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EVALUATION OF THE ROLE OF ZINC AS ADD-ON THERAPY ON GLYCAEMIC CONTROL AND SYMPTOMS AND SIGNS OF NEUROPATHY IN THE PATIENTS WITH DIABETES MELLITUS

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ABSTRACT: Introduction: Diabetic neuropathy occurs in about half of the individuals with long-standing diabetes manifested as polyneuropathy, mononeuropathy and autonomic neuropathy. There is evidence indicating the involvement of zinc in diabetes. **Aim:** To evaluate the effect of Zinc as add-on therapy in Diabetic Neuropathy on the basis of clinical signs and symptoms and glycaemic control. **Materials and Methods:** This prospective study was conducted in the Department of Pharmacology at Sarojini Naidu Medical College and associated Hospital Agra, Uttar Pradesh, India. A total of 105 patients of either type-1 or type-2 diabetes mellitus with complication of diabetic neuropathy were included and divided randomly into control and study groups of 52 and 53 patients each. Control group received standard anti-diabetic therapy plus Pregabalin 75 mg/day and Methylcobalamin 1500 mcg/day, while the participants of study group received standard anti-diabetic therapy plus Pregabalin 75 mg/day and Methylcobalamin 1500 mcg/day plus Zinc acetate 50mg/day as add-on therapy. Symptoms and signs of sensory-motor neuropathy, autonomic dysfunction and neuropathy were recorded at baseline and on subsequent follow up at 3 months and 6 months. Simultaneously laboratory parameters such as fasting blood sugar and post prandial blood sugar were measured. **Results:** There were statistically insignificant differences in paraesthesia, hypoesthesia, cramps, palpitation, constipation or diarrhoea in the study group at 3rd and 6th months of follow-up ($p>0.05$). There was a statistically significant difference ($p<0.05$) in the fasting blood sugar at the follow up at 6th month. **Conclusions:** Oxidative stress is a common pathological factor of diabetic complications and zinc supplementation appears to have some role in the glycaemic control of diabetic patients.

INTRODUCTION: Diabetes Mellitus (DM) refers to a group of common metabolic disorders presenting as hyperglycaemia due to insulin deficiency or due to unresponsiveness to insulin.

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Diabetes is an "Iceberg" disease. Continuous escalation in all age groups is now seen. The rising prevalence of diabetes in developing countries is closely linked with industrialization and socio-economic development [1]. It is estimated that 20% of current global diabetic population resides in South-East Asia region. Based on current trends more than 592 million people are projected to have diabetes by year 2035.Worldwide estimate projects that in 2030 the greatest number of individuals with diabetes will be 45-64 years of age. The prevalence

is increasing in every country and major economic, social and healthcare impacts will be seen in developing countries [2]. With preventive strategies and anti-diabetic medications diabetes can be well controlled, moreover stringent control of diabetes curtails its various complications such as neuropathy. Diabetic neuropathy occurs in 50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy and/or autonomic neuropathy. Distal symmetric polyneuropathy is the most common form of diabetic peripheral neuropathy where loss of function appears in a stocking-glove pattern. Sensory involvement usually occurs first and is generally bilateral, symmetric and associated with dulled perception of vibration, pain, and temperature. Peripheral neuropathy, autonomic neuropathy, and trauma also predisposes to the development of Charcot arthropathy.

In some patients, hypersensitivity to light touch and occasionally severe "burning" pain particularly at night can become physically and emotionally disabling. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Gastroparesis and bladder emptying abnormalities are often caused by the autonomic neuropathy seen in DM. Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking which increases the risk of foot ulcers. More than 70% of all diabetic patients die from complications of diabetes mellitus [3].

The most important aspect of prevention and treatment of diabetic neuropathy are to strictly control the blood sugar. Management of diabetic neuropathy should begin at the initial diagnosis of diabetes. Criteria for "acceptable" control includes the following: (1) blood glucose levels of 90–130 mg/dl before meals and after an overnight fast, (2)levels no higher than 180 mg/dl one hour after meals and 150 mg/dl two hours after meals. In most individuals the target HbA_{1c} should be <7% [4]. In Type 1 DM, "Insulin" is indicated. Six analogues of human insulin three rapidly acting (insulin lispro, insulin aspart, insulin glulisine) and three long-acting (insulin glargine, insulin detemir and insulin degludec) - have been approved by the FDA for clinical use. In Type 2 DM, Metformin is the first line drug. Other antidiabetics used are- Sulfonylureas, Pioglitazone, α-glucosidase inhibitors (acarbose, miglitol), the GLP-1 receptor agonists (exenatide and liraglutide) and DPP-4 inhibitors (sitagliptin and others) [3]. The treatment of Diabetic Neuropathy is less than satisfactory. Two agents Duloxetine and Pregabalin have been approved by the U.S. Food and Drug Administration (FDA) for pain associated with diabetic neuropathy. Capsaicin, a topical irritant, has been found to be effective in reducing local nerve pain. Addition of Methylcobalamin helps regenerate damaged nerve fibres [5].

There is a significant body of evidence indicating the involvement of zinc in diabetes. Zinc plays a relevant role in the treatment of diabetes; its antioxidant effect gives defence in diabetic patients by acting through different protection mechanisms. Zinc is an essential cofactor for superoxide dismutase enzyme [6]. Also it promotes phosphorylation of insulin receptor by enhancing glucose transport into cells thus improving chronic hyperglycaemia symptoms and thus curtailing diabetes complications. Zinc is important in insulin action and carbohydrate metabolism. Zinc is highly concentrated in the pancreas, especially within the islets. Insulin can associate to form hexamers in the presence of zinc. The zinc hexamers can then be packed together to form a stable structure. It is well documented that zinc is an important mediator of insulin storage and secretion from the pancreas [7].

Some studies have been done previously on the role of zinc in diabetic neuropathy; few of them were in favour of the role of zinc while some denied it. Review of the published articles on zinc in diabetes has shown limited number of studies in this region and none of them have combined the assessment of the roles of zinc in both glycaemic controls as well as in the signs and symptoms of neuropathies [8, 9, 10]. Keeping the above facts in mind, the present study was aimed to assess the role of Zinc acetate as add-on therapy in diabetic neuropathy.

MATERIALS AND METHODS: The present prospective randomized study was conducted in the PG Department of Pharmacology in collaboration with Department of Medicine, Pathology and

Biochemistry at Sarojini Naidu Medical College and associated hospital Agra, Uttar Pradesh, India, after taking approval from the Institutional Ethical Committee (Letter No. IEC/2021/69, dated 10/05/2021).

The diabetic cases attending medicine O.P.D, diabetic clinic and admitted in medicine ward constituted the material for the study. A total of 105 patients of either type-1 or type-2 diabetes with symptoms and signs of neuropathy were recruited and informed consent was taken from the patients. The enrolled patients were subjected to a protocol which included a detailed history regarding the duration of diabetes and evaluation of the symptoms and signs of neuropathy.

Inclusion Criteria: Diagnosed cases of diabetes mellitus according to the WHO guidelines [3] with clinical signs and symptoms of neuropathy:

1. Symptoms of diabetes plus random blood sugar concentration > 200mg/dl.
2. Fasting plasma glucose > 126mg/dl.
3. Two-hours plasma glucose > 200 mg/dl during oral glucose tolerance test (75 gm of glucose).

Exclusion Criteria:

1. Pregnant women, lactating mothers and children.
2. Causes of peripheral neuropathy other than diabetic neuropathy.
3. Patients with advanced hepatic, renal or cardiac disease.
4. Patients with diabetic ketoacidosis.

Sample size Calculation: Sample size was calculated by using the formula $\{z^2\ pq/d^2\}$ Where z=1.96, p is 50%, q=1-p and d=10% [11]. The calculated sample size comes to be 96, which were rounded up to 100.

Statistical Analysis: The collected data were expressed as frequencies, percentage and Mean±SD. Statistical comparison was done by using Chi-square test and t-test. P-value less than 0.05 were considered significant. All tests were done using SPSS version 16.0.

Study Procedure: The enrolled patients were randomly divided into two groups. The control group enrolled 52 patients of diabetic neuropathy receiving standard anti-diabetic therapy plus Pregabalin 75 mg/day and Methylcobalamin 1500 mcg/day. The study group enrolled 53 patients of diabetic neuropathy receiving standard anti-diabetic therapy plus Pregabalin 75 mg/day and Methylcobalamin 1500 mcg/day with Zinc 50mg/day (Zinc Acetate containing 50 mg elemental zinc) as add-on therapy. Two patients from the control group and three from the study group did not come in the subsequent follow up.

Evaluation and follow up: A detailed clinical history with emphasis on features of diabetes such as polyuria, polydipsia, polyphagia, age of onset of diabetes, duration of diabetes, current treatment, smoking, dietary habits, profession of patient, lifestyle, physical activity, family history of diabetes and important features of diabetic neuropathy such as loss of sensation in hands, tingling sensation in feet or hands, pain in legs, weakness in lower limbs, palpitation, erectile dysfunction in males, constipation, diarrhoea, abnormal sweating, difficulty in micturition was taken followed by physical examination in each case. Pulse rate and blood pressure for each patient was measured as per standard procedure. For measuring orthostatic hypotension patient was put in supine position and cuff was placed on arm with blood pressure apparatus at heart level. After measuring blood pressure in supine position, patient was instructed to stand up and immediately blood pressure was again measured. Fall in systolic blood pressure of less than 20 mm Hg or diastolic blood pressure of at least 10 mm Hg confirms orthostatic hypotension [12]. Patients were assessed in both the groups for 3 months and 6 months. Examination for diabetic neuropathy included the BP, heart rate, tendon reflexes, muscle strength and touch, vibration, position senses and by investigations to assess the glycaemic control like fasting blood sugar and post-prandial blood sugar. Patients were advised to abstain from smoking and alcohol intake during the study period.

RESULTS: As depicted in **Table 1** maximum no. of cases in the study and control groups were in 50 – 64 years age. Mean age in the study group was 52 ± 12.67 years and in Control group it was 51 ±

12.33 years. The statistical difference in the age distribution of study participants was insignificant (P value=0.915639). Male to Female ratio in Study group was 2.3: 1 while in Control group it was 1.8: 1. The statistical difference in the gender distribution of study participants was insignificant (P value=0.523468) **Table 2**. The distribution of diabetic patients in both the study and control group according to duration of diabetes shows that majority of them were suffering from diabetes for 11-15 years **Table 3**.

In the comparison of symptoms of sensory and motor neuropathy between the study and control group at baseline and subsequent follow up, paraesthesia and hypoesthesia were the commonest symptoms followed by cramps and pain and muscle weakness **Table 4**. In the comparison of symptoms of autonomic neuropathy, constipation or diarrhoea, palpitation and abnormal sweating were the commonest symptoms followed by erectile dysfunction and bladder symptoms, in both the study and control groups **Table 5**. In the signs of neuropathy, vibration sense loss, position sense loss, loss of reflexes and orthostatic hypotension were more common as compared to resting tachycardia **Table 6**.

There were statistically insignificant differences in the improvement of signs and symptoms of sensory-motor and autonomic neuropathy (P value>0.05), though there were greater reduction in the frequency distribution of study group as compared to control group **Table 4, 5, 6**. The mean values of fasting and post-prandial blood glucose in the study and control group were reduced at the follow up by 3rd and 6th months and the difference was found statistically significant in the case of fasting blood glucose at the follow-up of 6th month (P value < 0.05) **Table 7, 8.**

TABLE 1: AGE DISTRIBUTION OF STUDY PARTICIPANTS

Age-range (in years)	Study group (n=50)	Control group (n=50)
20-34	6 (12%)	4 (8%)
35-49	9 (18%)	10 (20%)
50-64	15 (30%)	16 (32%)
65-79	13 (26%)	15 (30%)
80 and above	7 (14%)	5 (10%)
Chi Square statistic 0.9611, df=4, P value=0.915639. The result is not significant at P value< 0.05		

TABLE 2: GENDER DISTRIBUTION OF STUDY PARTICIPANTS

Gender	Study group (n=50)	Control group (n=50)
Female	15 (30%)	18 (36%)
Male	35 (70%)	32 (64%)
Chi Square statistic 0.4071, P value=0.523468.The result is not significant at P value< 0.05		

TABLE 3: DISTRIBUTION OF PATIENTS ACCORDING TO DURATION OF DIABETES MELLITUS

Duration (in years)	Study group (n=50)	Control group (n=50)
less than 5	4 (8%)	5 (10%)
5-10	17 (34%)	14 (28%)
11-15	25 (50%)	23 (46%)
Above 15	4 (8%)	8 (16%)
Chi Square statistic 1.8181, P value=0.611004. The result is not significant at P value< 0.05		

TABLE 4: COMPARISON OF SYMPTOMS OF MOTOR AND SENSORY NEUROPATHY BETWEEN STUDY AND CONTROL GROUP AT BASELINE AND FOLLOW UP AT 3RD AND 6TH MONTHS

Symptoms	Study group (N=50)			Control group (N=50)		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month
Paraesthesia	45 (90%)	41 (82%)	27 (54%)	48 (96%)	43 (86%)	40 (80%)
Hypoesthesia	44 (88%)	38(76%)	26 (52%)	41 (82%)	41 (82%)	38 (76%)
Cramps and Pain	25 (50%)	21 (42%)	17 (34%)	27 (54%)	27 (54%)	26 (52%)
Muscle weakness	23 (46%)	19 (38%)	12 (24%)	25 (50%)	21(42%)	19 (38%)
Baseline versus 3rd month	Chi Square statistic 0.0887, P value=0.993162			Chi Square statistic 0.3262, P value=0.955027		
3rd month versus 6th month	Chi Square statistic 0.3344, P value=0.953427			Chi Square statistic 0.0236, P value=0.999042		
Baseline versus6th month	Chi Square statistic 0.3167,			Chi Square statistic 0.4531,		

	P value=0.956855	P value=0.929072
Study versus Control at 3rd month	Chi Square statistic 0.3391, P value=0.952506	
Study versus Control at 6th month	Chi Square statistic 0.0383, P value=0.99803	
Test of significance: Chi square test		
The results were not significant at P value< 0.05		

TABLE 5: COMPARISON OF SYMPTOMS OF AUTONOMIC NEUROPATHY BETWEEN STUDY AND CONTROL GROUP AT BASELINE AND FOLLOW UP AT 3RD AND 6TH MONTHS

Symptoms	Study group (N=50)			Control group (N=50)		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month
Palpitation	31 (62%)	25(50%)	17(34%)	33(66%)	29(58%)	27(54%)
Erectile dysfunction	23(46%)	18(36%)	15(30%)	22(44%)	20(40%)	19(38%)
Constipation/Diarrhoea	38(76%)	34(68%)	24(48%)	39(78%)	37(74%)	35(70%)
Bladder symptoms	18(36%)	14(28%)	10 (20%)	20(40%)	17(34%)	15(30%)
Abnormal sweating	27(54%)	23(46%)	18(36%)	28(56%)	25(50%)	23(46%)
Baseline versus3rd month	Chi Square statistic 0.1889, P value=0.995813			Chi Square statistic 0.0933, P value=0.998945		
3rd month versus6th month	Chi Square statistic 0.2576 , P value=0.992387			Chi Square statistic 0.0331, P value=0.999865		
Baseline versus6th month	Chi Square statistic 0.3227, P value=0.988302			Chi Square statistic 0.2151, P value=0.994617		
Study versusControl at 3rd month	Chi Square statistic 0.0924, P value=0.998966					
Study versusControl at 6th month	Chi Square statistic 0.3808, P value=0.984022					
Test of significance: Chi square test						
The results were not significant at P value< 0.05						

TABLE 6: COMPARISON OF SIGNS OF NEUROPATHY BETWEEN STUDY AND CONTROL GROUP AT BASELINE AND FOLLOW UP AT 3RD AND 6TH MONTHS

Signs	Study group (N=50)			Control group (N=50)		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month
Vibration sense loss	30 (60%)	25 (50%)	19 (38%)	31 (62%)	28 (56%)	25 (50%)
Position sense loss	32 (64%)	27 (54%)	22 (44%)	31 (62%)	24 (48%)	18 (36%)
Reflexes loss or diminished	28 (56%)	23 (46%)	20 (40%)	30 (60%)	27 (54%)	24 (48%)
Orthostatic hypotension	31 (62%)	26 (52%)	22 (44%)	27 (54%)	25 (50%)	23 (46%)
Resting tachycardia	22 (44%)	18 (36%)	11 (22%)	23 (46%)	22 (44%)	21 (42%)
Baseline versus3rd month	Chi Square statistic 0.0087, P value=0.999991			Chi Square statistic 0.3465, P value=0.986618		
3rd month versus6th month	Chi Square statistic 0.6352, P value=0.959078			Chi Square statistic 0.3621, P value=0.985461		
Baseline versus6th month	Chi Square statistic 0.7508, P value=0.944915			Chi Square statistic 1.3919, P value=0.845603		
Study versus Control at 3rd month	Chi Square statistic 0.8866, P value=0.926473					
Study versus Control at 6th month	Chi Square statistic 3.3423, P value=0.502263					
Test of significance: Chi square test. The results were not significant at P value< 0.05						

TABLE 7: COMPARISON OF FASTING BLOOD SUGAR AT BASELINE AND FOLLOWUP AT 3RD AND 6TH MONTHS

Fasting blood sugar	Study group			Control group		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month
Mean	138.76	132.34	126.22	137.14	133.08	131.86
SD	8.84	8.58	10.38	8.67	9.62	10.79
Baseline versus3rd months	P value=0.0004 (highly significant)			P value=0.0289 (significant)		
Baseline versus6th months	P value=0.0001 (highly significant)			P value=0.0082 (very significant)		
3rdversus6th months	P value=0.0018 (very significant)			P value=0.5520 (insignificant)		
Study versusControl at 3rd month	P value=0.6857 (insignificant)					
Study versusControl at 6th month	P value=0.0090 (very significant)					
Test of significance: Paired and unpaired t-test. Statistical significance were considered at P value< 0.05						

TABLE 8: COMPARISON OF POST-PRANDIAL BLOOD SUGAR AT BASELINE AND FOLLOW UP AT 3RD AND 6TH MONTHS

PP blood sugar	Study group			Control group		
	Baseline	3rd month	6th month	Baseline	3rd month	6th month
Mean	216.92	210.84	200.04	214.74	210.98	204.68
SD	23.13	23.05	35.39	23.09	22.79	32.41
Baseline versus3rd months	P value=0.1910 (insignificant)			P value=0.4145 (insignificant)		
Baseline versus6th months	P value=0.0058 (very significant)			P value=0.0769 (insignificant)		
3rdversus6th months	P value=0.0736 (insignificant)			P value=0.2636 (insignificant)		
Study versusControl at 3rd month	P value=0.9757 (insignificant)					
Study versusControl at 6th month	P value=0.4958 (insignificant)					

Test of significance: Paired and unpaired t-test. Statistical significance were considered at P value< 0.05

DISCUSSION: Diabetes mellitus is a chronic disease characterized by hyperglycaemia and associated micro-vascular and macro-vascular complications. The goal of therapy in the management of diabetes is strict glycaemic control which reduces the signs and symptoms of diabetes and also retards its complications. Zinc is important for beta cell functioning and glucose homeostasis apart from being a part of antioxidant enzymes [13]. On reviewing the literature, studies were found that reported the lower level of serum zinc in the patients of diabetes with or without neuropathy. There were some contradictory findings too where some studies reported a higher level of serum zinc in the patients with type-1 Diabetes mellitus [14, 15].

In the present study, we combined the assessment of signs and symptoms of diabetic neuropathy and associated glycaemic control after add-on therapy of zinc to the standard therapy of type-1 or type-2 diabetic patients. Maximum number of patients belonged to 50-64 years of age group and this could be due to chronic nature of the disease whose prevalence increases with age. It was also found that long duration of diabetes was more related to neuropathy since 50% of the participants in the study group and 46% in the control group were suffering from diabetes mellitus for more than 10 years. These findings were consistent with other studies [16, 17].

In the signs and symptoms of neuropathy, most of the patients presented with paraesthesia followed by hypoesthesia, cramps and muscle weakness. In autonomic neuropathy, constipation or diarrhoea after meals were the commonest manifestations followed by palpitation, abnormal sweating, erectile dysfunction in males and bladder symptoms. The findings of sensory and motor neuropathy were consistent with other studies, while the reported incidence of constipation or diarrhoea was low in some studies and it could be due to dietary pattern, lifestyle habits or worm infestations [18, 19].

In this study the comparison of the signs and symptoms of sensory-motor and autonomic neuropathy at baseline and subsequent follow up shows greater reduction in the frequency distribution in the study group as compared to control group, though the statistical difference was found insignificant (P value > 0.05) **Table 4, 5, 6**. This was in contrast to the studies conducted by Hussein M *et al*. (2021) and Luo YY *et al.* (2015) where they found statistically significant difference in the comparison of signs and symptoms of neuropathy [20, 21]. Although there is a considerable variation amongst the studies on the role of zinc in diabetic neuropathy, a systematic review and metaanalysis conducted by Jayawardena R. *et al* 2012 concluded improved glycaemic control and other metabolic and clinical benefits with improvement in the antioxidant status [22]. In the present study the glycaemic control was improved at the follow up by 3rd and 6th months and the difference was found statistically significant (P value < 0.05) with fasting glucose at 6th month **Table 7, 8.**

Zinc supplementation causes significant reduction in fasting blood glucose, post-prandial blood glucose and HbA1C as shown in the studies conducted by Al-Maroof RA (2006) [23]. The present study was consistent with the findings of these studies with regards to glycaemic control as shown by fasting blood sugar at 6th month, but on the other hand the studies conducted by Niewoehner CB *et al.* (1986) and Seet RCS *et al.* (2011) found no beneficial effects on glycaemic control [24, 25]. Although the exact reason behind this observation

could not be ascertained, the less number of study participants in some studies could be one limitation. Animal studies have demonstrated the insulin-mimetic and hypoglycaemic activities of zinc [26, 27]. Zinc may play a role in improving the responsiveness to insulin by enhancing insulin mediated glucose transport [28]. The protein tyrosine pyrophosphatase 1B (PTP1B) is one of the molecular target of zinc which is involved in the phosphorylation of insulin receptor [29]. Islet-restricted zinc transporter ZnT8 (SLC30 A8) acts as an important regulator of insulin secretion [30].

The systematic review and meta-analysis conducted by Jayawardena *et al* (2012) found significant reduction (-0.6%) in HbA1C in the zinc treated groups as compared to controls [22]. Oxidative stress can cause biochemical alterations in glucose and lipid metabolism as frequently observed in the patients of diabetes mellitus. Zinc supplementation helps to improve anti-oxidant status and decreases the chances of lipid peroxidation, but the studies showing beneficial effects of zinc supplementation were not exclusive for zinc only because other anti-oxidant vitamins and minerals were co-administered in these studies [31].

The other possible mechanisms for the metabolic benefits of zinc include decreased glucose absorption and enhanced glucose metabolism and storage. Zinc plays important role in the functioning of islet cells of pancreas by efficient packaging of insulin into the vesicles. It also increases insulin sensitivity by enhancing the binding of insulin to its receptors [32]. The present study showed improvements in the symptoms and signs of sensory-motor neuropathy as well as autonomic neuropathy at follow-up and the improvement were more in the study group as compared to control group as shown by greater reduction in the frequency distribution in the study group, though the statistical differences were not significant (P value>0.05).

The glycaemic control as measured by fasting and post-prandial blood glucose were more strict in the study group as compared to control group as shown by greater reduction in the mean value of fasting and post-prandial blood glucose in the study group and the statistical differences were significant (P value<0.05) in the case of fasting blood glucose while insignificant (P value>0.05) in the case of post-prandial blood glucose at the follow up of 6th months.

Limitation(s): Baseline and follow-up values of serum zinc level were not included in the present study. The study involved only zinc supplementation as add-on therapy to standard anti-diabetic treatment, the role of other (if any) minerals and vitamins could not be ascertained. Further studies including different groups of pre-diabetic and diabetic population with supplementation of zinc alone versus zinc with other minerals and vitamins are anticipated.

CONCLUSION: Zinc supplementation has role in the glycaemic control of diabetic patients. It may have some roles in the reduction of signs and symptoms of sensory-motor neuropathy and autonomic neuropathy the long term complications of uncontrolled diabetes. Further studies should be conducted involving big sample size and inclusion of other minerals and multivitamins apart from zinc to see their roles.

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CONFLICTS OF INTEREST: None declared.

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