# A RETROSPECTIVE CASE CONTROL STUDY OF SERUM ZINC (Zn) LEVEL IN DIABETES MELLITUS PATIENTS AND ITS ASSOCIATION WITH COMPLICATIONS OF DM IN THANJAVUR MEDICAL COLLEGE

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**ABSTRACT**

**BACKGROUND**

Zn is an essential trace mineral directly involved in the physiology and action of insulin. Insulin is stored as Zn crystals in the β cells of the pancreas. It has been suggested that abnormal Zn metabolism may play a role in the pathogenesis of diabetes and some of its complications. Zn depletion has several potential clinical implications. It is speculated that Zn repletion could improve insulin sensitivity in patients with DM and reduce the severity of certain complications of this disease. In order to understand the underlying pathobiochemical interrelationships of the late complications of diabetics in more detail, this study was undertaken.

The aim of the study is to-

1. Detect serum zinc level in patients with diabetes mellitus.
2. Compare the serum zinc level in newly-diagnosed diabetic patients and in those with complications.
3. Find out the relationship between zinc deficiency and complications of diabetes.

**MATERIALS AND METHODS**

Study Centre- Thanjavur Medical College and Hospital.
Study Duration- 6 months.
Study Design- Retrospective case control study.
Sample Size- 100 patients (cases) and 50 controls.

**RESULTS**

There was no significant statistical variation in serum zinc levels between the various macrovascular complications. There was a significant negative correlation between HbA1c and serum zinc levels. It was also found in our study that compared to the newly-diagnosed patients with longstanding diabetes mellitus had lower levels of zinc. Also, patients with poor glycaemic control had lower zinc levels compared to the subjects with a better glycaemic control.

**CONCLUSION**

Diabetic individuals have significantly lower levels of zinc when compared to normal healthy individuals. Patients with longstanding DM have lower zinc levels than those who are newly diagnosed. Patients with poor glycaemic control have lower zinc levels compared to the subjects with a better glycaemic control. Zinc supplementation may have a therapeutic role in control and prevention of complications in DM. Further studies are needed to clarify this aspect.

**KEYWORDS**

Diabetes Mellitus, Zinc Level, Complications of Diabetes.

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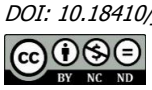

## BACKGROUND

Zinc is an essential trace element necessary for plants,[1] animals and microorganisms. It is "typically, the second most abundant transition metal in organisms" after iron and it is the only metal, which appears in all enzyme classes.[1] There are 2-4 grams of zinc distributed throughout the human body. Most zinc is in the brain, muscle, bones, kidney and liver with the highest concentrations in the prostate and parts of the eye.

**Metabolism of Zinc**

In blood plasma, zinc is bound to and transported by albumin (60%, low-affinity) and transferrin (10%). Since transferrin also transports iron, excessive iron reduces zinc absorption and vice versa. A similar reaction occurs with copper. The concentration of zinc in blood plasma stays relatively constant regardless of zinc intake. Cells in the salivary gland, prostate, immune system and intestine use zinc signaling as a way to communicate with other cells. Zinc maybe held in metallothionein reserves within microorganisms or in the intestines or liver of animals. Metallothionein in intestinal cells is capable of adjusting absorption of zinc by 15-40%. However, inadequate or excessive zinc intake can be harmful. Excess zinc particularly impairs copper absorption because metallothionein absorbs both metals.

**Effects of Diabetes on Zinc Metabolism**

Hypozincaemia maybe the result of hyperzincuria or decreased gastrointestinal absorption of Zn or both in diabetes. It appears the hyperzincuria is a result more of hyperglycaemia than of any specific effect of endogenous or exogenous insulin on the renal tubule. Isbir et al demonstrated a 20% decrease in serum Zn ($p<0.01$) in type I diabetes, apparently the result of hyperzincuria.[2]

El Yazigi et al evaluated both type I and II diabetics and found that the absolute and creatinine corrected urinary excretions were greater in diabetics than in matched controls and found a positive correlation between Zn excretion and HbA1c concentrations.[3]

It has also been postulated that hyperglycaemia interferes with the active transport of Zn back into the renal tubular cells. Administration of insulin reduces, but does not appear to completely ameliorate the hyperzincuria.[4]

McNair et al[5] confirmed that hyperzincuria occurs in relationship to the degree of hyperglycaemia, but not glycosuria. Kinlaw et al[6] demonstrated abnormal Zn tolerance tests in diabetic patients suggestive of decreased absorption.

While it is clear that urinary excretion of Zn is markedly increased in individuals with diabetes, if hyperglycaemia is the primary aetiology, replacement with oral Zn supplementation should provide sufficient treatment.[7]

**MATERIALS AND METHODS**

Study Centre- Thanjavur Medical College and Hospital.
Study Duration- 6 months.
Study Design- Retrospective case control study.
Sample Size- 100 patients (cases) and 50 controls.

**Inclusion Criteria**

1. Patients with newly-diagnosed diabetes mellitus attending diabetology OPD.
2. Patients admitted to the medical wards with complications of diabetes mellitus.
3. Both type 1 and type 2 diabetes mellitus patients were included in the study.

**Exclusion Criteria**

Patients with following diseases were excluded from the study-

1. Infections- Tuberculosis, HIV.
2. Malignancy.
3. Cirrhosis.
4. Inflammatory bowel disease.
5. Pregnancy.
6. Sickle cell disease.

**Data Collection Methods**- Collection of data as per proforma with consent from patients with diabetes mellitus in the Department of Internal Medicine Wards and in Diabetology OPD.

**Selection Criteria**- Diagnostic criteria for diabetes.

Symptoms of diabetes mellitus plus random blood glucose concentration 11.1 mmol/L (200 mg/dL) or fasting plasma glucose 7 mmol/L (126 mg/dL) or HbA1c >6.5% or 2-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test.

Random is defined as without regard to time since the last meal. Fasting is defined as no-caloric intake for at least 8 hrs. The test should be performed in laboratory certified according to A1c standards of the Diabetes Control and Complications Trial. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use. In the absence of unequivocal hyperglycaemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

**Zinc Estimation[8,9]**

**Method- Calorimetric Method**- Principle- Zinc is an alkaline medium reacts with nitro-PAPS to form a purple coloured complex. Intensity of the complex formed is directly proportional to the amount of zinc present in the sample. Normal serum zinc level is 60-120 micrograms/dL. In urine, 100-1000 micrograms/24 hrs.

**Statistical Analysis**- Following statistical methods have been employed in the present study. Independent samples 't' test and One-way Analysis of Variance (ANOVA) has been used to find the significance of the study parameters between cases and controls. All data analysis was performed with SPSS package version 13.0. Microsoft excel and word has been used to generate graphics, tables, etc. The study was approved by ethics committee of the hospital.

**OBSERVATION AND RESULTS**

| Age (Years) | Number of Patients | Percentage |
|---|---|---|
| 10 to 20 | 4 | 4 |
| 21 to 30 | 11 | 11 |
| 31 to 40 | 13 | 13 |
| 41 to 50 | 24 | 24 |
| 51 to 60 | 35 | 35 |
| 61 to 70 | 8 | 8 |
| >70 | 5 | 5 |

***Table 1. Age Incidence***

In the study group of 100 patients with diabetes, 35% were seen in the age group of 51-60 years, 24% were seen in the age group of 41-50 years. Maximum incidence - 35% was seen in the age group of 51-60 years (Table 1).

| Age | Total | | Male | | Female | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| 10 to 20 | 4 | 4 | 3 | 75 | 1 | 25 |
| 21 to 30 | 11 | 11 | 8 | 72 | 3 | 28 |
| 31 to 40 | 13 | 13 | 9 | 69 | 4 | 31 |
| 41 to 50 | 24 | 24 | 17 | 70 | 7 | 30 |
| 51 to 60 | 35 | 35 | 22 | 62 | 13 | 38 |
| 61 to 70 | 8 | 8 | 5 | 62 | 3 | 38 |
| >70 | 5 | 5 | 2 | 40 | 3 | 60 |

***Table 2. Age and Sex Distribution***

In the study group of 100 patients with DM, 66% were males, 34% were females. Male:female ratio - 1.9:1 (Table 2).

| | Total | Male | % | Female | % |
|---|---|---|---|---|---|
| | No. | No. | | No. | |
| Type 1 | 15 | 11 | 73 | 4 | 27 |
| Type 2 | 85 | 55 | 65 | 30 | 35 |

***Table 3. Type of Diabetes***

In the study group of 100 patients with DM, 85% belonged to type 2 DM, of which 65% were males, 35% females. Patients with type 1 DM formed 15%, of which 73% were males, 27% were females (Table 3).

In our study, 34% patients were newly-diagnosed DM, of which 61% were males, 39% were females. 14% patients were diabetics of <5 years duration. 37% had a duration of 5 to 10 years and 15% had diabetes of more than 10 years (Table 4).

| Duration | Total | | Male | | Female | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| New | 34 | 34 | 21 | 61 | 13 | 39 |
| <5 | 14 | 14 | 9 | 64 | 5 | 36 |
| 5-10 yrs. | 37 | 37 | 23 | 62 | 14 | 38 |
| >10 | 15 | 15 | 13 | 86 | 2 | 14 |

***Table 4. Duration of Diabetes***

In our study, most common risk factor was systemic hypertension 26%, followed by obesity (23%), smoking (22%), alcoholism (13%) and dyslipidaemia (11%) (Table 5).

| Risk Factors | Total | Male | | Female | |
|---|---|---|---|---|---|
| | No. | No. | % | No. | % |
| Systemic hypertension | 26 | 19 | 73 | 7 | 27 |
| Dyslipidaemia | 11 | 7 | 64 | 4 | 36 |
| Smoking | 22 | 22 | 100 | 0 | 0 |
| Alcoholism | 13 | 13 | 100 | 0 | 0 |
| Obesity | 23 | 16 | 70 | 7 | 30 |
| **Total** | **95** | **77** | | **18** | |

***Table 5. Risk Factors***

The most common microvascular complication was nephropathy (28%) of patients, followed by retinopathy (22%) of patients (Table 6).

| | Total | Male | | Female | |
|---|---|---|---|---|---|
| | No. | No. | % | No. | % |
| Retinopathy | 22 | 20 | 91 | 2 | 9 |
| Neuropathy | 11 | 9 | 82 | 2 | 18 |
| Nephropathy | 28 | 22 | 79 | 6 | 21 |
| **Total** | **61** | **51** | | **10** | |

***Table 6. Microvascular Complications***

In our study, the most common macrovascular complication was stroke, which was present in 11% patients, followed by coronary artery disease seen in 10% patients (Table 7).

| | Total | Male | | Female | |
|---|---|---|---|---|---|
| | No. | No. | % | No. | % |
| CAD | 10 | 7 | 70 | 3 | 30 |
| CVA | 11 | 9 | 82 | 2 | 18 |
| PAD | 2 | 2 | 100 | 0 | 0 |
| **Total** | **23** | **18** | | **5** | |

***Table 7. Macrovascular complication***

In our study, 84% patients were on treatment with OHA, out of which, 64% were males, 36% were females. 16% patients were getting insulin treatment (Table 8).

| | Total | Male | | Female | |
|---|---|---|---|---|---|
| | No. | No. | % | No. | % |
| Insulin | 16 | 12 | 75 | 4 | 25 |
| OHA | 84 | 54 | 64 | 30 | 36 |
| **Total** | **100** | **66** | | **34** | |

***Table 8. Treatment Regimen***

In our study, 100 patients when compared to 50 controls had significant lower levels of zinc with a p value of <0.0001 (Table 9).

| Parameter | Subject (n=100) | Control (n=50) | P value |
|---|---|---|---|
| Mean age | 47 | 48 | 0.6379 |
| Mean zinc levels | 63.08 | 75.48 | 0.0001 |

***Table 9. Comparison of Serum Zinc Levels between Patients and Control***

In our study, it was found that 47 people had low levels of zinc (<60 micrograms) of which majority (19) belonged to the 61-70 micrograms category. 2 persons had values in the range of 10-20 µg (Table 10).

| Zinc Levels (µg) | Total | Male | | Female | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| 10-20 | 2 | 2 | 100 | 0 | 0 |
| 21-30 | 4 | 4 | 100 | 0 | 0 |
| 31-40 | 8 | 8 | 100 | 0 | 0 |
| 41-50 | 14 | 11 | 78 | 3 | 22 |
| 51-60 | 19 | 12 | 63 | 7 | 37 |
| 61-70 | 27 | 15 | 55 | 12 | 45 |
| 71-80 | 11 | 7 | 63 | 4 | 37 |
| 81-90 | 6 | 2 | 33 | 4 | 67 |
| 91-100 | 4 | 1 | 25 | 3 | 75 |
| 101-110 | 4 | 3 | 75 | 1 | 25 |
| >110 | 1 | 1 | 100 | 0 | 0 |
| **Total** | **100** | **66** | | **34** | |

***Table 10. Serum Zinc Levels in Males and Females***

In our study, patients with microvascular complications, there was no significant variation in serum zinc levels in each groups (retinopathy, nephropathy and neuropathy) with p value of 0.8431. In patients with macrovascular complications also, there was no significant variation in serum zinc level in each groups (CAD, CVA and PAD) with 'p' value of 0.4537 (Table 11).

| Parameter | Microvascular | Macrovascular |
|---|---|---|
| Number of patients | 61 | 23 |
| Mean Zn level (µg) | 46.52 | 43.86 |

***Table 11. Correlation of Zinc Level in Micro and Macrovascular Complications***

In our study, there was a significant relation between serum HbA1c level and zinc levels. Patients with poor glycaemic control had low serum zinc level compared to patients with good glycaemic control, which was statistically significant with 'p' value of <0.0001 (Table 12).

| HbA1c Level | Total Number of Patients | Mean Zinc Level |
|---|---|---|
| 5-5.5 | 2 | 78 |
| 5.6-6 | 36 | 70 |
| 6.1-6.5 | 28 | 64 |
| 6.6-7 | 19 | 52 |
| 7.1-7.5 | 9 | 50 |
| >7.5 | 6 | 46 |

***Table 12. Comparison of Zinc Level and HbA1c Level***

Patients with longstanding diabetes had lower zinc levels than newly-diagnosed patients, which was found to be statistically significant with 'p' value <0.0035 (Table 13).

| Duration | Number of Patients | Serum Mean Zinc Level | |
|---|---|---|---|
| Newly diagnosed | 34 | 69.74 | p value <0.05 |
| 1-4 years | 14 | 69.78 | |
| 5-10 years | 37 | 56.16 | |
| >10 years | 15 | 51.93 | |

***Table 13. Comparison of Serum Zinc Level with Duration of DM***

## DISCUSSION

The total number of patients analysed were 100, out of which 66% were males and 34% were females (Table 2) (Figure 2). The prevalence of diabetes was found to increase as the age advances. Most of the patients in the study group were in the age group of 51-60 years (35%) (Table 1) (Figure 1). 85% of patients had type 2 DM (Table 3) (Figure 3). 26% of patients in our study group had systemic hypertension. Obesity was found in 23% of patients. Other risk factors like smoking (22%), alcohol (13%) and dyslipidaemia (11%) were also present (Table 5) (Figure 5).

Of the 100 patients in the study, 84 were on oral hypoglycaemic agents and the remaining 16 were on insulin therapy (Table 8) (Figure 8). 23% of the subjects had macrovascular complications in the form of CAD (10%), CVA (11%) and PAD (2%) (Table 7) (Figure 7). 61% of the subjects had microvascular complications in the form of nephropathy (28%), retinopathy (22%) and neuropathy (11%) (Table 6) (Figure 6).

Our study showed decreased levels of serum zinc in diabetic individuals compared to normal subjects. The minimum zinc value found in the present study was similarly reported by a number of other studies. It was also found in our study that compared to the newly-diagnosed patients with longstanding diabetes mellitus had lower levels of zinc.

Among the subjects with microvascular complications, 90% with neuropathy, 82% of those with nephropathy, 81% with retinopathy had low serum zinc levels. But, there was no significant statistical variation in serum zinc levels between the various microvascular complications.

Among the subjects with macrovascular complications, 100% with PAD, 90% with CAD and 81% with CVA had lower levels of zinc (Table 11). But, there was no significant statistical variation in serum zinc levels between the various macrovascular complications. There was a significant negative correlation between HbA1c and serum zinc levels (Table 12).

It was also found in our study that compared to the newly-diagnosed patients with longstanding diabetes mellitus had lower levels of zinc (Table 13). Also, patients with poor glycaemic control had lower zinc levels compared to the subjects with a better glycaemic control.

### Limitations of the Study

- Zinc supplementation was not done, hence its effect on the subjects could not be ascertained.
- Urinary and stool zinc levels were not measured.

## CONCLUSION

- Diabetes is more commonly seen in males (66%) compared to females (34%).
- Diabetes is commonly diagnosed in the age group of 51-60 yrs.
- Among those with diabetes, the microvascular complications (61%) occur more often than the macrovascular complications (23%).
- Nephropathy (28%) is the commonest microvascular complication closely followed by retinopathy (22%).
- Diabetic individuals have significantly lower levels of zinc when compared to normal healthy individuals.
- Patients with longstanding DM have lower zinc levels than those who are newly diagnosed.
- Patients with poor glycaemic control have lower zinc levels compared to the subjects with a better glycaemic control.
- Zinc supplementation may have a therapeutic role in control and prevention of complications in DM. Further studies are needed to clarify this aspect.

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