Serum Zinc and Magnesium Levels in Type 2 Diabetes Mellitus Patients on Metformin Therapy

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Abstract: In diabetes mellitus, the deficiency of trace elements is said to be linked to poor glycemic control and oxidative stress related complications. The deficiency of magnesium and zinc accelerate the disease and its complications. Our study assessed the correlation of serum magnesium and zinc levels with glycemic control in type 2 diabetes patients. Methods: This cross sectional study included 150 study participants. 76 type 2 diabetes patients were cases and 74 healthy participants were grouped to controls. Samples for fasting and postprandial blood glucose, HbA1c, magnesium and zinc were collected and analysed in a fully automated analyser. Data was analysed by Graph Pad Prism software. Results: Cases had higher levels of fasting, postprandial, HbA1c levels as compared to controls with p<0.0001. Cases had significant reduction in serum levels of zinc and magnesium. Zinc and magnesium showed a significant inverse correlation with glycemic control with r values of -0.56 and -0.48 respectively. Conclusion: Low serum magnesium and zinc levels can worsen the complications of disease. So, early detection of its deficiency and supplementation alleviates the disease progression.

Keywords: Diabetes mellitus, zinc, magnesium, glycemic status, oxidative stress

1. INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disease causing death of 1 in 20 individuals. [1] The prevalence of DM is predicted to globally hit 366 million in 2030 with a maximum increase in developing countries like India. [2] Type 2 DM (T2DM), most commonly prevalent ~90–95% is usually associated with predominant insulin resistance, relative insulin deficiency, and a poor insulin secretion. [3] In past decades, it has become apparent that deficiencies of trace elements are commonly associated with T2DM. [4–6]

Magnesium, a divalent cation is one among the common micro mineral deficiency established in DM. [7,8] Decreased serum magnesium levels and increased urinary magnesium losses have been recognized in both type 1 and type 2 DM. Decreased dietary magnesium intake has been associated with increased incidence of T2DM. [9] Hypomagnesaemia and hypermagnesuria was reported to be associated with diabetes complications. [7,10,11] Thus, magnesium has drawn considerable attention for its potential role in improving insulin sensitivity and preventing DM.

Zinc, another important trace element, acting as a cofactor for several biochemical processes has a major role in health status. [12] There is substantiating evidence indicating the importance of zinc in DM. Impaired zinc metabolism, decreased plasma zinc and hyperzincuria has been reported as a consequential effect of glucose absorption. [13,14] Few studies have revealed that zinc supplementation assist in control of glycemic status, correlating with significant decrease in fasting glucose and glycated haemoglobin. [15,16]

Treatment of T2DM targets on alleviating hyperglycaemia with balanced health status as well as minimising co morbid complications. Based on the mode of action, safety aspect and tolerability, drugs that act by augmenting insulin secretion, decreasing hepatic glucose production, postponing digestion and absorption of carbohydrate and improving insulin action are being recommended. [17] Amongst many agents, Metformin, a biguanide derivative, is the first line of choice of hypoglycaemic agent that acts by reducing hepatic glucose production with minimal side effects. [18,19] It has been commonly prescribed along with diet and exercise and combination therapies in irregular glycemic control. Recently, it has been shown that even metformin monotherapy is equivalent to metformin combination therapies. [20] Pleiotropic properties of metformin have several beneficial actions like cardiovascular protection, preventing obesity related inflammation, treating fertility and therefore, widely prescribed for various therapies. [21,22]

In India, the T2DM population is exploding exponentially and assessment of mineral status in patients with hypoglycaemic treatment has not been done during the glycemic management. Hence, this study was taken up to assess the association of serum Zinc and Magnesium level with different glycemic status in T2DM patients who were on metformin monotherapy.

2. Materials and Methods

This cross sectional study included 150 participants who attended the outpatient department of Medicine, Sri Venkateshwaraa Medical College Hospital and Research Centre, at a tertiary care hospital in Puducherry. 76 T2DM patients, with age of 35-55 years including both genders were recruited as cases in this study. 74 controls were those volunteer subjects who participated in the health check up in our hospital and found to be healthy apparently.

Inclusion criteria: Patients who received only metformin of 500 mg twice a day were included.

Exclusion criteria: Patients with chronic illness, pregnant women, Type I Diabetes mellitus patients, patients taking supplements, any other oral hypoglycaemic drugs were excluded from the study.

The study was conducted as per the World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects. The Institutional Ethics Committee for Human studies approved the study. After an informed consent, 5 ml of fasting venous blood samples were collected and assessed for blood glucose, HbA1c, zinc and magnesium. Then 2 mL of blood sample was drawn for post prandial blood glucose estimation under aseptic precautions.

3. Laboratory assay

The biochemical parameters – serum glucose was measured by glucose oxidase-peroxidase enzymatic method, HbA_{1c} was measured by immunoturbidimetry method using reagents from Diatek lab and measured by the Diatek analyzer, a compact fully automated clinical chemistry analyzer, produced by Wuxi Hiwell Diatek Instruments. Serum magnesium and zinc were measured colorimetrically using reagents from Tulip diagnostics, India.

4. Statistical analysis

Sample size calculation: Using the formula Z2S2/d2 where Z = 1.96, S = 17.23 and d as 4, the sample size is calculated as 74 [23]. Independent 't' test was used to compare variables between cases and controls. Pearson correlation analysis was used to correlate between the HbA_{1c} and zinc, magnesium concentration. Data were expressed as mean ± SD. The analysis was done at 5% level of significance and a two-sided $p<0.05$ was considered significant. All the statistical analysis and graphs were performed using Graph Pad Prism 5 [GraphPad Software, Inc., United States of America]

5. Results

This study included 76 diabetics (cases) and 74 non-diabetics (controls). Case group had 58% males and 42% females. Controls had 59% of males and 41% females.

Table 1 shows age and BMI distribution of the study population. The mean duration of the diabetes in the case group is 6.38±3.79 years.

Table 2 shows a comparison of serum biochemical parameters among cases and controls. T2DM patients had significantly higher levels of fasting, postprandial, HbA1c levels as compared to non- diabetics ($p<0.0001$). Zinc and magnesium was significantly reduced in diabetics with p value <0.0001. Amongst cases, zinc and magnesium showed a significant inverse correlation with HbA1c with r = -0.56 and r = -0.48 respectively as given in figure 1 &2.

The Cases were divided into 3 groups based on their glycemic status. Group 1 included patients with HbA1c < 6%; group 2 with HbA1c 6-8% and group 3 with HbA1c >8%. Mean zinc and magnesium value decreases with increase in HbA1c with a significant p value <0.0001.(Table 3)

Table 4 summarizes the correlation of HbA1c with zinc and magnesium levels among diabetics, where group 2 and group 3 with HbA1c of 6-8 % and >8% showed significant inverse correlation with serum magnesium and zinc levels, while group 1 showed non-significant inverse correlation. (Figure 3 &4)

6. Discussion

Zinc and magnesium are important trace elements that play vital roles in several biochemical functions. [12, 24, 25] In diabetes, these minerals attract importance due to its association with insulin sensitivity, insulin secretion and blood glucose regulation. [7,9,15, 26, 27]

In this study of 150 subjects, 76 DM patients on metformin treatment and 74 non diabetic controls were assessed for serum zinc and magnesium. Among the 76 patients, 20% were in good control, 47% had moderate control and 33% had poor control. This is in harmony with previous study having high HbA1c levels in T2DM [28, 29]. Present study's mean zinc concentration of 93.2 µg/mL in diabetes is in agreement with several other studies. [12, 16, 23, 30] Similarly, Williams et al showed 17% reduction in zinc concentration in diabetes. [31] Low zinc concentration is associated with oxidative stress related complications in diabetes. [32]

Diabetics had lower serum magnesium in our study than controls which is in association with Arpaci et al study where hypomagnesemia was closely associated with poor glycemic status along with microalbuminuria and other complications. [11] Sharma et al showed hypomagnesemia could be an early predictor for poor glycemic status and its associated complications [33]. Hypomagnesemia due to increased urinary loss of magnesium [34] is caused by reduced tubular reabsorption of magnesium. [35] With respect to serum magnesium levels, Kundu et al showed a significant association of hypomagnesemia with diabetic retinopathy patients which suggests hypomagnesemia could be a probable risk factor in the development and progression of diabetic complications [36]. SP et al study also observed a significant decrease in mean serum zinc and magnesium concentration in all diabetics than controls [$p<0.0001$] similar to our study. [37]

We reported a decrease in zinc and magnesium levels with increase in HbA1c levels, as proved by zinc supplementation improves glycemic status and aids in diabetic prevention. [15]

Few studies showed the association of glycemic status with zinc levels as our study. Dasarathan et al showed a significant inverse relationship ($r = -0.54$) of zinc concentration with HbA1c which is parallel to our study ($r = -0.56$). [23] McNair et al and Farooq et al reported that serum zinc levels were inversely related to glycemic status. [38, 39]

Regarding the relationship between metformin therapy and trace element, our study demonstrated a negative relation of magnesium with metformin monotherapy in accordance with Peters et al [40]. Gastrointestinal loss of magnesium in metformin monotherapy was said to contribute to low magnesium levels in T2DM patients [41] and low magnesium levels progress to diabetic related complications like hypertension, dyslipidemia, and retinopathy. While, Study by Ewis et al have demonstrated that there is no alteration in serum magnesium whereas there was an increase in hepatic intracellular magnesium in the diabetic rats after treatment with metformin.[42] Reduction of zinc is due to increased absorption and increased urinary loss in diabetes. [43] But the reduction cannot be attributed to metformin therapy. [44]

7. Limitations of the study

In our study, dietary history was not included. Magnesium and zinc status of the patients receiving other hypoglycemic drugs was not evaluated. Also, Trace element status pre and post treatment was not done.

8. Conclusion

Zinc and magnesium had significant reduction inT2DM patients with a negative correlation with HbA1c. Early detection of trace element status could help us in preventing the complications and improve insulin sensitivity and glucose regulation.

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Table 1: Demographic details of the study participants

	Controls (n=74)	Cases (n=76)	p value
Age (years)	48.73±5.42	49.91±6.56	0.23
BMI (kg/(m^2)	23.02±1.89	25.50±3.41	<0.0001

Table 2: Comparison of the serum biochemical parameters between T2DM and non diabetic controls

Parameters	Controls (n=74)	Cases (n=76)	p value
Fasting blood glucose (mg/dL)	94.86±8.87	134.75±34.57	<0.0001
Postprandial blood glucose (mg/dL)	127.8±7.5	196.4±55.45	<0.0001
HbA1c (%)	5.24± 0.33	7.51±1.73	<0.0001
Zinc (µg/mL)	93.20±14.76	55.37±12.62	<0.0001
Magnesium (mg/dL)	2.9±0.49	2.18±0.53	<0.0001

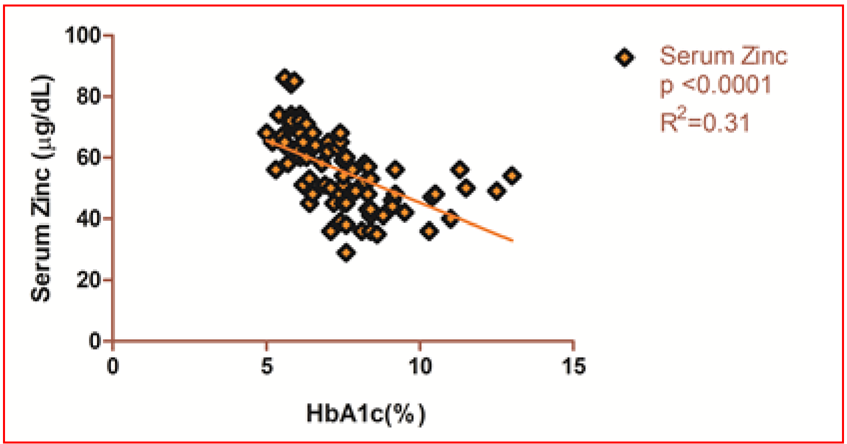

Figure 1 – Correlation of Zinc with HbA1c among all cases

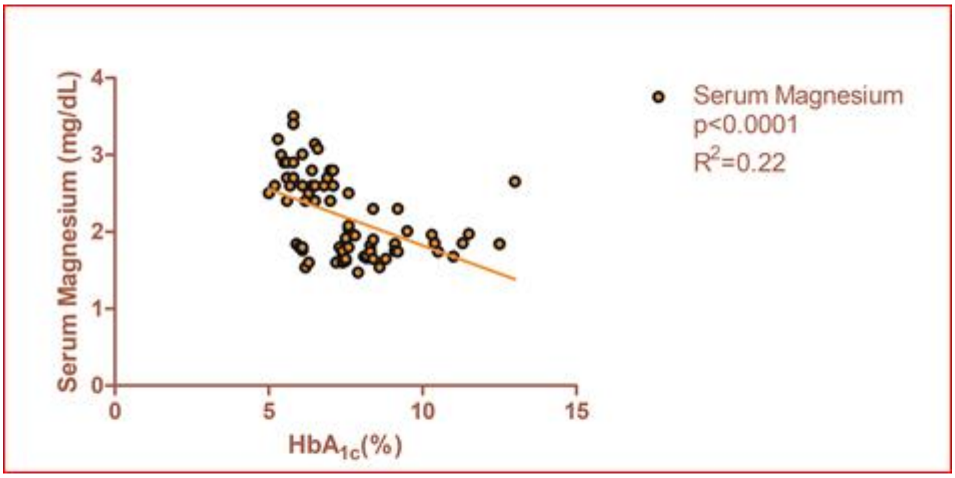

Figure 2- Correlation of Magnesium with HbA1c among all cases

Table 3: Comparison of variables in patients with T2DM on Metformin Therapy based on glycemic status

Parameters	Group 1 (n=15)	Group 2 (n=36)	Group 3(n=25)	p value
BMI (kg/(m^2)	25.59±2.9	26±3.8	24.75±2.45	0.34
Fasting blood glucose (mg/dL)	96.13±8.54	127.90±23	167.8±27.57	<0.0001
Postprandial blood glucose (mg/dL)	138.4±10.62	184.8±31.59	247±54.92	<0.0001
HbA1c (%)	5.6±0.28	6.96±0.58	9.48±1.436	<0.0001
Zinc (μg/mL)	70.01±9.32	55.5±11.03	46.36±7.05	<0.0001
Magnesium(mg/dL)	2.73±0.48	2.18±0.51	1.8±0.25	<0.0001

Table 4: Correlation of HbA1c with zinc and magnesium among groups.

	Group 1 (n=15)		**Group 2 (n=36)**		**Group 3 (n=25)**	
	Correlation coefficient, r	P value	Correlation coefficient, r	P value	Correlation coefficient, r	P value
Zinc (μg/mL)	- 0.31	0.26	-0.47	0.004	-0.48	0.01
Magnesium (mg/dL)	-0.19	0.49	-0.43	0.007	-0.45	0.02

* p < 0.05 – significant; **p < 0.001- highly significant; *** p < 0.0001- extremely significant

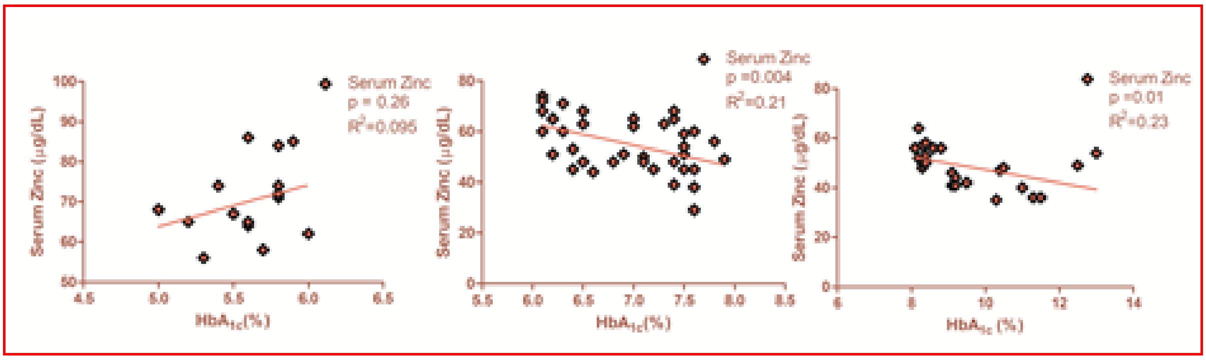

Figure 3 - Correlation of serum Zinc in cases with different glycemic status

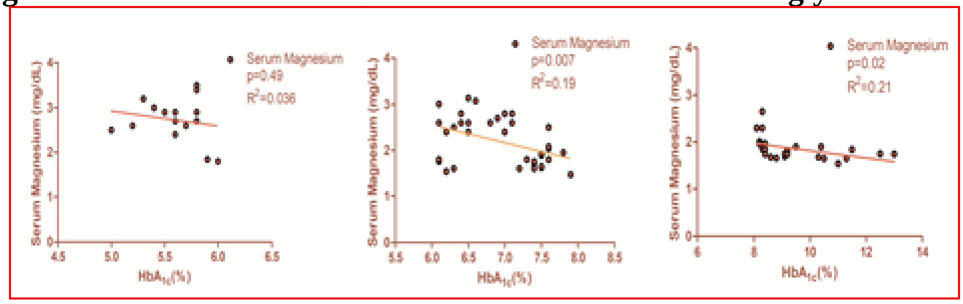

Figure 4 - Correlation of serum magnesium in cases with different glycemic status