Int.J.Curr.Res.Aca.Rev.2017; 5(7): 61-69

EXCELLENT PUBLISHERS

International Journal of Current Research and Academic Review

ISSN: 2347-3215 (Online) Volume 5 Number 7 (July-2017)

Journal homepage: http://www.ijcrar.com

doi: https://doi.org/10.20546/ijcrar.2017.507.009

Zinc Supplementation Significantly Improves Neurophysiological and Glycemic Measures in Patients with Diabetic Neuropathy

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Abstract

Though tight glycemic control remains the cornerstone for prevention and management of Diabetic Neuropathy (DN), it is often inadequate. Zinc supplementation may offer symptomatic and functional improvement in these patients. We tried to evaluate the effects of zinc supplementation on Nerve Conduction Study (NCS) parameters and glycosylated hemoglobin (HbA1c) level in patients with DN and search for whether duration of diabetes affect outcome. Patients of type 2 diabetes mellitus (T2DM) with peripheral neuropathy, presenting at Diabetes clinic were enrolled for baseline and follow-up (after 12 weeks) evaluation of NCS parameters along with HbA1c for Cases (received zinc therapy100mg/day) and Controls (did not receive zinc). Cases divided into three groups according to diabetes duration and evaluated for any significant differences in the response to the zinc, reflected by NCS parameters and HbA1c.The observational follow-up study on 45 patients showed highly significant ($p<0.01$) improvement for Median and Tibial motor amplitude, Median sensory (amplitude, velocity) and Sural (latency, amplitude) after 12 weeks of zinc supplementation in Cases. Significant difference ($p<0.05$) in changes was seen among Cases ($n=25$) compared to Controls ($n=20$) in amplitude and velocity (motor parameters) and latency, amplitude, velocity (sensory parameters) along with HbA1c. Median motor latency and HbA1c level, after zinc therapy varied significantly in individuals with longest diabetes duration.

Article Info

Accepted: 02 July 2017
Available Online: 20 July 2017

Keywords

Nerve conduction study,
Diabetic neuropathy,
Zinc,
HbA1c

Introduction

Diabetes mellitus (DM) is the most common metabolic disorder in the world. The International Diabetes Federation predicts that 642 million people will have diabetes by 2040. Most of the morbidity and mortality in diabetes are due to its chronic complications. Diabetic neuropathy (DN) is one of the most common and troublesome of all diabetes complications. It is defined as the presence of symptoms and/or signs of peripheral

nerve dysfunction in people with diabetes after exclusion of other causes. DN occurs in 50% of patients with underlying type1 and type 2 diabetes mellitus. Long diabetes duration and poor glycemic control correlates with neuropathic symptoms. The most common form of DN is distal symmetric polyneuropathy, in which the peripheral nerves are affected in a length dependent pattern with a predilection for early involvement of the longest axons of the somatic motor or sensory nerves beginning in the feet with proximal progression (Thomas and Eliasson, 1984). Sensory neuropathy, foot deformity arising from motor neuropathy, autonomic neuropathy and Charcot's foot place the foot in diabetes at high risk.

Patients with T2DM have insulin resistance, hyper-insulinaemia, β-cell dysfunction with subsequent β-cell failure (Stumvoll *et al.,* 2005). At high concentrations, insulin is organized as hexamers with two atoms of zinc. Zinc plays an important role in the synthesis, storage and also secretion of insulin (Chausmer, 1998). Decreased zinc levels affect ability of islet cells to produce and secrete insulin. Previous workers found lower blood zinc levels in diabetes (Khandelwal *et al.,* 1981; Isbir *et al.,* 1994; Garg *et al.,* 1994).

Nerve conduction studies (NCS) are the gold standard for detection and follow-up of neuropathies, including DN. Clinical studies found that zinc supplementation reduces DN severity and helps improving glycemic control (Gupta *et al.,* 1998; Hayee *et al.,* 2005; Jayawardena *et al.,* 2012). In studies where subjects received high doses of zinc (660 mg / day), none explored two important parameters of NCS, latency and amplitude (Gupta *et al.,* 1998; Hayee *et al.,* 2005). This study also tried to determine if diabetes duration had any impact on the response to zinc therapy in DN as assessed by NCS and HbA1c level.

Materials and Methods

An observational longitudinal follow-up study was conducted in the Department of Physiology of R.G. Kar Medical College and Hospital, Kolkata from October 2015 to September 2016 after proper ethical clearance. 56 T2DM patients between 18 to 65 years with subjective and objective evidence of peripheral neuropathy were recruited from Diabetic Clinic.

Among 56 patients, 28 received zinc supplementation (100mg/day) for 12 weeks along with their usual care from diabetes Out Patient Department (OPD) of our hospital. They were termed Cases. Remaining 28 patients not receiving zinc supplementation but receiving their usual care were labelled Controls. Informed consent was taken from all patients. After baseline evaluation of symptoms, signs and HbA1c, baseline NCS study was performed in the Neurophysiology Laboratory of the Department of Physiology on all the patients.

After 12 weeks, patients were subjected to NCS studies again. Out of 56 patients, 45 patients (25 Cases and 20 Controls) attended for follow-up evaluation by NCS, the remaining were lost to follow-up.

The 25 Cases were divided into three groups according to DM duration (Gr 1, Gr 2 and Gr 3 with diabetes duration < 5, 5 to 10 and > 10 years respectively).

Patients with type 1 diabetes mellitus, nephrotic syndrome, chronic diarrhea, malignancy, acute illness, history of dyspepsia and gastrointestinal irritation, patients on multivitamin treatment, pregnant ladies, alcohol abuse and patients with chronic renal failure stage 3 to 5 were excluded from the study.

Detailed history, including duration of disease and treatment, subjective symptoms of neuropathy like tingling, numbness and paresthesia were noted. General physical examination along-with comprehensive foot examination and clinical examinations for objective neuropathy were done.

Patients underwent examination with a 10-g monofilament; tests for joint sense, touch and pain sensation; vibration test; examination for muscle wasting and power; and reflexes.

Follow-up value of HbA1c after 12 weeks was noted in all.

Baseline NCS for Median (motor and sensory), Tibial (motor) and Sural (sensory) was done using RMS EMG-EP, MARK-2, 2011, computerized machine. Distal motor latency (DML), Compound muscle action potential (CMAP), Motor nerve conduction velocity (MNCV) for motor nerves and Distal sensory latency (DSL), Sensory nerve action potential (SNAP), Sensory nerve conduction velocity (SNCV) were noted for sensory components.

The data was summarized and results were analyzed by Microsoft Excel (2016), IBM-SPSSv20. The means of Cases and Controls were compared by paired t test (baseline and follow up values), unpaired t test (values

that followed normal distribution), Wilcoxon signed rank test, Kruskal Wallis and Mann Whitney test (values that did not follow normal distributions). Values of each subgroup of Cases were further compared by ANOVA and Post-hoc analysis.

Results and Discussion

A total of (n=45) patients (25 Cases and 20 Controls) with DN were available for analysis. Mean age of the study population was (51.32± 8.93) years in Cases and (49.35 ± 8.62) years in Controls.

Of 25 Cases 13 (52%) had diabetes for less than 5 years [Gr1], 8 (32%) had disease for 5-10years [Gr2], and rest 4 (16%) had DM for >10years [Gr3].

The baseline characteristics of different NCS parameters (motor and sensory) and glycemic status (HbA1c) were comparable between Cases and Controls (Table1).

There was significant improvement (p value < 0.05) in NCS parameters [CMAP of Median and Tibial, Median sensory parameters (SNAP, SNCV) and (Sural DSL, SNAP)] among Cases after 12 weeks of zinc supplementation compared with their baseline values, though the HbA1c value in Cases did not differ significantly at 12 weeks follow up compared to their baseline (Table 2).

Change (increase or decrease) of each NCS parameter and HbA1c level from baseline to follow-up values in Cases and Controls were calculated and compared.

Statistically significant (p value <0.05) improvement of NCS parameters (CMAP of Median and Tibial, MNCV of Median, SNAP and SNCV of Median and DSL, SNAP and SNCV of Sural) along with HbA1c level was seen among Cases individuals compared to Controls (Table 3; Figure 1).

The changes (increase or decrease) of each NCS parameter and HbA1c level from baseline to follow-up values among individuals of three groups of Cases (Gr1, Gr2 and Gr3) were compared (Table 4A, 4B).

There was a statistically significant difference (p value<0.05) only for Median DML along with HbA1c between Groups 1, 2 and 3 in the Cases (Table 4A).

Significant differences within groups were shown by Post–hoc analysis (Table 4B).

When we compared the baseline and follow-up values of different NCS parameters in Cases, statistically highly significant improvement was found for CMAP Median (p<0.001), CMAP Tibial (p=0.001), Median SNAP (p<0.001), SNCV (p=0.003), Sural DSL (p=0.019) and SNAP (p<0.001).

Baseline values of CMAP Median and Tibial, Median SNAP, SNCV, Sural DSL and SNAP (3.94±2.54)mv, (3.07±3.26)mv, (17.27±12.39)µv, (40.73±12.41)m/s, (5.84±1.66)ms, (4.38±1.24)µv improved to (10.05±4.34)mv, (7.12±4.79)mv, (32.11±18.20)µv, (46.42±11.28)m/s, (4.85±1.30)ms, (7.36±3.69) µv respectively (Figure 2).

MNCV of Median in Cases also improved from its baseline value (49.47±8.39)m/s to (52.41±7.27)m/s, though this change was statistically not significant (p>0.05).

Analysis of the difference in values (increase or decrease) of different NCS parameters from baseline to follow-up in Cases and Controls showed that there was significant increment of CMAP Median (p<0.001), CMAP Tibial (p<0.001), MNCV Median (p=0.035), Median SNAP (p<0.001), Median SNCV (p=0.001), Sural SNAP (p<0.001), Sural SNCV (p=0.013) and statistically significant decrement of Sural DSL (p=0.002) in Cases compared to Controls.

Thus there was improvement in the neurophysiological findings in DN after zinc therapy in Cases. When we classified the Cases into three groups according to diabetes duration and evaluated their response to zinc, it was seen that there was significant difference in decrement of only Median DML (p=0.001).

The Change in Median DML (12 week value-baseline= Δ Med DML) was 0.27±0.53, -0.33±0.47 and -1.9±1.85 in Groups 1, 2 and 3 respectively, thereby showing the best response in Group3, followed by group 2 and 1 respectively. T

hus individuals with longest diabetes duration had the best improvement in Median DML.

Fig.1 Comparison between change of values of NCS parameters and HbA1c among cases and controls

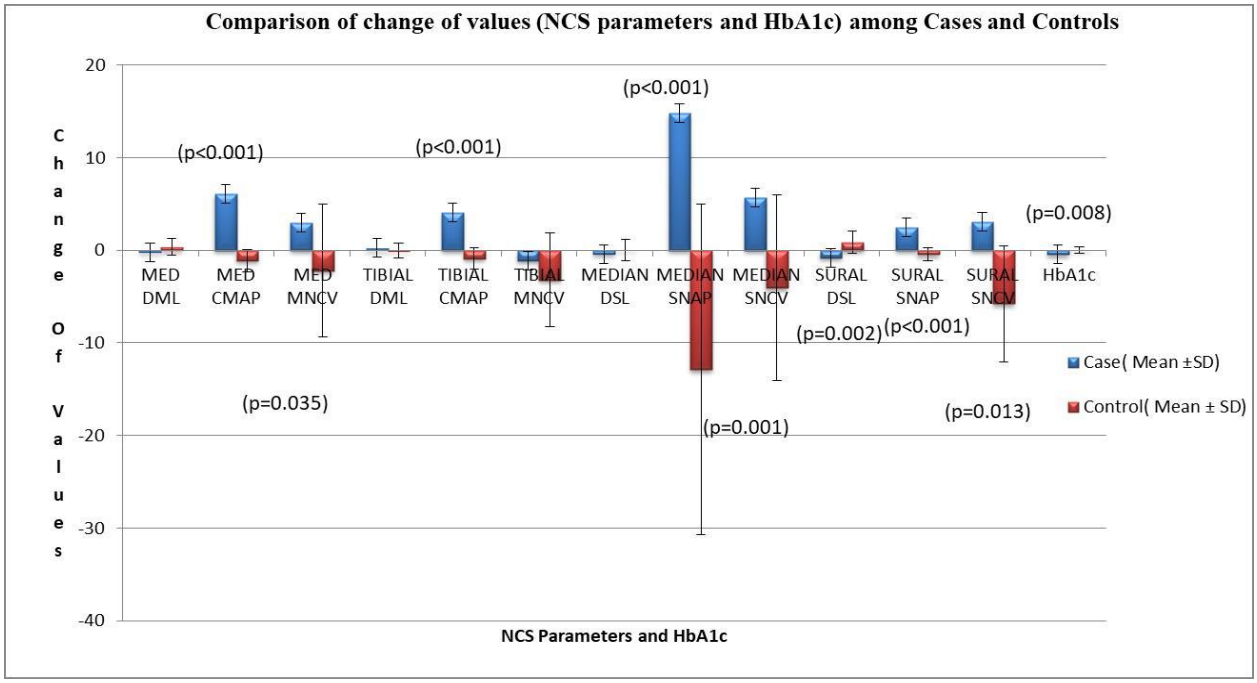

Fig.2 Tracing of Median SNC recording before (A) and after (B) zinc therapy and Tibial MNC recording before (C) and after (D) zinc therapy in cases

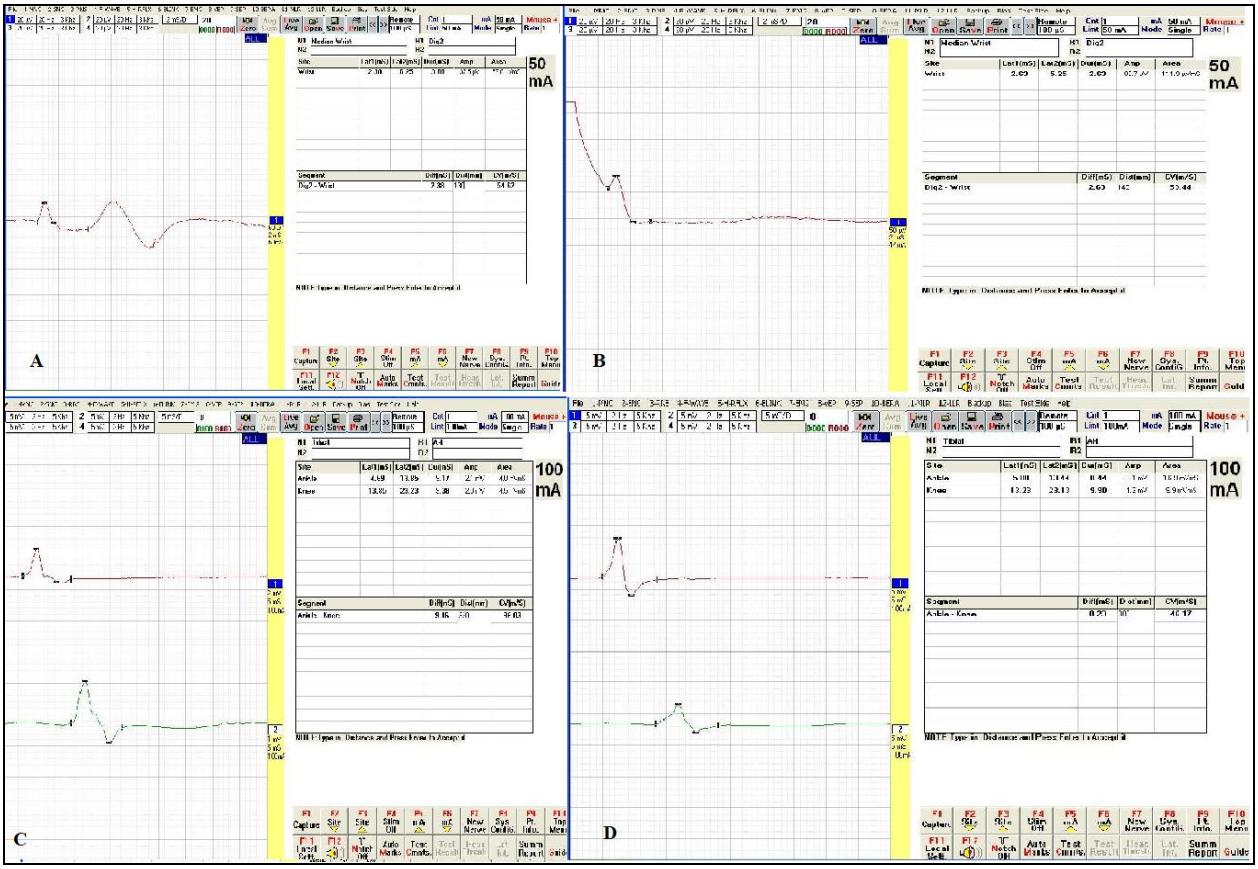

Table.1 Baseline values of HbA1c and NCS parameters among cases and controls

Parameters		Baseline values in Cases (Mean ± SD[g])	Baseline values in Controls (Mean ± SD[g])	p Value
Glycemic status(HbA1c)		7.51±1.66	7.94±1.31	0.445
MEDIAN	DML[a]	(3.99± 1.34)ms	(4.13±1.29)ms	0.223
	CMAP[b]	(3.94 ± 2.54)mv	(5.87±2.92)mv	0.328
	MNCV[c]	(49.47 ±8.39)m/s	(51.33±7.95)m/s	0.454
TIBIAL	DML[a]	(5.18± 0.90)ms	(5.42±0.85)ms	0.447
	CMAP[b]	(3.07±3.26)mv	(3.31±2.18)mv	0.357
	MNCV[c]	(41.49±8.74)m/s	(41.54±7.21)m/s	0.181
MEDIAN	DSL[d]	(3.87±1.80)ms	(4.07±1.51)ms	0.743
	SNAP[e]	(17.27±12.39)µv	(26.23±19.21) µv	0.201
	SNCV[f]	(40.73±12.41)m/s	(42.42±12.46)m/s	0.560
SURAL	DSL[d]	(5.84±1.66)ms	(4.52±1.16)ms	0.298
	SNAP[e]	(4.38±1.24)µv	(4.84±1.85)µv	0. 325
	SNCV[f]	(20.77±6.87)m/s	(27.11±7.54)m/s	0.756

a. DML-Distal Motor Latency, b. CMAP-Compound Muscle Action Potential, c. MNCV-Motor Nerve Conduction Velocity, d. DSL-Distal Sensory Latency, e. SNAP-Sensory Nerve Action Potential, f. SNCV-Sensory Nerve Conduction Velocity, g. SD-Standard Deviation

Table.2 Comparison between baseline and follow up values of NCS parameters and HbA1c by paired t test and Wilcoxon signed rank test among cases

Parameters		Baseline value (Mean ± SD[g])	Follow-up value (Mean ± SD[g])	p Value
MEDIAN	DML[a]	(3.99± 1.34)ms	(3.73±0.82)ms	0.241
	CMAP[b]	(3.94 ± 2.54)mv	(10.05±4.34) mv	<**0.001***
	MNCV[c]	(49.47 ±8.39)m/s	(52.41±7.27)m/s	0.192
TIBIAL	DML[a]	(5.18± 0.90)ms	(5.37±1.18)ms	0.515
	CMAP[b]	(3.07±3.26)mv	(7.12±4.79)mv	**0.001***
	MNCV[c]	(41.49±8.74)m/s	(40.36±5.91)m/s	0.595
MEDIAN	DSL[d]	(3.87±1.80)ms	(3.43±1.02)ms	0.352
	SNAP[e]	(17.27±12.39)µv	(32.11±18.20) µv	**<0.001***
	SNCV[f]	(40.73±12.41)m/s	(46.42±11.28)m/s	**0.003***
SURAL	DSL[d]	(5.84±1.66)ms	(4.85±1.30)ms	**0.019***
	SNAP[e]	(4.38±1.24)µv	(7.36±3.69)µv	**<0.001***
	SNCV[f]	(20.77±6.87)m/s	(23.79±8.34)m/s	0.095
Glycemic Status (HbA1c)		7.51±1.66	6.98±1.42	0.088

Table.3 Comparison between change of values of NCS parameters and HbA1c among cases and controls by t test and Mann Whitney test

Change of parameters		Change of values among Cases (Mean ± SD[g])	Change of values among Controls (Mean ± SD[g])	p Value
MEDIAN	DML[a]	-0.20±1.22	0.35±0.87	0.082
	CMAP[b]	6.08±4.25	-1.10±1.21	**<0.001***
	MNCV[c]	2.94±8.38	-2.20±7.17	**0.035***
TIBIAL	DML[a]	0.24±1.53	-0.05±0.82	0.557
	CMAP[b]	4.04±3.83	-0.90±1.12	**<0.001***
	MNCV[c]	-1.12±10.38	-3.20±5.02	0.400
MEDIAN	DSL[d]	-0.40±1.15	0.00±1.12	0.203
	SNAP[e]	14.80±13.77	-12.90±17.85	**<0.001***
	SNCV[f]	5.64±8.57	-4.05±10.02	**0.001***
SURAL	DSL[d]	-0.80±1.91	0.85±1.18	**0.002***
	SNAP[e]	2.98±2.45	-0.45±0.69	**<0.001***
	SNCV[f]	3.08±8.68	-5.80±6.24	**0.013***
Glycemic Status (HbA1c)		-0.48±0.77	0.00±0.32	**0.008***

Table.4A Comparison of change of values of NCS parameters and HbA1c among three different groups of cases by ANOVA[h] and Kruskal-Wallis test

Change of Parameters		Groups	p Value
MEDIAN	DML[a]	Between groups	**0.001***
	CMAP[b]	Between groups	0.730
	MNCV[c]	Between groups	0.268
TIBIAL	DML[a]	Between groups	0.197
	CMAP[b]	Between groups	0.746
	MNCV[c]	Between groups	0.096
MEDIAN	DSL[d]	Between groups	0.110
	SNAP[e]	Between groups	0.292
	SNCV[f]	Between groups	0.708
SURAL	DSL[d]	Between groups	0.858
	SNAP[e]	Between groups	0.287
	SNCV[f]	Between groups	0.274
Glycemic Status (HbA1c)		Between groups	**0.004***

h. ANOVA- Analysis Of Variance

Table.4B Post-hoc analysis of significant observations within groups

Parameters	Within groups		p Value
NCS Parameters (MEDIAN DML)	**Gr 1(n=13)**	**Gr 2**	0.294
		Gr 3	**<0.001***
	Gr 2(n=8)	**Gr 1**	0.294
		Gr 3	**0.014***
	Gr 3(n=4)	**Gr 1**	**<0.001***
		Gr 2	**0.014***
Glycemic Status (HbA1c)	**Gr 1(n=13)**	**Gr 2**	0.451
		Gr 3	**0.003***
	Gr 2(n=8)	**Gr 1**	0.451
		Gr 3	**0.042***
	Gr 3(n=4)	**Gr 1**	**0.003***
		Gr 2	**0.042***

Gupta *et al.,* (1998) found significantly improved Median and Common Peroneal Nerve conduction velocity after 6 weeks of zinc (660 mg /day). Hayee *et al.,* in 2005 found highly significant improvement of MNCV of both Median and Common Peroneal nerve after 6 weeks of Zinc therapy (660 mg /day) in patients of DN compared to controls, without any significant adverse effect. Previous studies did not explore any effect of zinc on sensory and other motor nerve conduction study parameters (latency and amplitude) other than MNCV.

The commonest neurophysiological abnormality in diabetes is reduction in the amplitude of motor or sensory action potential because of axonopathy (Mishra and Kalita, 2014). In a comparative SNC study done by Verma *et al.,* (2013) there was a significant decrease of SNAP amplitude of Median, Radial, Ulnar, Superficial Peroneal and Sural nerves in patients with Non-Insulin Dependent Diabetes Mellitus even without symptoms of peripheral neuropathy and healthy volunteers (Verma *et al.,* 2013). Another study showed significant decrease in amplitude and velocity in diabetes with increased latency of motor and sensory nerves compared to controls (Pandya *et al.,* 2013). Decrease of Nerve Conduction Velocity (NCV) is one of the earliest neuropathic abnormalities in DM and may present at diagnosis in type 2 DM (Thomas and Eliasson, 1984).

Numerous studies show decreased serum zinc level in diabetes. High concentrations of glucose and other secretagogues decrease the islet cell labile zinc; and zinc concentration in islet cells were related to the synthesis, storage and secretion of insulin as shown by video fluorescence analysis (Zalewski *et al.,* 1994). Low serum zinc level in diabetes has been attributed to inadequate absorption or increased urinary excretion or both (Chausmer, 1998).

In our study, we noted baseline HbA1c and value after 12 weeks in Cases and Controls. Baseline HbA1c value of Cases changed from (7.51±1.66) to (6.98±1.42) after 12 weeks, though this difference was statistically not significant ($p>0.05$). But comparing the difference in values (decrement) from baseline to follow-up between Cases and Controls, it was found that there was statistically significant decrease of HbA1c in Cases (0.48± 0.77) compared to Controls (0.00±0.32); $p=0.008$.

Comparing this change among three different groups of Cases, statistically significant difference ($p=0.004$) was found for the decrease of HbA1c.Change in HbA1c (12 week-baseline= Δ HbA1c) was -0.25±0.34, -0.56±0.25 and-1.35±1.32 in Groups 1, 2 and 3 respectively, thereby showing the best response in Group 3.Thus patients with the longest disease duration had the best HbA1c response to zinc.

Our study concurs well with previous studies done by Al-Maroof *et al.,* (2006) and Afkhami-Ardekani *et al.,* (2008). Similar reduction of HbA1c along with reduction of fasting plasma glucose, 2 hour post-prandial plasma glucose, total Cholesterol (TC) and TC/HDL ratio was also found (Gunasekara *et al.,* 2011). In the same year, Farvid *et al.,* (2011) also found significant reduction of HbA1c and neuropathic score in type 2 diabetic patients by micronutrient supplementations. Similar results was also found by other workers in previous studies (Hussain

et al., (2006), Parham *et al.*, 2008), though the study by Niewoehner *et al.*, (1986) did not find improvements in diabetes control.

Apart from improving neuropathy and glycemic status, zinc also has an important effect on improving nephropathy as shown by Farvid *et al.*, (2005). Improvement of glycemic status and nephropathy was further supported by another study (Khan *et al.*, 2013). Zinc also has some promising role in reduction of BP and lipid profile (Farvid *et al.*, 2004a, Farvid *et al.*, 2004b).

In our study, zinc therapy showed marked improvement on neurophysiological findings in DN as reflected by significant changes of NCS parameters when compared with their baseline value. The change (increment or decrement) of different NCS parameters from baseline to follow-up level showed significant difference among Cases and Controls for both motor and sensory parameters favoring Cases. Improvements of sensory nerve parameters were quite uniform and consistent. Apart from conduction velocity, it was the amplitude (both motor and sensory nerves) which showed highly significant change after zinc therapy. Not only NCS parameters, decrement of HbA1c from baseline to follow-up was higher in Cases compared to Controls, which meant that zinc supplementation improved glycemic status in Cases. Comparing the changes (NCS parameters and glycemic status) among the three different groups of Cases, significant decline of Median latency (motor) and HbA1c level, suggesting these parameters, after zinc therapy, varied significantly according to duration of diabetes with the best response in those with the longest diabetes duration.

The present study is unique in that, we measured baseline and follow-up latency and amplitude (for both motor and sensory nerves) along with conduction velocity in patients with diabetic neuropathy who received zinc and compared the values those who did not receive zinc.

From this study we conclude that zinc is an extremely promising therapeutic modality in patients with diabetic neuropathy and zinc supplementation may contribute to improved glycemic outcomes in patients with DN. It is interesting that the Median DML and HbA1c improved most in those with the longest duration of diabetes. If these findings (improvement) can be confirmed by other studies, it is indeed promising, as established therapeutic modalities fail with increase in duration of diabetes. More studies are required on a larger population preferably with measurement of serum zinc levels. Basic research on the exact mechanisms of the benefits of zinc in DN will expand our understanding further. Our observation that zinc supplementation also improves glycemic outcome is exciting and needs further research for confirmation and explanation.

Conflict of interest

None of the authors have potential conflicts of interest to disclose.

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How to cite this article:

Sumana Gupta, Indira Maisnam, Tapobrata Guharay, Sandip Ghosh, Apurba Kumar Mukherjee and Anil Baran Singha Mahapatra. 2017. Zinc Supplementation Significantly Improves Neurophysiological and Glycemic Measures in Patients with Diabetic Neuropathy. *Int.J.Curr.Res.Aca.Rev.* 5(7), 61-69.
doi: https://doi.org/10.20546/ijcrar.2017.507.009