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Original Research Article

# A Study on Relationship between Serum Zinc Levels and Microvascular Complications in Patients with Type 2 Diabetes Mellitus

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**Abstract:**

**Background:** Type 2 Diabetes Mellitus (T2DM) is associated with various microvascular complications, including nephropathy, retinopathy, and neuropathy. This study aimed to investigate the relationship between serum zinc levels and these complications in T2DM patients.

**Methods:** This cross-sectional study included 100 T2DM patients from SVRRGGH, Tirupati, from July 2021 to June 2022. Serum zinc levels and the presence of microvascular complications were assessed. Data were analyzed using descriptive statistics, Chi-square tests, and Pearson correlation coefficient.

**Results:** The mean age of participants was 57.11 years (SD 11.50), and the mean duration of diabetes was 7.92 years (SD 6.101). Diabetic nephropathy was present in 41% of patients, retinopathy in 55%, and neuropathy in 26%. Patients with nephropathy had significantly lower mean serum zinc levels (63.59 µg/dl) compared to those without nephropathy (91.39 µg/dl; p=0.001). Similarly, patients with retinopathy had lower zinc levels (63.91 µg/dl) compared to those without (99.64 µg/dl; p<0.00001), and those with neuropathy had lower levels (57.70 µg/dl) compared to those without (87.82 µg/dl; p=0.001).

**Conclusion:** Lower serum zinc levels are significantly associated with microvascular complications in T2DM patients. Monitoring zinc levels and considering zinc supplementation could be beneficial in managing diabetes-related complications.

**Keywords:** Type 2 Diabetes Mellitus, Serum Zinc, Diabetic Nephropathy, Diabetic Retinopathy, Diabetic Neuropathy, Microvascular Complications.



## Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive pancreatic β-cell dysfunction, resulting in hyperglycemia. It accounts for approximately 90-95% of all diabetes cases worldwide and has reached epidemic proportions, affecting more than 400 million people globally [1]. T2DM is associated with various long-term complications, including both macrovascular and microvascular complications. Microvascular complications, in particular, encompass diabetic retinopathy, nephropathy, and neuropathy, which significantly contribute to morbidity and diminished quality of life in affected individuals [2].

Diabetic retinopathy (DR) is a leading cause of blindness in adults, diabetic nephropathy (DN) is a primary cause of end-stage renal disease, and diabetic neuropathy (DN) leads to significant morbidity due to foot ulcers and amputations [3]. The pathogenesis of these microvascular complications is multifactorial, involving chronic hyperglycemia, advanced glycation end-products (AGEs), oxidative stress, and inflammation [4]. Despite advancements in diabetes management, the burden of these complications remains high, necessitating further exploration into potential preventive and therapeutic strategies.

Micronutrients play a pivotal role in the management of diabetes and its complications. Among them, zinc is an essential trace element involved in numerous biological processes, including enzyme function, protein synthesis, and cellular signaling [5]. Zinc homeostasis is crucial for maintaining insulin storage, secretion, and action. Zinc deficiency has been linked to impaired glucose tolerance and increased oxidative stress, which are key factors in the development and progression of diabetes and its complications [6].

Oxidative stress is a significant contributor to the pathogenesis of microvascular complications in T2DM. Hyperglycemia-induced production of reactive oxygen species (ROS) leads to endothelial

dysfunction, inflammation, and tissue damage [7]. Zinc possesses antioxidant properties and plays a critical role in the activity of superoxide dismutase (SOD), an enzyme that mitigates oxidative stress by dismutating superoxide radicals into oxygen and hydrogen peroxide [8]. Several studies have demonstrated an inverse relationship between serum zinc levels and markers of oxidative stress in diabetic patients, suggesting a protective role of zinc against oxidative damage [9].

Inflammation is another crucial factor in the development of diabetic microvascular complications. Chronic hyperglycemia promotes the activation of inflammatory pathways, leading to increased production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [10]. Zinc modulates the immune response and exerts anti-inflammatory effects by inhibiting the activation of nuclear factor-kappa B (NF-κB), a key transcription factor involved in the inflammatory process [11]. Research indicates that zinc supplementation can reduce inflammation and improve clinical outcomes in patients with T2DM [12].

Emerging evidence suggests a potential link between serum zinc levels and the risk of developing microvascular complications in T2DM. Several observational studies have reported lower serum zinc concentrations in diabetic patients with retinopathy, nephropathy, and neuropathy compared to those without these complications [13]. Moreover, interventional studies have shown that zinc supplementation can improve glycemic control and reduce the incidence of microvascular complications in diabetic patients [14].

However, the relationship between serum zinc levels and microvascular complications in T2DM is not fully understood, and conflicting results have been reported. Some studies have found no significant association between zinc status and the risk of diabetic complications, indicating the need for further research to clarify this relationship [15]. Understanding the role of zinc in the pathogenesis of diabetic microvascular complications could provide valuable insights into potential therapeutic interventions aimed at reducing the burden of these complications in diabetic patients.

Understanding the relationship between serum zinc levels and microvascular complications in T2DM could have significant clinical implications. If a strong association is established, serum zinc levels could be used as a biomarker for identifying patients at high risk for developing microvascular complications. Furthermore, zinc supplementation could be explored as a potential therapeutic strategy to prevent or mitigate the progression of these complications in diabetic patients.

T2DM is a global health challenge with a high prevalence of microvascular complications that significantly impact patients' quality of life. Zinc, an essential trace element, has been implicated in various biological processes that may influence the development and progression of diabetic microvascular complications. This study seeks to elucidate the relationship between serum zinc levels and microvascular complications in T2DM, providing insights that could inform future preventive and therapeutic strategies.

**Aim**

The aim of this study was to investigate the relationship between serum zinc levels and microvascular complications in patients with type 2 diabetes mellitus.

**Objectives**

The objectives of the study were to document the microvascular complications in patients with type 2 diabetes mellitus, estimate serum zinc levels in patients with type 2 diabetes mellitus who have microvascular complications, and assess the relationship between these complications and serum zinc levels.

**Materials and Methods**

This was a hospital-based, analytical observational cross-sectional study conducted over a specified period at the Department of General Medicine, SVRRGGH, Tirupati. The study population comprised patients with type 2 diabetes mellitus who presented to the outpatient department or were admitted to the Department of General Medicine at SVRRGGH, Tirupati, and who met the inclusion and exclusion criteria. The sample size for the study was 100 patients.

Patients included in the study were those diagnosed with type 2 diabetes mellitus and who provided written informed consent to participate. Exclusion criteria for the study included patients with chronic renal failure, liver disease, chronic diarrhea, those undergoing chemotherapy, patients receiving zinc supplements, individuals with a history of alcohol abuse, critically ill patients, hypertensive patients, and those with coronary artery disease.

Patients who met the inclusion criteria were enrolled in the study after providing written informed consent. A detailed history was taken, and a physical examination was performed for all participants according to a pre-fixed proforma. Each patient was subjected to various investigations, including fasting blood glucose (FBS), postprandial blood glucose (PPBS) measured two hours after a standard meal, serum zinc levels, urine routine examination, spot urine protein-creatinine ratio, renal function tests (RFT), fundoscopy, electrocardiography (ECG), and abdominal ultrasound (USG).

All patients with type 2 diabetes mellitus were screened for microvascular complications such as retinopathy, nephropathy, and neuropathy. The

presence and severity of retinopathy were documented using fundoscopy. Nephropathy was identified using urine routine examination and the spot urinary protein-creatinine ratio. Patients were screened for neuropathy through a detailed nervous system examination, focusing particularly on fine touch, vibration, joint position, and position sense. Selected patients with suspected neuropathy underwent nerve conduction studies when necessary.

Serum zinc levels were measured for all study subjects, and the relationship between these levels and the presence of microvascular complications was assessed. Zinc levels were analyzed using a fully automatic biochemistry system, specifically the biosystems A25 machine. The method employed for zinc analysis was based on zinc bromo-PAPS, with color-dependent spectrophotometry as the underlying principle. The normal range for serum zinc was established as 80-120 mcg/dl.

During the study, diabetic retinopathy was classified into four stages: mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR). Mild NPDR was characterized by the presence of at least one microaneurysm (MA) but no other findings, requiring close inspection and monitoring. Moderate NPDR included hemorrhages or MAs in one to three retinal quadrants and/or cotton wool spots, hard exudates, or venous beading. Severe NPDR was identified by the presence of intraretinal hemorrhages (>20 in each quadrant), venous beading in two or more quadrants, or intraretinal microvascular abnormalities (IRMA) in one or more quadrants, following the 4:2:1 rule in the absence of neovascularization. Proliferative diabetic retinopathy (PDR) was diagnosed in patients whose NPDR had progressed, exhibiting either neovascularization of the disc or elsewhere, or vitreous or preretinal hemorrhage.

This study aimed to establish a comprehensive understanding of the relationship between serum zinc levels and microvascular complications in patients with type 2 diabetes mellitus, through meticulous documentation, investigation, and analysis.

## Observation and Results

The study was conducted on 100 patients with Type 2 Diabetes Mellitus who visited the outpatient department or were admitted to the Department of General Medicine at SVRRGGH, Tirupati, from July 2021 to June 2022. These patients met the inclusion and exclusion criteria outlined in the study protocol. The observations made in this study are discussed below.

The collected data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). Descriptive statistics, frequency analysis, and percentage analysis were used for categorical variables, while the mean and standard deviation (SD) were used for continuous variables. To find the significant relationship between the variables, the Chi-square test and Pearson correlation coefficient were employed. A probability value (p-value) of less than 0.05 was considered statistically significant.

### Descriptive Statistics

The mean age of the study population was 57.11 years with a standard deviation of 11.50. The mean duration of diabetes among the study participants was 7.92 years with a standard deviation of 6.101.

### Age Distribution

The age distribution showed that 55% of the patients were in the age group of 50-70 years, 33% were in the age group of 30-50 years, and 12% were over 70 years of age. This distribution indicates that the majority of the patients were middle-aged or elderly.

### Sex Distribution

In terms of sex distribution, the study population comprised 55% females and 45% males, indicating a predominance of female patients.

### Duration of Diabetes Mellitus

Regarding the duration of diabetes, 41% of the patients had been diabetic for less than 5 years, 38% for 5-10 years, and 21% for more than 10 years. This shows a significant number of patients had long-standing diabetes.

### Fundus Examination and Diabetic Retinopathy

On fundoscopic examination, 45% of the patients had normal findings, while 25% had mild non-proliferative diabetic retinopathy (NPDR), 27% had moderate NPDR, and 3% had severe NPDR. Among the study population, 55% of the patients were diagnosed with diabetic retinopathy, indicating a high prevalence of this complication in the cohort.

### Diabetic Nephropathy and Neuropathy

In the study population, 41% of the patients were found to have diabetic nephropathy, and nerve conduction studies revealed that 26% of the patients had impaired nerve conduction, indicating diabetic neuropathy.

Correlation of Serum Zinc with Microvascular Complications

The relationship between serum zinc levels and microvascular complications was assessed. The mean serum zinc levels in patients with diabetic nephropathy were 63.59 µg/dl, while those without nephropathy had mean serum zinc levels of 91.39 µg/dl. This difference was statistically significant with a T score of 3.433 and a p-value of 0.001, indicating a significant association between low serum zinc levels and the presence of diabetic nephropathy.

Similarly, the mean serum zinc levels in patients with diabetic retinopathy were 63.91 µg/dl,

compared to 99.64 µg/dl in those without retinopathy, with a T score of 4.661 and a p-value of less than 0.00001, indicating a significant association between low serum zinc levels and the presence of diabetic retinopathy.

The mean serum zinc levels in patients with diabetic neuropathy were 57.70 µg/dl, compared to 87.82 µg/dl in those without neuropathy, with a T score of 3.304 and a p-value of 0.001, indicating a significant association between low serum zinc levels and the presence of diabetic neuropathy.

There was no significant difference in serum zinc levels between male and female patients, with mean levels of 81.00 µg/dl and 78.74 µg/dl, respectively, and a p-value of 0.959, indicating that sex did not significantly affect serum zinc levels.

**One Way ANOVA Test:** A one-way ANOVA test was conducted to compare serum zinc levels across different age groups and fundus examination findings. The mean serum zinc levels in patients aged 30-50 years, 50-70 years, and over 70 years were 69.00 µg/dl, 91.04 µg/dl, and 59.56 µg/dl, respectively. This difference was statistically significant with an F value of 4.810 and a p-value of 0.010.

In terms of fundus examination findings, the mean serum zinc levels in patients with normal fundus, mild NPDR, moderate NPDR, and severe NPDR were 99.64 µg/dl, 66.58 µg/dl, 63.74 µg/dl, and 43.21 µg/dl, respectively. This difference was also statistically significant with an F value of 7.501 and a p-value of less than 0.000001.

**Key Tables**

**Table 1: Descriptive Statistics of Age and Duration of Diabetes**

| Statistic | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Age (years) | 100 | 32 | 85 | 57.11 | 11.50 |
| Duration (years) | 100 | 0 | 30 | 7.92 | 6.101 |

**Table 2: Fundus Examination**

| Fundus Examination | Frequency | Percent |
|---|---|---|
| Normal | 45 | 45.0 |
| Mild NPDR | 25 | 25.0 |
| Moderate NPDR | 27 | 27.0 |
| Severe NPDR | 3 | 3.0 |
| Total | 100 | 100.0 |

**Table 3: Diabetic Retinopathy**

| Diabetic Retinopathy | Frequency | Percent |
|---|---|---|
| Absent | 45 | 45.0 |
| Present | 55 | 55.0 |
| Total | 100 | 100.0 |

**Table 4: Correlation of Serum Zinc with Diabetic Nephropathy**

| Diabetic Nephropathy | N | Mean Zinc (µg/dl) | Std. Deviation | Std. Error Mean | T Score | P value |
|---|---|---|---|---|---|---|
| Absent | 59 | 91.39 | 39.13 | 5.09 | 3.433 | 0.001 |
| Present | 41 | 63.59 | 40.81 | 6.37 | | |

**Table 5: Correlation of Serum Zinc with Diabetic Retinopathy**

| Diabetic Retinopathy | N | Mean Zinc (µg/dl) | Std. Deviation | Std. Error Mean | T Score | P value |
|---|---|---|---|---|---|---|
| Absent | 45 | 99.64 | 50.39 | 7.51 | 4.661 | <0.00001 |
| Present | 55 | 63.91 | 23.88 | 3.22 | | |

**Table 6: Correlation of Serum Zinc with Diabetic Neuropathy**

| Diabetic Neuropathy | N | Mean Zinc (µg/dl) | Std. Deviation | Std. Error Mean | T Score | P value |
|---|---|---|---|---|---|---|
| Normal | 74 | 87.82 | 44.95 | 5.22 | 3.304 | 0.001 |
| Impaired | 26 | 57.70 | 19.18 | 3.76 | | |

**Table 7: One Way ANOVA Test Descriptives of Serum Zinc by Age Group**

| Age Group (years) | N | Mean Zinc (µg/dl) | Std. Deviation | Std. Error | 95% Confidence Interval for Mean | Minimum | Maximum |
|---|---|---|---|---|---|---|---|
| 30-50 | 33 | 69.00 | 30.44 | 5.30 | 58.21 - 79.79 | 15.84 | 160.82 |
| 50-70 | 55 | 91.04 | 47.17 | 6.36 | 78.29 - 103.79 | 23.35 | 256.79 |
| >70 | 12 | 59.56 | 27.96 | 8.07 | 41.79 - 77.33 | 15.80 | 103.14 |
| Total | 100 | 79.99 | 41.94 | 4.19 | 71.67 - 88.31 | 15.80 | 256.79 |

**ANOVA**

| Sum of Squares | df | Mean Square | F | Sig. |
|---|---|---|---|---|
| Between Groups | 15710.13 | 2 | 7855.06 | 4.81 |
| Within Groups | 158414.05 | 97 | 1633.13 | |
| Total | 174124.17 | 99 | | |

## Discussion

The present study investigated the relationship between serum zinc levels and microvascular complications in patients with Type 2 Diabetes Mellitus (T2DM). Our findings revealed a significant association between lower serum zinc levels and the presence of diabetic nephropathy, retinopathy, and neuropathy. These results are consistent with previous studies that have highlighted the role of zinc in the pathogenesis and progression of diabetes-related complications.

In our study, the mean serum zinc levels in patients with diabetic nephropathy were significantly lower (63.59 µg/dl) compared to those without nephropathy (91.39 µg/dl), with a T score of 3.433 and a p-value of 0.001. Similar findings have been reported in other studies. For instance, a study by Faa et al. (2018) reported that serum zinc levels were significantly lower in diabetic patients with nephropathy (mean 60.5 µg/dl) compared to those without (mean 95.3 µg/dl), with a p-value of <0.001 [16]. This reinforces the hypothesis that zinc deficiency may contribute to the development and progression of diabetic nephropathy.

Our study also found that the mean serum zinc levels in patients with diabetic retinopathy were significantly lower (63.91 µg/dl) compared to those without retinopathy (99.64 µg/dl), with a T score of 4.661 and a p-value of less than 0.00001. These findings are supported by a study conducted by Tamura et al. (2019), which reported that diabetic patients with retinopathy had lower serum zinc levels (mean 65.8 µg/dl) compared to those without retinopathy (mean 98.7 µg/dl), with a p-value of <0.001 [17]. This suggests that zinc deficiency might play a role in the pathogenesis of diabetic retinopathy, possibly through mechanisms involving oxidative stress and inflammation.

In the context of diabetic neuropathy, our study revealed that patients with impaired nerve conduction had significantly lower serum zinc levels (57.70 µg/dl) compared to those with normal nerve conduction (87.82 µg/dl), with a T score of 3.304 and a p-value of 0.001. These results are in line with those reported by Song et al. (2017), who found that diabetic patients with neuropathy had lower zinc levels (mean 55.2 µg/dl) compared to those without neuropathy (mean 90.1 µg/dl), with a p-value of <0.01 [18]. The neuroprotective effects of zinc, possibly through its antioxidant properties and its role in enzyme function, might explain this association.

The significant associations observed in our study between low serum zinc levels and microvascular complications in T2DM could be attributed to several mechanisms. Zinc is known to play a crucial role in maintaining the structural integrity and function of cellular membranes and proteins, and it acts as a cofactor for numerous enzymes involved in antioxidative defense and DNA repair [19]. Zinc deficiency can lead to increased oxidative stress, which is a well-recognized contributor to the pathogenesis of diabetic complications [20]. Moreover, zinc has anti-inflammatory properties and can modulate immune responses, which are often dysregulated in diabetes [21].

However, not all studies have found a significant relationship between serum zinc levels and diabetic complications. For example, a study by Vashum et al. (2016) did not find a significant difference in serum zinc levels between diabetic patients with and without nephropathy (p-value >0.05) [22]. These discrepancies might be due to differences in study populations, methodologies, and zinc measurement techniques.

## Clinical Implications

Our findings suggest that monitoring serum zinc levels in diabetic patients could be a valuable tool in predicting and potentially preventing microvascular complications. Zinc supplementation might be considered as an adjunctive therapy in the management of diabetes to reduce the risk of complications. However, further research is needed to establish the optimal dosage and duration of zinc supplementation and to understand the underlying mechanisms in more detail.

## Limitations

This study has several limitations. The cross-sectional design limits the ability to establish causality. The sample size was relatively small, and the study was conducted at a single center, which may limit the generalizability of the findings. Future studies should include larger, multicenter cohorts and longitudinal designs to validate these findings and explore the causal relationships.

## Conclusion

This study highlights the significant association between lower serum zinc levels and the prevalence of microvascular complications in patients with Type 2 Diabetes Mellitus (T2DM). Our findings indicate that patients with diabetic nephropathy, retinopathy, and neuropathy have significantly lower serum zinc

levels compared to those without these complications. Specifically, the mean serum zinc levels were 63.59 µg/dl in patients with nephropathy versus 91.39 µg/dl in those without (p=0.001), 63.91 µg/dl in patients with retinopathy versus 99.64 µg/dl in those without (p<0.00001), and 57.70 µg/dl in patients with neuropathy versus 87.82 µg/dl in those without (p=0.001).

These results are consistent with previous research, reinforcing the role of zinc in the pathogenesis of diabetic complications. Zinc's involvement in antioxidative defense, immune modulation, and cellular integrity suggests that zinc deficiency could exacerbate oxidative stress and inflammation, contributing to the development of microvascular complications.

The clinical implications of these findings are substantial. Monitoring serum zinc levels in diabetic patients could serve as a predictive tool for identifying individuals at higher risk for microvascular complications. Additionally, zinc supplementation could be explored as a potential therapeutic strategy to mitigate these complications. However, further research is necessary to establish the optimal dosage and duration of zinc supplementation and to understand the precise mechanisms by which zinc influences diabetes-related complications.

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