chronic diarrhea, on diuretics, chronic alcoholics were excluded from the study. Fifty subjects healthy volunteers normoglycemic with no features of diabetes and no abnormal clinical findings particularly in the context of metabolic and nutritional derangements were randomly selected as healthy controls to compare and correlate the study findings.

Subgroups Clinical States of Study Subjects

Group I: Newly diagnosed cases of DM not under any treatment.

Group II: Stabilized DM under treatment and control.

Group III: Long course, uncontrolled DM associated with noted complications (recorded from case files as hypertension, microvascular complications, retinopathy, peripheral neuropathy, and foot ulcers).

BLOOD COLLECTION AND BIOCHEMICAL ANALYSIS

Five milliliters of intravenous blood sample were collected in aseptic precautions after an overnight fast by the use of relevant vacutainers from all study subjects. Blood samples were centrifuged at 3000 r.p.m. for 5 minutes. And plasma and serum were separated for biochemical analysis of study analytes. Separated clear serum samples were labeled and stored in a deep freezer in polythene vials before magnesium analysis was carried on atomic absorption spectrophotometer. The fasting plasma glucose levels were estimated by the glucose oxidase peroxidase method. Serum lipid analytes triacylglycerol (TAG) and total cholesterol were measured by specific kit methods. Statistical comparisons between different groups were done with ANOVA and Pearson's correlation co-efficient. Study data were expressed as a percentage, mean \pm SD. The level of statistical significance was taken as $p \leq 0.05$.

RESULTS AND OBSERVATIONS

The present study randomly included 250 study subjects that comprised 200 DM subjects with 108 males and 92 females. The percentage of male diabetes (54%) was higher than the percentage of female DM subjects (46%), which may be due to differences in their lifestyles. Fifty-two (26%) study subjects were of T1DM and 148 (74%) subjects were of T2DM, which truly depicted that T2DM was the most commonly suffered type of diabetes. Fifty healthy controls randomly selected included 29 males (58.62%) and 21 females (41.38%).

"Table 1 shows the sex-wise distribution of DM and control study subjects". All study subjects included were ranged from 10 to 60 years of age with approximate 12% of DM subjects between 10 years and 20 years of age, whereas the highest number of 88 (58%), diabetes patients were of 41 years and 60 years.

"Table 2 shows age and sex-wise distribution of DM study subjects in subgroups". Group I had 50% of newly diagnosed subjects visited the hospital, with no initiation of treatment. Group II comprised 30% subjects diagnosed with DM were on follow-up treatment, clinically stabilized or controlled subjects of DM. Group III constituted 20% of study subjects clinically classified as uncontrolled DM with associated complications.

Table 1: Sex-wise distribution of diabetes mellitus and control study subjects

S. no.	Groups	Total no. of subjects (N = 250)	Percentage
1	Diabetes mellitus subjects (n = 200)		
	Male	108	54.00
	Female	92	46.00
	Type 1 DM	52	26
	Type 2 DM	148	74
	Group I (newly diagnosed diabetes mellitus)	100	50
	Group II (stabilized diabetes mellitus)	60	30
	Group III (diabetes mellitus with a long course, uncontrolled, with associated complications)	40	20
2	Controls—apparently normal non-diabetes mellitus subjects (n = 50)		
	Male	29	58.62
	Female	21	41.38

“Table 3 shows the distribution of study subjects of DM as per types and clinical phases”. The study found hypomagnesemia associated with hyperglycemic and hyperlipidemic conditions in clinical cases of both T1DM and T2DM. Severe overt hyperglycemia, hypertriacylglycerolemia, hypercholesterolemia, and hypomagnesemia were depicted in group III clinical cases categorized as uncontrolled with clinical complications of DM with the highest statistically significant values of $p < 0.001$ when compared with healthy controls. Group I showed a moderate rise in plasma glucose, serum TAG, and cholesterol, and a mild decrease in magnesium with a statistical significance of $p < 0.01$. Group II subjects as newly diagnosed cases showed all estimated analytes within reference ranges and showed no statistically significant variations with $p > 0.05$ when compared with healthy controls.

“Table 4 shows a comparison of biochemical analytes of study subjects in subgroup I, II, and III vs healthy controls”. Statistical insignificance with $p > 0.05$ in on comparison of T1DM subjects with T2DM of each I, II, and III subgroup subjects was noted for all studied analytes.

“Table 5 shows a comparison of biochemical analytes in T1DM and T2DM subjects of group I, II, and III”. Statistical insignificance with $p > 0.05$ was noted for studied subjects of T1DM when compared with T2DM of each I, II, and III subgroup subjects.

“Table 6 shows a correlation of serum magnesium with serum total cholesterol and serum triacylglycerol in group I, II and III subjects of DM”. Pearson’s correlation coefficient obtained for serum magnesium with serum cholesterol and triacylglycerol in newly diagnosed DM subjects of group I showed a negative correlation coefficient $-0.75, p < 0.001$, and -0.1 with $p < 0.001$, respectively. Group II controlled DM subjects reported no correlation with r values $0.02, p > 0.05$ and uncontrolled DM subjects of group III showed a negative correlation with $-0.156, p < 0.01$ and $-0.47, p < 0.01$, respectively. Thus, these study results suggested biochemical varied hypomagnesemia was inversely correlated

with dyslipidemias and overt hyperglycemia in T1DM and T2DM of studied subjects.

DISCUSSION

Present observational hospital-based cross-sectional study design, conducted to evaluate serum magnesium with lipid analytes in different clinical groups of DM of type 1 and type 2, showed biochemical variations of hypomagnesemia, inversely correlated with hyperglycemia, hypertriacylglycerolemia, hypercholesterolemia when compared and correlated with normoglycemic healthy controls. Statistically significant inverse correlations of studied analytes observed with ($p < 0.001$) in group III subjects associated with symptomatic complications, ($p < 0.01$) in group I newly diagnosed non-treated diabetes subjects, and non-significant ($p > 0.05$) in group II clinically stabilized study subjects. However, the study results noted statistical insignificant values for study analytes with $p > 0.05$ when compared for studied subjects of T1DM with T2DM for each subgroup A, B, and C. Thus, the present study identified hypomagnesemia in severe hyperglycemic-hyperlipidemic with similar approaches for all biochemical varied and correlated analytes in both T1DM and T2DM subjects in studied clinical cases. The study results of hypomagnesemia may be linked to the kidney’s osmotic diuresis ability to excrete magnesium during a phase of severe hyperglycemia. Hypomagnesemia depicted paralleled hypomagnesemia in young diabetic subjects in Bangladesh.²⁰ Osmotic diuresis due to overt hyperglycemia excreted out urine magnesium which lowered blood levels of magnesium to cause chronic complications of diabetes, further magnesium supplementation in these patients has been suggested to improve proven hypomagnesemia and its complications.²¹ Present study results were concordant to previous research studies that showed hypomagnesemia frequently present in cases of DM with an inadequate metabolic control in DM. Hypomagnesemia may be directly related to micro- and macrovascular complications that lead to cardiovascular disease, retinopathy, and neuropathy.²² Hypomagnesemia noted in 65% Ethiopians with DM,²³ reported poor glycemic control in hypomagnesemia patients when compared with normomagnesemia patients, and magnesium levels had shown a positive correlation with the severity of diabetes.^{24,25}

Hussain KSA in their case-control study of serum lipid profile and serum magnesium levels in newly diagnosed type 2 diabetes subjects and normal individuals depicted similar results as reported in the present study with low serum magnesium and high TAG and total cholesterol mean levels significantly ($p < 0.001$) in diabetics compared with the controls.²⁶ Poor glycemic regulation affects serum Mg levels in DM, which affects both glycemic regulation and the occurrence of complications.²⁷ Egyptian children study with type 1 diabetes evidenced out hypomagnesemia with poor diabetes control and higher atherogenic lipid parameters and suggested low serum magnesium may be a factor in the pathogenesis of poor glycemic control and abnormal lipid profile.²⁸ Correction of hypomagnesemia in type 1 diabetes children with oral Mg supplements was associated with optimization of glycemic control and reduction of atherogenic lipid fraction with an increase in protective lipid fraction.²⁶ Ramadass with his co-workers pointed out that hypomagnesemia was linked to poor control of DM type 2 and depletion of serum magnesium occurred exponentially with duration of disease. Degree of control of diabetes and magnesium status, studied by Khubchandani and Sanghani reported hypomagnesemia and increased serum

Table 2: Age and Sex-wise distribution of diabetes mellitus study subjects

S. no.	Age group in years	Number of males (N = 108)	Number of females (N = 92)	Total 200	Percentage
1	10–20	13	11	24	12.00
2	21–40	32	28	60	30.00
3	41–60	63	53	116	58.00

Table 3: Distribution of diabetes mellitus study subjects as per types and conditions

S. no.	Group of DM	Number of T1DM	Number of T2DM	Total DM subjects	Percentage
1	Group I newly diagnosed DM	26	74	100	50.00
2	Group II controlled DM	16	44	60	30.00
3	Group III uncontrolled DM with associated complications	10	30	40	20.00
		52	148	200	100

Table 4: Comparison of biochemical analytes of study subjects in subgroup I, II, and III v/s healthy controls

S. no.	Biochemical parameters	Healthy controls (N = 50) Mean ± S.D.	Group I subjects (N = 100) Mean ± S.D.	"p" value	Group II subjects (N = 60) Mean ± S.D.	"p" value	Group III subjects (N = 40) Mean ± S.D.	"p" value
1	Fasting plasma glucose (mg/dL)	92.25 ± 4.39	186.16 ± 17.72	<0.01	100.75 ± 6.10	>0.05	262.00 ± 23.49	<0.001
2	Serum magnesium (mmol/L)	2.002 ± 0.03	1.562 ± 0.03	<0.01	1.976 ± 0.04	>0.05	1.396 ± 0.025	<0.001
3	Serum total cholesterol (mg/dL)	179.0 ± 19.69	248.32 ± 16.66	<0.01	183.73 ± 31.27	>0.05	292.2 ± 12.04	<0.001
4	Serum triacylglycerol (mg/dL)	81.6 ± 21.47	132.9 ± 9.48	<0.01	94.2 ± 18.40	>0.05	210.7 ± 31.72	<0.001

cholesterol and triglyceride levels were responsible for micro- and macrovascular complications in diabetes.^{29,30} Manonmani and Manimekhalai in their study with the south Indian population also reported hypomagnesemia in type 2 DM and an inverse correlation with the duration of diabetes.³¹ Old age, poor glycemic control, and low eGFRcr were significant predictors of low serum magnesium in Nepalese patients of DM.³² Biochemical indicators of low magnesium, high TAG in association with enhanced HbA1c percent could serve as a reliable for insulin sensitivity, and resistance of insulin status and action.³³ Sendhav et al. also depicted a significant inverse correlation with hypomagnesemia and dyslipidemia with raised fasting plasma glucose in DM patients when compared to healthy controls.³⁴ Dineshbabu and Tonk in their recent study concluded hypomagnesemia in T2DM was correlated with various complications and stated magnesium can be considered as a nutritional supplement in patients with diabetes to reduce the incidence of vascular complications.³⁵ Subjects with type 2 diabetes showed a strong relationship with foot ulcers with depleted serum magnesium.³⁶ Duration of diabetic foot ulcers (grade I and II) increased with duration of diabetes increase and serum magnesium decrease.²⁵ Both extracellular and intracellular chronic latent magnesium deficiency in overt clinical hypomagnesemia was frequently associated with T2DM especially in those with poorly controlled glycemic profiles.⁹ A recently published systematic review and meta-analysis by Rodrigues et al. fairly depicted an association between reduced levels of magnesium and poor glycemic control in patients with T1DM.³⁷ Previous studies depicted further depletion of magnesium decreased atherogenic lipid fractions and reduced insulin-stimulated glucose uptake,

considered as a hidden link between the pathogenesis of diabetes and its complications. Early recognition of dysregulated magnesium metabolism with correction of an electrolyte imbalance could be crucial in the prevention of diabetic complications. Glucokinase, potassium-ATP channels, L-type Ca²⁺ channels in pancreatic β-cells for preceding insulin secretion are regulated by intracellular Mg²⁺, moreover, intracellular Mg²⁺ concentrations make Mg²⁺ a direct factor in the development of insulin resistance linked with insulin receptor autophosphorylation.³⁸ A study showed decreased serum total cholesterol, serum low-density lipoprotein (LDL)-cholesterol, and apolipoprotein B through acute and chronic Mg supplementation. Oral MgO supplementation decreased insulin-stimulated glucose uptake by 35% after 24 weeks, food ingestion is rich in magnesium corrected low levels of magnesium with reduction of DM complications.^{39–41} Uncertainty was associated in the measurement of serum total magnesium concentration and depiction of extracellular Mg deficiency in patients with arrhythmia and DM, Mg deficiency in patients with essential hypertension was not supported by intracellular accumulation of Mg.^{42,43} Song with his co-workers reported oral magnesium supplementation for 4–16 weeks effectively reduced fasting plasma glucose and raised HDL cholesterol in patients with type 2 diabetes, however, long-term benefits and safety of magnesium treatment on glycemic control could not be determined.⁴⁴ The limitation of the present study is an estimation of total extracellular magnesium alone without knowledge of intracellular and extracellular free ionized physiological magnesium levels, to get a holistic magnesium metabolic approach, which had the challenge to correlate its deficiency as a bidirectional association between dyslipidemia in



Table 5: Comparison of biochemical analytes in T1DM and T2DM Subjects of groups I, II, and III

S. no.	Biochemical analytes	Subgroup I		Subgroup II		Subgroup III	
		T1DM (N = 52) Mean ± S.D.	T2DM (N = 148) Mean ± S.D.	T1DM (N = 52) Mean ± S.D.	T2DM (N = 148) Mean ± S.D.	T1DM (N = 52) Mean ± S.D.	T2DM (N = 148) Mean ± S.D.
1	Fasting plasma glucose (mg/dL)	191.9 ± 14.1	184.0 ± 18.9	88.5 ± 22.0	93.50 ± 16.3	264.4 ± 28.5	259.6 ± 16.6
2	Serum magnesium (mmol/L)	1.57 ± 0.02	1.57 ± 0.02	1.95 ± 0.04	1.94 ± 0.03	1.39 ± 0.03	1.39 ± 0.02
3	Serum total cholesterol (mg/dL)	251.4 ± 19.8	249.8 ± 15.79	97.2 ± 5.7	100.7 ± 6.13	2.96 ± 13.5	288.8 ± 9.3
4	Serum triacylglycerol (mg/dL)	130.3 ± 9.94	129.7 ± 9.97	169.1 ± 32.2	176.14 ± 23.4	213.4 ± 37.17	208.0 ± 24.82
				<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05
				<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05	<i>p</i> > 0.05

Table 6: Correlation of serum magnesium with serum total cholesterol and serum triacylglycerol in group I, II, and III subjects of diabetes mellitus

Biochemical parameters	Group I n = 100	Group II n = 60	Group III n = 40
Correlation	Correlation coefficient	Correlation coefficient	Correlation coefficient
Serum magnesium with	-0.75	0.02	-0.156
Serum total cholesterol	<i>p</i> < 0.001	<i>p</i> > 0.05	<i>p</i> < 0.01
Serum magnesium with serum triacylglycerol	-0.1	0.01	-0.47
	<i>p</i> < 0.001	<i>p</i> > 0.05	<i>p</i> < 0.01

clinical conditions and complications of T1DM and T2DM. Based on biochemical varied study data, compared and correlated in conjunction with previous research studies, estimation of serum magnesium along with lipid profile to be included as an initial diagnostic protocol for both T1DM and T2DM and advice for dietary supplementation of magnesium may prevent its deficiency and have a reductionist approach toward its complications as an anti-diabetic treatment protocol.

CONCLUSION

The present study depicted biochemical variations of hypomagnesemia in an overt hyperglycemic-hyperlipidemic studied clinical groups of both T1DM and T2DM. In conjunction with reviewed research findings, it is suggested to prescribe estimation of serum magnesium as a routine or extended diagnostic profile investigation in known clinical cases of both T1DM and T2DM for early screening, periodic monitoring for its deficiency, and better management of clinical cases through its supplementation to prevent the development of long-standing critical diabetes complications. Prospects might remain to conduct population-based prospective cohort studies for clarification of facts and obtain a holistic approach with both extracellular, intracellular, total, and ionized magnesium concentrations in different types, clinical states, and complications of DM.

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