

A Medley Correlation of Serum Zinc with Glycemic Parameters in T2DM Patients

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Abstract

Background: Studies in diabetic have reported zinc deficiency due to zincuria. Effective treatment of oral antidiabetic drugs should improve glycemic status correcting serum zinc levels. This study evaluated serum zinc level and its correlation with glycemic parameters in type 2 Diabetes Mellitus (T2DM) patients receiving oral antidiabetics. **Aim:** To study correlation of serum zinc and glycemic parameters in patients receiving oral antidiabetics. **Materials and Methods:** It was a prospective cross sectional pilot study, conducted for 1 year, with the approval of IEC. Patients of T2DM satisfying inclusion/exclusion criteria were enrolled. Serum zinc and glycemic parameters were estimated. The data was stratified into- Group A: Metformin ($n = 20$), Group B: Metformin and glimiperide ($n = 13$). Correlation analysis of serum zinc and glycemic parameters was carried. **Result:** The mean age and duration of 33 patients was 57 ± 9.1 and 6.30 ± 6.52 years respectively. The mean FBG, PPBG, HbA1c and zinc were 164 ± 35 , 257 ± 63 mg/dL, $9.3 \pm 2.2\%$ and 58 ± 23 ug/dL respectively. Thirty patients had HbA1c $>6.5\%$. The percentage of zinc deficiency was 76.92 and 90 in group A and B, respectively. Correlation of serum zinc and glycemic parameters was insignificant in overall group. It varied at different HbA1c levels and in different groups. A positive correlation existed between serum zinc level and HbA1c at $\geq 9.5\%$. **Conclusion:** Zinc deficiency was common in T2DM and to a greater extent in combination group. Correlation of serum zinc levels with glycemic parameters varied at different HbA1c and treatment groups.

Keywords: Diabetes mellitus, glycated hemoglobin, zinc

INTRODUCTION

Trace elements are essential for the normal metabolism of proteins, carbohydrates and lipids. In 1938, Scott and Fisher first reported that pancreatic zinc levels in cadavers of diabetic patients were approximately 50% of those in nondiabetic persons, suggesting an association between zinc and Diabetes mellitus.^[1]

Zinc deficiency occurs in a subset of subjects with T2DM but is not related to diabetes control.^[2] Higher zinc intakes may be associated with a slightly lower risk of T2DM.^[3] It has been reported that oral zinc administration in the diabetic patients may be helpful in wound healing and in the prognosis of the complications of diabetes mellitus.^[4]

An inverse correlation between glycated hemoglobin (HbA1c) and serum zinc levels may be expected in diabetes mellitus. Effective treatment with oral antidiabetic drugs should improve glycemic status, resulting in improved serum zinc levels.

Consequently, diabetic patient receiving oral antidiabetic drugs will show improved glycated hemoglobin as well as serum zinc levels; retaining the aforementioned inverse correlation between glycated hemoglobin and serum zinc levels. Studies involving use of antidiabetic drugs and serum zinc levels are sparse.

The purpose of the present study was to evaluate serum zinc levels and to correlate it with glycemic parameters including HbA1c in T2DM patients receiving oral antidiabetic drugs.

MATERIAL AND METHODS

The present study is a pilot project carried out at tertiary care hospital. All the tenets of Helsinki were followed during

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the study. The study was approved by Institutional Ethics Committee. Patients were enrolled as per following inclusion and exclusion criteria after taking written informed consent.

Inclusion criteria

Patients of T2DM defined as per American diabetes Association, receiving oral antidiabetic drugs for at least one year. In the present institute, T2DM patients were treated with metformin alone or in combination with glimiperide.

Exclusion criteria

Pregnant and lactating women, cigarette smoking and chronic alcoholism, patient complaining of diarrhea, patient on hormonal therapy and/or drugs affecting serum zinc levels (Omeprazole/Proton pump inhibitors, H₂-blockers, Chloroquine), patients with anemia, major systemic illnesses including hemoglobinopathies.

Assay methods

For estimation of laboratory parameters fasting venous blood sample was collected.

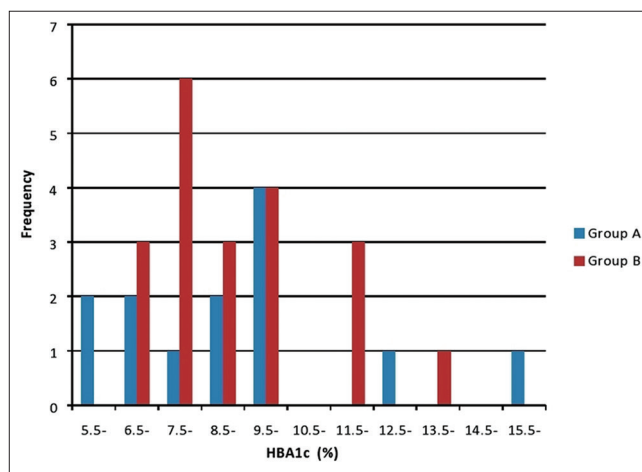
Blood glucose was estimated by Glucose-oxidase and peroxidase method using auto-analyser. HbA1c was measured using High performance liquid chromatography. Serum zinc was measured by Calorimetric method. Normal reference value of serum zinc was 60-70 µg/dL.

DISCUSSION

Previous studies related to zinc and HbA1c have not mentioned use of oral antidiabetic drugs specifically. Metformin and glimiperide alone or in combination are commonly used oral antidiabetic drugs in T2DM patients. The interplay between zinc and oral antidiabetic drugs is less clear. The existing gap in the knowledge of role of zinc and/or its relation with glycemic status in patients taking oral antidiabetic drugs tempted us to study relation between serum zinc levels and glycated hemoglobin in patients receiving oral antidiabetic drugs.

In the present study, the glycemic parameters in the study population were high, indicating poor control of blood sugar levels [Table 1]. It is observed that 93.94% of patients had high HbA1c levels. Maximum number of patients (24.24%, n = 8) had HbA1c between 9.5 and 10.4%. None of the patients receiving combination therapy had normal HbA1c levels [Graph 1].

The mean serum zinc levels were low [Table 1]. The frequency distribution of serum zinc is shown in Graph 2. Maximum number of patients (27.27%) belonged to class interval of 50-. The percentage of patients showing less than normal serum zinc levels was very high (84.85%). The present result is in accordance with previous studies and substantiates the presence of zinc deficiency in T2DM patients. The authors have reported lower mean serum zinc in diabetics as compared to the matched controls. Refaat A *et al.* have compared effect of zinc supplementation on glycemic control in T2DM patients. The authors have reported reduced serum zinc levels in the patients as compared to the control group. The baseline mean serum value of zinc in their study was 68.9 ± 11.9 µg/dL.^[5] Kanchana *et al.* have reported that, the mean serum zinc level in diabetic patients as compared to the control group (nondiabetic) was lesser (69.65 ± 5.6 v/s 86.54 ± 9.3 µg/dL) and the mean HbA1c level was higher in the patients as compared to control group (7.03 ± 0.67 v/s 5 ± 0.29%). As compared to the present study the mean zinc level is higher and mean HbA1c level is lower. This could be because of the patients enrolled in their study were newly diagnosed. The authors have explained the reason for decreased serum zinc in diabetics may be due to impaired absorption, increased urinary excretion due to altered renal function, or genetic factors or during infections in which zinc has a role. The authors have not reported fasting and postprandial blood sugar levels.^[6] B. Jyothirmayi, M. Vasantha have reported mean zinc level of



Graph 1: Frequency distribution of HbA1c

Table 1: Details of patients

Parameter	Overall (n=33)		Group-A (n=13)		Group B (n=20)	
	Mean ± S.D	Range	Mean ± S.D.	Range	Mean ± S.D.	Range
Age (years)	57±9.1	35-77	56±11	35-70	58±8.2	45-77
BMI (kg/m ²)	23±2.8	17.39-33.11	22.69±2.36	17.39-26.84	23.45±3.02	20.69-33.11
Duration of disease (years)	6.30±6.52	1-32	6.27±8.34	1-32	6.33±5.25	1.5-20
FBG (mg/dL)	164±35	88-224	162±44	88-224	166±29	104-220
PPBG (mg/dL)	257±63	116-380	249±73	116-380	262±56	180-380
HbA1c (%)	9.3±2.2	5.9-15.7	9.2±2.8	5.9-15.7	9.3±1.9	6.7-13.8
Serum Zinc (µg/dL)	58±23	36.80-115.8	65±27	36.80-114.2	53±15.51	37.2-115.8

BMI=Body mass index, FBG=Fasting blood glucose, PPBG=Post prandial blood glucose, HbA1c=Glycated hemoglobin

50 ± 12.5 µg/dL and mean HbA1c level 9.5 ± 2.5% in patients with diabetic complications as against those of 95 ± 2.5 and 6.5 ± 1.5 respectively in uncomplicated diabetic patients.^[7] It is observed that the values of zinc and HbA1c in the present study are comparable to those with diabetic patients with complications, though in the present study the patients were not diagnosed of diabetic complications.

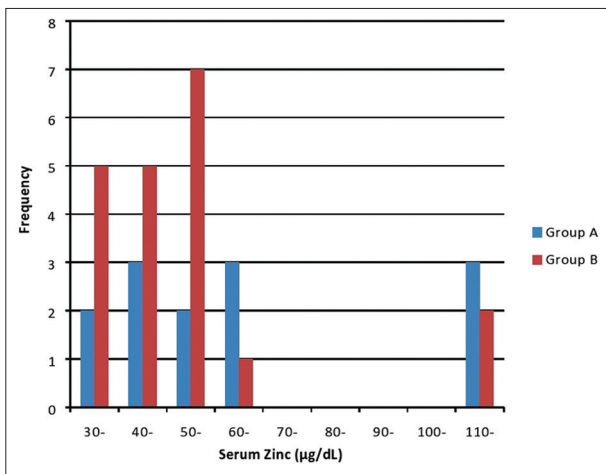
Patients in the present study were receiving either metformin as a monotherapy or combination of metformin and glimiperide. Since both these drugs act by different mechanisms, we stratified the data between two groups accordingly (Group A and Group B, respectively).

The glycemic parameters in the monotherapy and combination groups were comparable. The mean serum zinc levels in the combination group was decreased to a greater extent as compared to the monotherapy group and with a greater percentage of patients showing zinc deficiency

[Table 2 and Graph 2]. Failure to reach the level of significance may be because of less number of patients. Since the groups were comparable with respect to all other parameters, role of antidiabetic drugs in zinc homeostasis needs further studies. However, it can be assumed that the degree of severity of the disease would have been greater in patients who were put on combination therapy. A comparison of different parameters with respect to drug therapy with previous studies was not possible because we could not come across studies related to zinc and HbA1c specifying use of different oral antidiabetic drugs.

The results of correlational analysis of the present study are as follows [Table 3]. Serum zinc level did not show significant correlation with any of the glycemic parameters including HbA1c in overall study population. The mechanism of action of metformin and glimiperide differs. Glimiperide increases release of pancreatic insulin. As aforementioned zinc has physiological role in the insulin homeostasis. Therefore analysis of correlation of zinc with other parameters in both group A and group B discretely was needed. Serum zinc level showed insignificant inverse correlation with glycemic parameters in monotherapy and insignificant positive correlation with HbA1c in combination group [Table 3].

The inverse correlation coefficient between serum zinc and HbA1c was lesser in overall study group as compared to the monotherapy group, despite more number of patients in the former. The correlation coefficient between serum zinc and HbA1c in the combination group though insignificant was showing a positive sign. These two observations together lead us to stratify the data further, based on different HbA1c levels, assuming that the severity of the disease indicated by HbA1c may influence the results [Table 4]. The cut off for HbA1c was arbitrary (allowing about comparable number of patients in each group and was 9.5%). At lower HbA1c (<9.5%), serum zinc level showed insignificant inverse correlation with HbA1c in overall study group. Surprisingly, at higher HbA1c level (≥9.5%) it was observed that a significant positive correlation existed between serum zinc and HbA1c in overall study group. The positive correlation between serum zinc and higher level of HbA1c can be explained on the basis- that in T2DM patients as the severity of the disease advances, poor control of blood sugar may result in enhanced secretion of insulin and pancreatic zinc release, hence the positive correlation between serum zinc and HbA1c. However, in the present study fasting insulin levels were not measured. It is



Graph 2: Frequency distribution of Serum zinc

Table 2: Comparison of mean serum zinc and glycemic parameters between group A and group B

Parameter	Group A (n=13)	Group B (n=20)	P
Age (years)	56.38±10.56	57.65±8.216	0.7019
BMI (kg/m ²)	22.69±2.357	23.45±3.023	0.4538
FBG (mg/dL)	162±12	166±6.4	0.7855
PPBG (mg/dL)	249±20	262±13	0.5735
HbA1c (%)	9.2±0.76	9.3±0.42	0.8140
Serum zinc (µg/dL)	65±7.4	53±4.6	0.0775

Table 3: Correlation of serum zinc with duration of disease and glycemic parameters

Correlation of serum zinc with	Overall (n=33)		Group A (n=13)		Group B (n=20)	
	r	P	r	P	r	P
Duration of disease (years)	-0.085	0.6364	-0.361	0.226	0.276	0.239
FBG (mg/dL)	-0.17	0.3358	-0.22	0.4731	-0.10	0.6703
PPBG (mg/dL)	-0.26	0.1515	-0.22	0.4678	-0.26	0.2736
HbA1c (%)	-0.11	0.5349	-0.21	0.4966	0.018	0.9402

possible that higher Hb1Ac is because of advanced disease which may also involve pancreatic beta cell destruction releasing zinc in blood. These observations are suggestive of complexity of metabolism and derangement of zinc levels in T2DM patients. Ahmed HA *et al.* have reported higher levels of zinc in diabetic patients as compared to nondiabetic controls (132 ± 89.6 v/s 103.7 ± 82.5 $\mu\text{g/dL}$). The authors have explained increased zinc levels in diabetic patients on the basis of oxidative stress leading to destruction of beta cells releasing zinc into blood stream.^[8] A significant positive correlation between serum zinc and PPBG was observed at higher HbA1c levels in monotherapy group [Table 5]. These may be because of enhanced insulin release to cope up with increased PPBG and associated release of zinc in the blood. In combination group at lower HbA1c, the inverse correlation between serum zinc and HbA1c was persistent [Table 6], however at higher HbA1c, the correlation though insignificant was positive. Failure to reach the level significance may be because of less number of patients. The study reported by

Kanchana *et al.* shows negative correlation between serum zinc and HbA1c in diabetic patients. The discrepancy in the results may be because of low level of HbA1c and/or high number of patients in their study as aforementioned.

The above diverse results of the present study are suggestive of intricate role of zinc in diabetes mellitus and medley of its correlation with glycemic parameters particularly with HbA1c at different levels and different treatment groups.

The limitations of the present study are—urine zinc levels and fasting serum insulin levels were not measured. It was a pilot study involving few patients.

SUMMARY AND CONCLUSION

Zinc deficiency was observed in T2DM patients receiving metformin alone and in combination with glimeperide. High mean serum levels of FBG, PPBG, and HbA1c and low mean serum zinc level were observed in the study subjects. The different treatment groups were comparable with respect to glycemic parameters. A high percentage of patients (84.85%) were zinc deficit and mean serum zinc level was much lower in the combination group. Correlational analysis in overall study group revealed insignificant correlation between serum zinc and glycemic parameters. The correlation pattern between zinc and glycemic parameters varied at different levels of HbA1c and in different treatment groups. A positive correlation existed between serum zinc level and HbA1c at higher HbA1c ($\geq 9.5\%$). The observations of the present study are suggestive of complexity of metabolism and derangement of serum zinc levels in T2DM patients.

Recommendations

The study can further be extended by including more number of patients, estimating urinary zinc level and fasting serum insulin levels. The future zinc related studies in T2DM patients needs to consider different cut off levels of HbA1c in the correlation analysis. It can also be suggested that in T2DM patients absence of zinc deficiency based on serum levels without considering HbA1c may be deceptive.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Table 4: Correlation of serum zinc with duration of disease and glycemic parameters in overall at different HbA1c levels (n=33)

Correlation of serum zinc with	HbA1c <9.5 (n=19)		HbA1c \geq 9.5 (n=14)	
	r	P	r	P
Duration of disease (years)	-0.347	0.146	0.132	0.653
FBG (mg/dL)	-0.198	0.415	0.308	0.284
PPBG (mg/dL)	-0.373	0.116	0.251	0.386
HbA1c (%)	-0.248	0.306	0.621	0.018

Table 5: Correlation of serum zinc with duration of disease and glycemic parameters at different HbA1c levels in group A

Correlation of serum zinc with	HbA1c <9.5 (n=7)		HbA1c \geq 9.5 (n=6)	
	r	P	r	P
Duration of disease (years)	-0.392	0.3840	-0.406	0.425
FBG (mg/dL)	0.071	0.879	0.435	0.389
PPBG (mg/dL)	0.000	1.000	0.829	0.042
HbA1c (%)	0.214	0.645	0.600	0.20

Table 6: Correlation of serum zinc with duration of disease and glycemic parameters at different HbA1c levels in group B

Correlation of serum zinc with	HbA1c <9.5 (n=12)		HbA1c \geq 9.5 (n=8)	
	r	P	r	P
Duration of disease (years)	-0.51	0.875	0.441	0.274
FBG (mg/dL)	-0.333	0.291	0.177	0.675
PPBG (mg/dL)	-0.398	0.200	-0.148	0.726
HbA1c (%)	-0.609	0.035	0.519	0.187

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