ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 2, March - 2023, Page No. : 42 - 50

A study on relation between serum zinc level and microvascular complications in type 2 diabetic patients

[1]Dr. Naveena Somepalli, Junior Resident, Department of General Medicine, Katuri Medical College & Hospital, Guntur, Andhra Pradesh, India.

[2]Dr. Balina Sri Harsha, Junior Resident, Department of General Medicine, Katuri Medical College & Hospital, Guntur, Andhra Pradesh, India.

[3]Dr. Poosala Rohith Vinay Kumar, Junior Resident, Department of General Medicine, Katuri Medical College & Hospital, Guntur, Andhra Pradesh, India.

[4]Dr. Dumpa Ravindra Reddy, Assistant Professor, Department of General Medicine, Katuri Medical College & Hospital, Guntur, Andhra Pradesh, India.

Corresponding Author: Dr. Naveena Somepalli, Junior Resident, Department of General Medicine, Katuri Medical College & Hospital, Guntur, Andhra Pradesh, India.

How to citation this article: Dr. Naveena Somepalli, Dr. Balina Sri Harsha, Dr. Poosala Rohith Vinay Kumar, Dr. Dumpa Ravindra Reddy, "A study on relation between serum zinc level and microvascular complications in type 2 diabetic patients", IJMACR- March - 2023, Volume – 6, Issue - 2, P. No. 42 – 50.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Introduction: Diabetes leads to a few potentially disabling macro- and micro-vascular complications. Microvascular complications of diabetes include diabetic retinopathy (DR), diabetic nephropathy (DN), and diabetic peripheral neuropathy (DPN). Zinc plays an important role in both type 1 and type 2 diabetes (T2D). Serum zinc level is associated with Type2 diabetes mellitus, and loss-of-function mutations in zinc trans porter-8 gene protect against Type 2 Diabetesmellitus[1]

Aim of the study: The purpose of this study was to analyze the relationship between zin c level and each diabetic microvascular complication and identify the features related to low serum zinc level.

Materials and Methods: A cross sectional study was done among 120 type 2 diabetic patients without other co morbidities and without macrovascular complications. After getting consent following data were collected from all diabetic patients. Name, gender, age, duration of diabetes, treatment details including oral hypoglycemic drugs and insulin and detailed clinical examination was done. Fasting and Post Prandial blood sugars was done. Zinc level was assayed by atomic absorption spectrophotometer method. Diabetic Retinopathy was diagnosed ophthalmologically by

fundus examination. Diabetic Nephropathy will be diagnosed by urinary protein /creatinine ratio (PCR) and blood creatinine levels. Urinary infection and other types of nephropathies were excluded during the diagnosis of DN. Diabetic Neuropathy was diagnosed based on the results of physical examination and nerve conduction study.

Observation and Results: In our study total of 120 patients, 67 patients were males, and 53 patients were females. This distribution shows the predominance of males in type2 diabetes mellitus. The mean age of the participants was 52.21 ± 5.68 years, and the mean duration of diabetes was 8 years. Zinc levels exhibited values of 72.39±30.73 and urine PCR exhibited values were 0.52±0.89. 85% of the subjects had normal fundus and 11% had NPDR. 39% of the study population had impaired nerve conduction studies.

Conclusion: We can conclude that: Age, gender and glycemic parameters and duration of diabetes had no statistically significant role to play on analyzing the relationship between serum zinc level and microvascular complications in patients with type 2 diabetes. On internal comparison the following conclusions were observed Lower zinc levels associated with abnormal increase in urine PCR levels. Linear and inverse relationship with urine PCR Lower zinc levels associated with incidence of diabetic nephropathy. Lower zinc levels associated with incidence of diabetic neuropathy and retinopathy.

Keywords: Diabetic Peripheral Neuropathy; Diabetic Retinopathy; diabetic nephropathy; Type 2 Diabetes.

Introduction

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. The prevalence of type 2 diabetes mellitus is increasing rapidly accounting for 90-95 percent of the total diabetic population. Diabetes leads to several potentially disabling macro- and micro-vascular complications. Microvascular complications of diabetes include diabetic retinopathy (DR), diabetic nephropathy (DN),and diabetic peripheral neuropathy (DPN). Zinc plays a important role in both type 1 and type 2 diabetes (T2D). Serum zinc level is associated withType2 diabetes mellitus, and loss-of-function mutations in zinc trans porter-8 gene protect against Type 2 Diabetesmellitus[1,2].

The development of microvascular complications in diabetes is majorly due to oxidative stress. Zinc has an antioxidative effect. Also, itis a key component of many antioxidants. Lipid peroxidation induced damage is inhibited by zinc. Zinc induces the clearance of free radicals.[3]This suggest that zinc deficiency may be associated with the development of microvascular complications in diabetes mellitus.

It is well known that hyperglycemia accelerates the formation of advanced glycation end products (AGEs), which have been implicated in the pathogenesis of Diabetic retinopathy. They can stimulate ROS production in retinal pericytes, largely via activation of NADPH oxidase, which results in retinal pericyte apoptosis[4]. It is suggested that Zn might prevent retinal pericyte apoptosis via inhibition of NADPH oxidase in Diabetic retinopathy.

Ocularneo vascularization, which is most potently caused by hypoxia and ischemia, is also a key component in Diabetic retinopathy. It has been convincingly demonstrated that hypoxia inducible factor-1 (HIF-1) and VEGF are involved in the initiation and progression of neovascularization in DR[5]. Zn reduces inflammatory cytokine production by upregulating the Zn-finger protein, A 20, which inhibits

NF-κ B activation via the TRAF pathway[6] In addition, recent finding suggests that ZnT8 expression was reduced by ischemic insults and to restore the ZnT8 to its basal homeostatic levels can prevent ret in as from is chemia induced injury.

The nephropathy associated with diabetes has been attributed to oxidative stress[7]. Oxidative stress can be caused either by the increased production of reactive oxygen species (ROS) or a deficiency in antioxidant defense. Antioxidant deficiency can result from low intake of vitamins, such as vitamin C and E, or impaired synthesis of enzymes, such as super oxide dismutase, catalase, and glutathione per oxidase, due to zinc deficiency[8]. Chronic zinc deprivation generally results in an increased sensitivity to the effects of oxidative stress due to deficiency oftheseenzymes[9].

Zinc supplementations ameliorate severity of neuropathy symptoms in diabetic patients with mild to moderate peripheral neuropathy[10].

Zinc supplementation Sal one has also demonstrated a significant improvement in motor nerve conduction velocity following supplementation in patients with type-2diabetes.

Aim of The Study

1. To assess the serum zinc levels in subjects with type 2 diabetesmellitus.
2. To compare zinc levels in each microvascular complication.
3. To correlate between the zinc levels and micro vascular complications.

Materials and Methods

Study design: Cross sectional study.

Study population: Diabetic patients attending the Medicine Department in Katuri Medical college and hospital.

Study period: 1 year.

Sampling technique: Simple random sampling.

Sample size: 120.

Study Tools: FBS, PPBS, S. Zinc levels, U. PCR, Fundus examination, Nerve conduction study,

Inclusion criteria:

Type 2 diabetic patients in the age group of 40-65 yrs.

Exclusion criteria:

Patients who are

1. Hypertensives
2. Alcoholics, patients with Vit B12 deficiency
3. With history of acute infections and thyroiddys function.
4. With autoimmune diseases.
5. On chemo therapy
6. Non diabetic renal disease
7. With macrovascular complications CAD, CVA, PVD.

Study method

After getting consent from patient or patient's relatives, following data will be collected from all diabetic patients.

Name, gender, age, duration of diabetes, treatment details including oral hypoglycemic drugs and insulin and detailed clinical examination will be done

Fasting and Post Prandial blood sugars were done.

Zinc level (70-150microgram/dl) was assayed by atomic absorption spectrophotometer.

Diabetic Retinopathy was diagnosed ophthalmologically by fund us examination.

Diabetic Nephropathy was by diagnosed by urinary protein / creatinine ratio. DN diagnosed if the urinary PCR was higher than. 3. Urinary infection and other types of nephropathies were excluded during the diagnosis of DN.

Diabetic Neuropathy was diagnosed based on the results of physical examination and nerve conduction study.

The data of each patient will be collected in specific proforma which includes patient's name, age, sex, demographic details, presenting complaints, risk factors and all clinical data. All the relevant data and values are then entered in master chart in Microsoft excel format and then analyzed statistically.

Ethical Clearance

Ethical clearance was taken from Institutional Ethics Committee (IEC)

Data Analysis

The data was collected in the master chart obtained in the Microsoft excel format.

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analyzed with the unpaired test and ANOVA. Categorical variables were analyzed with the Chi-Square Test and Fisher Exact Test. Pearson's r correlation was done to assess relationship between variables. Statistical significance was taken as P < 0.05. The data was analyzed using SPSS version 16 and Microsoft Excel 2013.

Observation and Results

Table 1: Gender Distribution of Diabetes in Our Study

Gender	Frequency	Percentage
Male	67	55.8
Female	53	44.2
Total	120	100.0

Serum zinc levels when matched against gender status, it was observed that the mean serum zinc levels were 76.90 ± 30.36 in male patients and 66.70 ± 30.51 in female patients (p=0.071). The data subjected to unpaired test reveals the existence of statistically non-significant association between serum zinc distribution and gender (p >0.05).

Figure 1: Association between serum zinc and gender

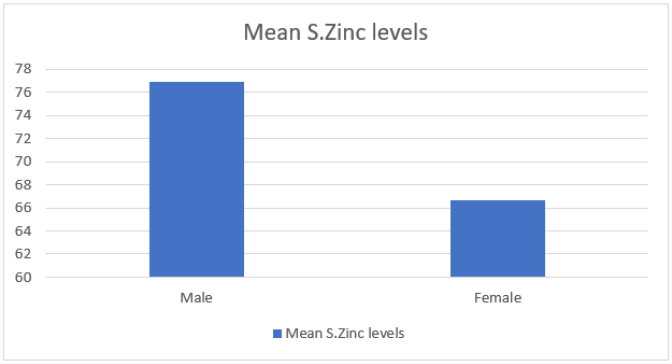


Table 2: Distribution of Age Group in Our Study

Age group	Frequency	Percent
<50years	47	39.2%
50to 60years	67	55.8%
>61years	6	5.0%

Figure 2: Distribution of age group In Our Study

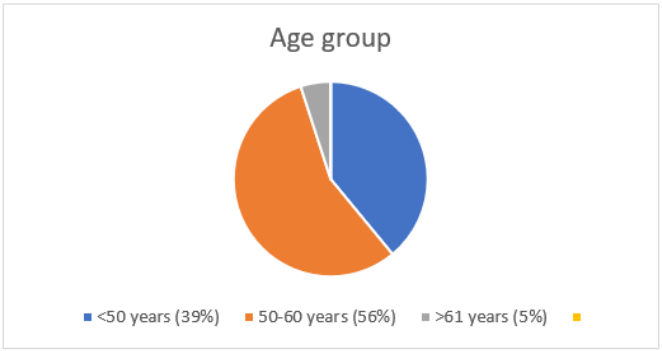
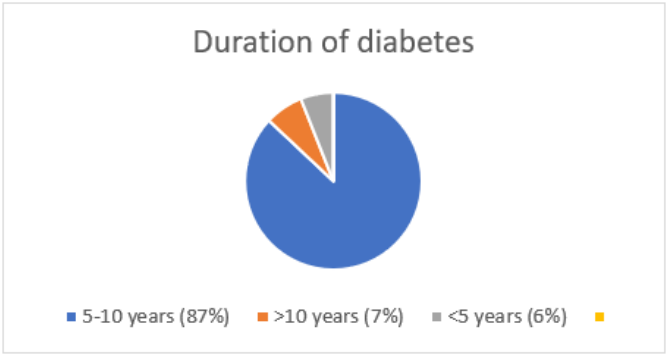
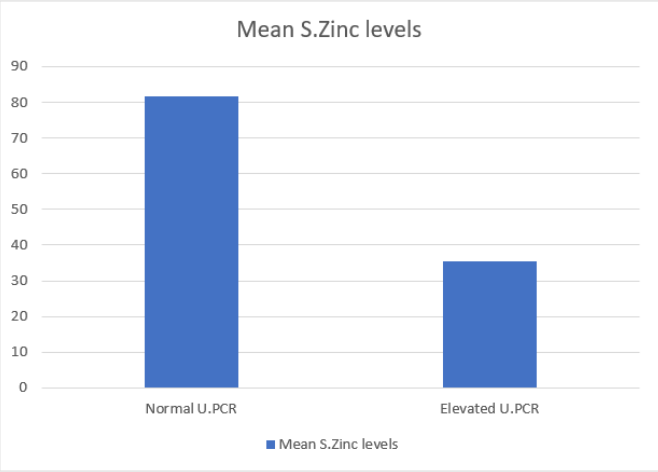


Figure 3: Distribution of duration of diabetes



In patients with T2DM, when the serum zinc levels were matched and correlated with duration of diabetes, the mean serum zinc level was 72.39 µmol/L and the mean duration of diabetes was 7.96 years. The difference in values is statistically non-significant as the p value is 0.301with a negative correlation as per Pearson's coefficient of -0.095.

Figure 4: Association between Zinc and urinepcr



Serum zinc levels when matched against urine PCR status, it was observed that the mean serum zinc levels were 81.63 ± 27.34 in normal urine PCR category and 35.46 ± 4.34 in elevate during PCR category (p=<0.0001). The data subjected to unpaired t test reveals the existence of statistically significant association between serum zinc distribution and urine PCR status(p<0.05).

In patients with T2DM, when the serum zinc levels were matched and correlated with urine PCR levels, the mean serum zinc level was 72.39 µmol/L and the mean urine PCR level was 0.52g/m mol. The difference in values is statistically significant as the p value is<0.0001witha negativecorrelationasperPearson'scoefficientof-0.479.

The decrease in serum zinc levels correlates negatively and strongly with the increase in urine PCR levels. The linear decrease in serum zinc level measurement in T2DM cases group in relation to increased urine PCR levels is true 48%oftimes.

Forevery1%decreaseinserumzinclevelsthereisacorrespon ding 0.22 % increase in urine PCR levels. This is indicated by the linear correlation formula y= -0.0138x + 1.5169.

Table 3: Mean and standard deviation of variables

Variables	Number	Mean	Standard Deviation
AGE	120	52.20	5.68
DM_DURATION	120	7.96	2.38
FBS	120	173.13	48.25
PPBS	120	218.07	55.43
ZINC	120	72.39	30.73
URINEPCR	120	0.52	0.89

Data collected from 120 selected T2DMsubjects were internally compared, tabulated, analyzed and interpreted by using descriptive and inferential statistics based on the formulated objectives of the study.

56% of the study subjects were males.

The mean age of the participants was 52.21 years

The mean duration of diabetes was 8 years.

Mean fasting blood sugar levels tabulated was 173.13 mg/dl.

Mean postprandial blood sugar levels was 218.07 mg/dl.

Mean S. Zinc levels are 72.39.

Mean U. PCR was 0.52.

Table 4: Association Between Serum Zinc Levels and Diabetic retinopathy

	Number	Mean	Standard Deviation	P value
Normal	102	78.88	28.73	<0.0001
PDR	5	32.00	2.00	
NPDR	13	37.00	4.22	

Serum zinc levels when matched against retinopathy status, it was observed that the mean serum zinc levels were 78.88±28.73 in normal fundus category, 32.00±2.00 in proliferative diabetic retinopathy category and 37.00 ± 4.22 in non-proliferative diabetic retinopathy category (p=<0.0001). The data subjected to

ANOVA test reveals the existence of statistically significant association between serum zinc distribution and presence / severity of retinopathy($p<0.05$).

Figure 5: Association Between Serum Zinc Levels And Diabetic retinopathy

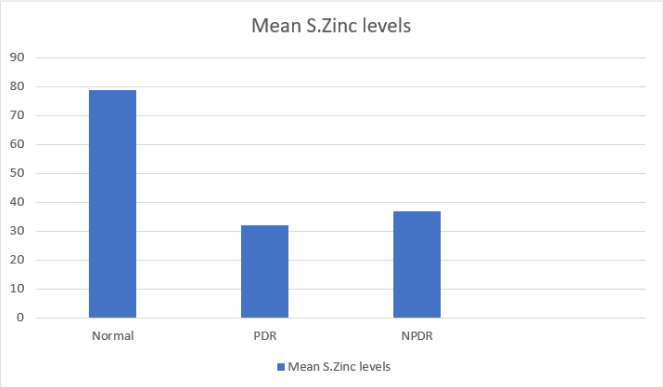
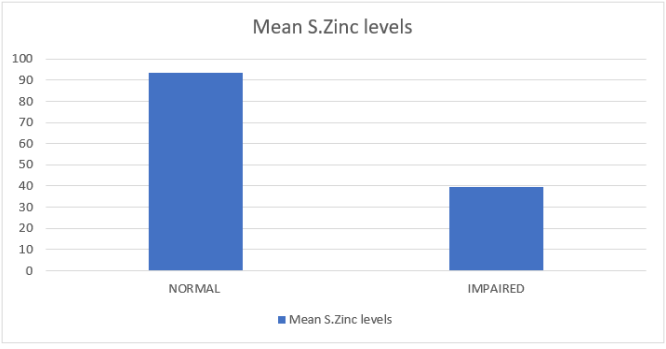


Table 5: Association Between Serum Zinc And Peripheral neuropathy

NCS	Number	Mean	Standard Deviation	P value
Normal	73	93.44	17.35	<0.0001
Impaired	47	39.70	13.27	

Serum zinc levels when matched against nerve conduction study status, it was observed that the mean serum zinc levels were 93.44±17.35in normal nerve conduction study patients, 39.70±13.27 in impaired nerve conduction study patients ($p= <0.0001$). The data subjected to chi squared test reveals the existence of statistically significant association between serum zinc distribution and nerve conduction study status ($p<0.05$).

Figure 6: Association Between Serum Zinc And Peripheral Neuropathy



Discussion

In our study total of 120 patients were included. All patients were included in study after getting consent, detail history and physical examination and after ruling out the exclusion criteria. Out of 120 patients 67 patients were male and 53 patients were females. This distribution shows the predominance of males in type2 diabetes mellitus. The mean age of the participants was 52.21 ± 5.68 years, and the mean duration of diabetes was 8years. Zinc levels exhibited values of 72.39±30.73 and urine PCR exhibited values were 0.52 ± 0.89. 85% of the subjects had normal fundus and 11% had NPDR. 39% of the study population had impaired nerve conduction studies.

In our study the distribution of mean serum zinc levels and the urine PCR status was meaningfully significant. This is evident by the decreased mean serum levels in elevated urine PCR category compared to normal urine PCR category (mean reduction difference of46.14 percentage points, 57% lower).

The same view was echoed in a study conducted by Al Timimi D Jet al which showed that significantly low levels of e-GFR and high levels of microalbuminuria were observed in diabetic patients with low serum zinc level as compared to normal serum zinc level[11]. It concluded that lower serum zinc levels lead to advancing nephropathy and indicated the need for determining serum zinc levels and the effectiveness of zinc supplementation in diabetic patients, particularly during the assessment of kidney damage.

Ying ying Lu et al in a study conducted in 412 patients concluded that zinc level was significantly lower in patients with elevated urinary albumin Creatinine ratio[12] and also suggested that serum zinc level was an in dependent risk factor for DN. Barman S et al explored

whether zinc supplementation protects against diabetic nephropathy through modulation of kidney oxidative stress and stress-induced expression related to the inflammatory process in streptozotocin-induced diabetic rats[13]. This study concluded that zinc supplementation has a significant beneficial effect in the control of diabetic nephropathy. Which was exerted through a protective influence on oxidative-stress-induced cytokines, inflammatory proliferation and consequent renal injury.

On internal comparison the significant conclusion observed was that higher urine PCR status was related to decreased serum zinc levels (2.30 times more chance of developing elevated urine PCR). Lower zinc level is a good, consistent and direct predictor of high urine PCR or diabetic nephropathy. Hence Lower serum zinc level can be considered as an in dependent risk factor for diabetic nephropathy.

In our study the distribution of mean serum zinc levels and the presence/severity of retinopathy status was meaningfully significant.

This is evident by the decreased mean serum levels in non- proliferative diabetic retinopathy category compared to normal fundus category (mean reduction difference of 41.88 percentage points, 53% lower) and decreased mean serum zinc levels in proliferative diabetic retinopathy category compared to non-prolife ratite diabetic retinopathy category (mean reduction difference of 5.00 percentage points,14% lower).

The same view was echoedina study conducted in Peking University People's Hospital, Beijing, China, in 412 hospitalized patients with type 2 diabetes mellitus which concluded that lower zinc levels are found in DR patients than in those without DR, suggesting that zinc might play an important role in the development of DR. Also suggested that in T2D patients with a relatively low zinc level, the protective effect of the anti-oxidative zinc may be reduced, and the risk of DR may be elevated.

A case control study conducted in 42 diabetic patients (14 without retinopathy [DC]; 14 with non-proliferative diabetic retinopathy [NPDR];14 with prolife rative diabetic retinopathy [PDR]) at Ebin Al-Haitham Specialized Hospital, Baghdad, Iraq showed significant reductions in serum means of Zn and Zn/ Cu ratios in all diabetic retinopathy as compared to DC. And concluded that both glycation and oxidative processes were involved in the development of diabetic retinopathy, and changes in the concentration of Zn have some impact on the diseaseprogression[14].

Miao X et al concluded that Zn supplementation seems beneficial for the patients with diabetes to control complications. Zn as an antioxidant or via induction of MT attenuates ROS effect. Zn might protect retina from ROS induced pericytes apoptosis, capillary leakage, and neo vascularization there by might have protective on DR[15].

On internal comparison the significant conclusion observed was that lower serum zinc level in Type 2 Diabetics patients was related to increased incidence of DR status (2.47 times more chance of developing diabetic retinopathy). Lower zinc level is a good, consistent and direct predictor of non-prolife rative diabetic retinopathy and prolife rative diabetic retinopathy. Hence lower serum zinc level can be considered as an in dependent risk factor for diabetic retinopathy.

In our study the distribution no f mean serum zinc levels and the nerve conduction study status was meaningfully significant. This is evident by the decreased mean serum

levels in impaired nerve conduction study category compared to normal nerve conduction study category (mean reduction difference of53.74 percentage points, 58% lower).

The same view was echoedbya double-blind study conducted by Hayeeetal which showed that serum zinc level sat base line are significantly lower in patients with diabetic neuropathy when compared with healthy controls. conduction velocity was altered significantly in patients who received zinc supplement and conducted that zinc therapy may lead to better glycemic control and improvement in DPN[16].

Migdalis et al demonstrated a negative relationship between zinc level and lipid peroxidation[17]. Increased lipid peroxidation with low levels of zinc lead to neuropathy. A double-blind randomized study conducted on 50 subjects by Gupta R et al included 20 age and sex matched healthy controls; 15 patients of diabetes mellitus with neuropathy received placebo for 6 weeks and 15 patients of diabetes mellitus with neuropathy were given supplemental zinc sulphate. It concluded that oral zinc supplementation help sin achieving better glycemic control and improvement in severity of peripheralneuropathy[18].

On internal comparison the significant conclusion observed was that decreased serum zinc level in Type 2 diabetics was related to increased incidence of impaired nerve conduction study status (2.35 times more chance of developing diabetic neuropathy). Lower zinc level is a good, consistent and direct predictor of diabetic neuropathy. Hence Lower serum zinc level can be considered as an independent risk factor for diabetic neuropathy.

Conclusion

We can conclude that age, gender and glycemic parameters and duration of diabetes had no statistically significant role to play on analyzing the relationship between serum zinc level and microvascularcomplicationsinpatientswithtype2diabetes.

On internal comparison the following conclusions were observed:

1. Lower zinc levels associated with abnormal linear increase in urine PCR levels
2. Linear and inverse relationship with urine PCR.
3. Lower zinc levels associated with incidence of diabetic nephropathy.
4. Lower zinc levels associated with incidence of diabetic neuropathy and retinopathy.

This study is a hypothesis proving study. Hence results have high clinical significance.

References

1. Flannick J, Thorleifsson G, Beer NL, Jacobs SB, Grarup N, Burtt NP, etal. Loss-of-function mutations in SLC 30 A 8 protect against type 2 diabetes. Nat Genet 2014;46:357-63.
2. Shan Z, Bao W, Zhang Y, Rong Y, Wang X, Jin Y, et al. Interactions between zinc transporter- 8gene (SLC30A8) and plasma zinc concentrations for impaired glucose regulation and type 2 diabetes. Diabetes2014;63:1796-803
3. Thomas JP, Bachowski GJ, Girotti AW. Inhibition of cell membrane lipid peroxidation by cadmium- and zinc-metallothionein's. Biochim Biophys Acta 1986; 884:448-61
4. Harrison's Principle of internal medicine 19th edition.

5. Smidt K, Jessen N, Petersen AB, Larsen A, Magnusson N, Jeppesen JB, etal. SLC 30 A 3 responds to glucose and zinc variations in beta-cells and is critical for insulin production and in vivo glucose-metabolism during beta-cell stress. PLoS One.2009;4(5):e5684–4.
6. Myers SA, Nield A, Chew GS, Myers MA. The zinc transporter, Slc39a7 (Zip7) is implicated in glycaemic control in skeletal muscle cells. PLoS One.2013;8(11):e79316.
7. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet.2005;365(9467):1333–1346.doi:10.1016/S0140-6736(05)61032-X.
8. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27(5):1047–1053. doi:10.2337/diacare.27.5.1047.
9. WHO Diabetes Fact Sheet.
10. Wang J, Song Y, Elsherif L, Song Z, Zhou G, Prabhu SD, et al Cardiac metallothi one in induction plays the major role in the prevention of diabetic cardiomyopathy by zinc supplementation. Circulation. 2006;113(4):544–54.
11. Al-Timimi DJ, Sulieman DM, Hussen KR.J Clin Diagn Res. 2014Nov;8(11):CC04-8
12. Luo YY, Zhao J, Han XY, Zhou XH, Wu J,Ji LN. Relationship Between Serum Zinc Level and Microvascular Complications in Patients with Type 2 Diabetes. Chin MedJ
13. Barman S ,Pradeep SR, Srinivasan K. J Nutr Biochem. 2018Apr;54:113-129. doi: 10.1016 / j. jnutbio. 2017.11.008. Epub2017Dec11.
14. Khan MI, Siddique KU, Ashfaq F, Ali W, Reddy HD, Mishra A. Effect of high-dose zinc supplementation with oral hypoglycemic agents onglycemiccontroland inflammation in type-2 diabetic nephropathy patients. J Nat Sci BiolMed.2013;4:336–40.
15. Miao X, Sun W, MiaoL, etal. Zinc and Diabetic Retinopathy. Journal of Diabetes Research. 2013; 2013: 425854.doi:10.1155/2013/425854.
16. Hayee MA, Mohammad QD, Haque A. Diabetic neuropathy and zinc therapy. Bangladesh Med Res CouncBull.2005;31:62–7.
17. Migdalis IN, Triantafilou P, Petridou E, Varvarigos N, Totolos V, Rigopoulos A. Lipid peroxides in type 2 diabetic patients with neuropathy. Res Commun MolPathol Pharmacol.2005;117-118:5
18. Gupta R, Garg VK, Mathur DK, Goyal RK. Oral zinc therapy in diabetic neuropathy. J Assoc Physicians India.