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Original Article

Effect of Low Level Laser Therapy on serum vitamin D and magnesium levels in patients with diabetic peripheral neuropathy – A pilot study

Anju M. [a], Lincy Chacko [a], Yenoshan Chettupalli [a], Arun G. Maiya [b], Saleena Ummer Velladath [a,*]

[a] Department of Medical Laboratory Technology, School of Allied Health Sciences, Manipal Academy of Higher Education, Manipal, India
[b] Department of Physiotherapy, School of Allied Health Science, Manipal Academy of Higher Education, Manipal, India

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ABSTRACT

Background: Diabetic Peripheral neuropathy (DPN) is the most distressing complication of diabetic population leading to loss of sensation, pain, and amputation. Low-level laser therapy (LLLT) has been used to manage nerve injuries as it holds the potential to induce a biostimulatory effect with no side effects. Hence we planned to study the biochemical effect and therapeutic outcomes of LLLT on patients with painful diabetic peripheral neuropathy as a preliminary work.
Materials and methods: Pre-posttest analysis was done on 40 patients diagnosed with DPN confirmed using 10 g Monofilament test and Michigan Neuropathy Screening Instrument (MNSI). Vibration sensation and pain measured by Vibration perception threshold (VPT) and Numeric pain rating scale (NPRS). All patients were given LLLT (3.1 J/cm^2) on plantar and dorsal of the foot for 10 days. Serum samples were collected at baseline and 4 weeks after LLLT to estimate Vitamin D and Magnesium and compared the results.
Results: There was a significant increase in Vitamin D and Magnesium levels after LLLT. We observed a considerable improvement in the quality of life after LLLT demonstrated by a decrease in VPT and MNSI and a reduction in NPRS in DPN patients.
Conclusion: In this study, we found that LLLT improved the QL and hence may be a useful therapeutic option in treating peripheral neuropathic pain in type 2 diabetic patients. The progress in the serum Magnesium and Vit. D levels were proportional to the QL and may be a good indicator of the prognosis of DPN after LLLT.

1. Introduction

According to the International Diabetes Federation in 2017, approximately 425 million adults are affected with DM globally [1]. Long-term association of diabetes leads to microvascular and macrovascular complications due to poor glycemic control [2]. Long duration of diabetes affects eyes, nerves, kidneys, heart, and feet leading to anatomical, functional, structural changes and multiple organ failure [3]. A multicentric study conducted by litwak et al. in diabetes patients reported 27% of macrovascular complication and 37–89% of microvascular complications. Among the microvascular complications, Diabetic Neuropathy had the highest incidence ranging from 25 to 83% [4]. Young et al. in his study reported a prevalence of diabetic neuropathy as 22.7% in type 1 DM and 32.1% in type 2 DM. An overall prevalence of neuropathy was reported as 28.5%. Increase in neuropathy was associated with age and duration of DM [5]. In India, the prevalence of various complications in diabetes is Cardiovascular (23.6%), Neuropathy (24.6%), Renal (21.1%), Eye (16.6%) and Foot ulcer (5.1%) [6].

Diabetic neuropathy is a group of nerve disorders caused by diabetes including peripheral, autonomic, proximal, and focal, where peripheral neuropathy being the most prevalent (50%) [7–9]. Diabetic peripheral neuropathy (DPN) is one of the chronic complications of Diabetes Mellitus affecting both somatic and autonomic nervous system. Patients with type 2 diabetes mellitus have a 45% lifetime incidence of neuropathy [10,11]. Most of the patients with DPN suffer from neuropathic pain. When a lesion or dysfunction affects the peripheral nervous system, it leads to Peripheral neuropathic pain [12,13]. It is estimated that 11–32% of DPN patients may present with neuropathic pain. The long-standing peripheral neuropathic pain is seen in one of six diabetic subjects associated with peripheral neuropathy [8]. If not

* Corresponding author.
E-mail address: Saleena.ummer@manipal.edu (V. Saleena Ummer).

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taken care properly it leads to foot ulceration and lower extremity amputations. Approximately 15% of people with diabetes have such amputation during their lifetime [14].

DPN is the main initiating factor of foot ulceration and ends up in lower limb amputations associated with more than 50% mortality within five years. An effective means of detecting and treating peripheral neuropathy would have a significant medical, social, and economic impact, as 80% of amputations are preceded by foot ulceration [9]. DPN remarkably decreases the quality of life and considerably increases the financial burden of treatment.

Current therapy for painful DPN is aiming for symptomatic relief through various drug administrations. These drugs are often associated with systemic side effects and do not retard the advancement of the underlying neuropathy [15]. There are various non-pharmacological management methods used in the treatment of PDNP, like acupuncture, infrared therapy, and various electrotherapies such as spinal cord electrostimulation and transcutaneous electrical nerve stimulation (TENS) [16]. Among the electrotherapy modalities, low-level laser therapy (LLLT) is more promising to manage nerve injuries as it holds the potential to induce a biostimulation effect on the nervous system [17]. LLLT uses low intensity light that generates a photochemical effect leading to some biochemical changes within the cell. LLLT uses a power range from 10 mW to 500 mW at a wavelength ranging from 660 to 905 nm. At low doses, it promotes cell proliferation [18].

Vitamin D deficiency is commonly seen in patient with diabetes. Several studies have reported that intake of Vit D may prevent or delay the onset of diabetes and reduces complications associated [19,20]. Vit. D deficiency is associated with the development of Diabetic peripheral neuropathy. Magnesium is a cofactor for various reactions that need ATP, it is an essential element in cell proliferation and an important factor for immune responses (cellular and humoral) [21,22]. Low serum magnesium is seen in diabetes mellitus [23–25].

This study aimed to evaluate the effect of LLLT on serum levels of Vit D and Mg+ in patients with DPN.

2. Material and methods

A prospective Pre-post study was conducted in patients attending diabetic foot clinic, Kasturba hospital, Manipal. After obtaining the ethical clearance from the institutional ethical committee (IEC 786/2016), patients with diabetic peripheral neuropathic pain were recruited into the study after obtaining written informed consent. Patients with diabetic peripheral neuropathic pain with age between 30 and 70 years were included in the study. Those patients with any other neurological disorder or morbid conditions, DPN with foot ulcer, undergoing chemotherapy and radiation and pregnant women were excluded from the study.

After fulfilling the eligibility criteria, a total of 40 Type II diabetic patients with peripheral neuropathic pain were recruited into the study. A detailed baseline evaluation including tests for neuropathic screening and blood tests were done to confirm the eligibility. Blood tests included Fasting blood sugar and Glycated hemoglobin test that confirmed the DM. The neuropathic testing was done using Michigan Neuropathy Screening Instrument (MNSI), 10 g Semmes Weinstein Monofilament and Vibration Perception Threshold (VPT). MNSI contains two separate assessments to assess distal symmetrical DPN. The first part includes 15 self-administered questionnaire and the second part includes brief physical evaluation of lower extremity by examination of foot and assessment of vibration sensation and angle reflexes [26]. VPT detects large fiber dysfunction [27]. 10 gm Semmes Weinstein monofilament was used for the detection of loss of protective sensation. Here the Monofilament was applied to the areas on feet perpendicularly by applying a force of 10 gm for about one second. If the patient failed to sense the filament after it bends at the test site is taken as considerable loss of sensation. This is considered to be the best method to detect loss of sensation [28,29]. The pain was assessed using numeric pain rating scale.

Baseline Serum samples were collected from all patients. Serum was separated and stored at −70 °C for further analysis of Vit.D and Magnesium.

2.1. LLLT treatment

All subjects included in the study were treated with two separate low level laser, for a period of 10 days. The EC laser of wavelength 632.8 nm with a dosage of 3.1 J/cm^2 for 9 min was used with scanning mode on the plantar and dorsum of foot and the Thor Laser of wavelengths 660 nm and 850 nm with dosage of 3.4 J/cm^2 and power density of 50–150 mW/cm^2 was used with contact method over popliteal fossa and the neck of fibula for 3 min and a frequency of 78 Hz.

All participants were reassessed with detailed clinical and biochemical evaluation for serum biomarkers, (Vit.D, Magnesium), Vibration Perception Threshold (VPT), Numeric pain rating scale and MNSI at four weeks after the start of laser intervention to assess the carryover effect of low-level laser therapy.

2.2. Biomarkers

Both serum samples at baseline and after four weeks of LLLT was collected and stored at −70 °C. Serum Magnesium levels were determined by Calmagite Method based on the principle that Magnesium combines with calmagite in an alkaline medium to form red colored complex which is measured colorimetrically at 510 nm [30–32]. Vit.D were estimated by ELISA using quantimicrolisa kit. It is based on competitive ELISA in which samples were diluted with Biotin labeled 25-OH vitamin D conjugate and incubated. Peroxidase labeled streptavidin enzyme conjugate was then added. After incubation and washing steps the substrate was added for color reaction and stopped after a defined time. The color intensity was measured which is inversely proportional to the concentration of 25-OH Vitamin D in the sample.

The data analysis was done using SPSS version 15. Baseline Mean score of VPT, MNSI and Numeric pain rating scale along with mean values of biomarkers were compared with that of 4 weeks after LLLT using Paired *t*-test. Correlation of biomarkers with NQL was done by Pearson's correlation coefficient.

3. Results

A total of 40 patients with diabetic neuropathy with age range of 30–70 yrs were studied. Among the patient's the majority were males (65%). The duration of Diabetes Mellitus was rangeing from 5 to 20 yrs. Table 1 shows the demographic characteristic of the patients obtained from the medical records. All patients were using oral glycemic drugs and completed the course of LLLT with no dropout and tolerated laser treatment without any adverse reactions. Mean FBS was 145 mg/dl and glycated Hb was 8.1%.

3.1. Evaluation of neuropathy

The baseline neuropathic evaluation showed a Median score of MNSI 6.5 and NPRS score from 7. At one month after LLLT the MNSI score showed a median decrease of 3 ($p < 0.001$) and NPRS score showed a median decrease of 1. This indicate a significant reduction in the pain ($p > 0.001$). The mean baseline VPT value was 39 and there was a significant improvement in the vibration perception

Table 1
Demographic characteristics of DPN patients.

Parameters	Patients with DPN (n = 40)
Age (years)	62.07 ± 11.95
Gender	Male- 26, Female - 14
BMI(Kg/m^2)	25.89 ± 3.49
Fasting blood sugar (mg/dl)	145.8 ± 44.22
Random Blood Sugar(mg/dl)	213.6 ± 62.72
Glycated Hemoglobin (HbA1C)%	8.1 ± 0.7
Duration of Type II Diabetes Mellitus (years)	12.07 ± 6.34
Duration of Peripheral Neuropathy (years)	7.52 ± 3.56

(22) after LLLT treatment ($p = 0.003$).

3.2. Effect of LLLT on serum vitamin D and magnesium

Out of the total 40 DPN patients 36 were having low levels of serum vitamin D. Hypomagnesemia was observed in 33 patients. There was a significant baseline elevation of both serum Magnesium ($p < 0.001$) and Vit D ($p = 0.002$) in all patients at four weeks after LLLT. Among the 36 patients with Vit D deficiency, 23 got corrected with the deficiency after LLLT. Out of 33 with hypomagnesaemia 25 had a rise in Magnesium level after LLLT and reached to normal. The pre-post changes in biomarkers are shown in Table 2.

3.3. Correlation of Vit D and magnesium with quality of life after LLLT

Pearson's correlation analysis revealed a moderate correlation of Vit. D variations with that of MNSI scores after the LLLT ($r = 0.5315$). Vit. D changes also showed a positive but a weak correlation with that of NPRS ($r = 0.0097$) which is shown in Table 3. But the variations in Magnesium level showed a very weak relationship with that of MNSI and NPRS scores. There was a strong positive correlation of Vit. D with Magnesium levels. We also observed a positive correlation of the baseline variations of these markers (Table 4 & Table 5).

3.4. Serum Vit.D and magnesium as a prognostic marker of DPN

The ROC analysis of baseline variations of Vit. D revealed an AUC of 0.80 (95% CI, 0.66–0.94) indicating the better performance of Vit. D as a prognostic marker of DPN after LLLT. The baseline variations of Magnesium showed an AUC of 0.62 (95% CI, 0.44–0.80) indicating its poor performance (Fig. 1). The cut of value for Vit. D variations was found to be 12.5 ng/ml at sensitivity of 77% and specificity of 71% (Table 6).

4. Discussion

The present study used Low Level Laser Therapy modality to investigate its effect on neuropathy pain in type 2 DM. This study holds a higher clinical significance in the management of neuropathic pain in DPN as our results show that LLLT could provide a significant reduction in neuropathic pain that was correlated with increase in biomarker levels. Magnesium deficiency is a proposed factor in the pathogenesis of diabetes-related complications, including neuropathy. In the central nervous system, Mg is also a voltage dependent blocker of *N*-acetyl −D-aspartate receptor channels involved in the abnormal processing of sensory information [33]. In this study, there was a significant rise in Magnesium levels after LLLT in DPN patients without any Magnesium supplementation. A recently conducted systematic review and meta-analysis including 1484 type 2 Diabetic patients reported Vitamin D has a significant impact on the of Diabetes mellitus and its associated neuropathy [39]. Vit D deficiency is associated with low neurotrophins which is required for the proper functioning of neurons. A study conducted by Soderstrom et al. in 591 diabetic patients with age above 40 years has been reported that 81% of the patients were having deficiency of Vit D (<30 ng/ml) which was greatly associated with neuropathy [38]. We observed a significant elevation of Vit D levels after LLLT with reduction in pain indicated by the decrease in Vibration Perception Threshold (VPT). The reason for the reduction in pain could be attributed to biostimulatory effects of Laser. The study conducted by Kudoh et al., 1989 and Chow et al., 2007 suggested that there could be an increase in nociceptive threshold following a specific dose of LLLT resulting in the neural blockade [34,35]. Inhibition of A and C nerve fibers that may be mediated by neural enzyme inhibition that also could play a significant role in pain inhibition. In addition it has been suggested that LLLT would lead to increased endorphin production [36] and nitric oxide that contribute for better healing [37]. The findings from the present study demonstrate that LLLT was effective in showing its positive effects on Vit. D and Magnesium levels to manage neuropathic pain in diabetic patients. One of the limitations of this study is that most of the patients are between 60 and 70 years old, inclusion of age groups with uniform distribution between 30 and 70 years could have been more significant. The results of this study are encouraging in terms of alternative therapy for DPN with a lower risk of side effects. Hence we recommend that a larger sample sized randomized control trials should be conducted to confirm our findings and identify further applicability.

Table 2
Pre-Post changes in clinical variables after low level laser therapy.

Parameter	Baseline	After 4 weeks	P Value
Vitamin D (ng/ml)	9.91 ± 6.71	16.81 ± 13.42	0.002
Magnesium (MEq/L)	0.88 ± 0.71	1.53 ± 0.85	<0.001
MNSI	5.77 ± 1.17	3.00 ± 0.85	<0.001
NPRS	6.77 ± 1.00	1.27 ± 0.75	<0.001
VPT	39 ± 11.4	22.8 ± 9.97	0.003

Table 3
Correlation of Vit D and magnesium with MNSI.

Parameter		Vit.D	Magnesium
MNSI	Pearson correlation coefficient	0.532	0.123
	P value	<0.001	0.448
	N	40	40

Table 4
Correlation of Vit.D and magnesium, with NPRS.

Parameter		Vit.D	Magnesium
NPRS	Pearson correlation coefficient	0.0097	0.016
	P value	<0.001	.921
	N	40	40

Table 5
Association of deficiency of Vit.D and Magnesium in DPN patients.

Parameter		Vit.D(baseline)	Vit. D(Variation from baseline)
Magnesium	Pearson correlation coefficient	0.758	0.373
	P value	<0.001	.018
	N	40	40

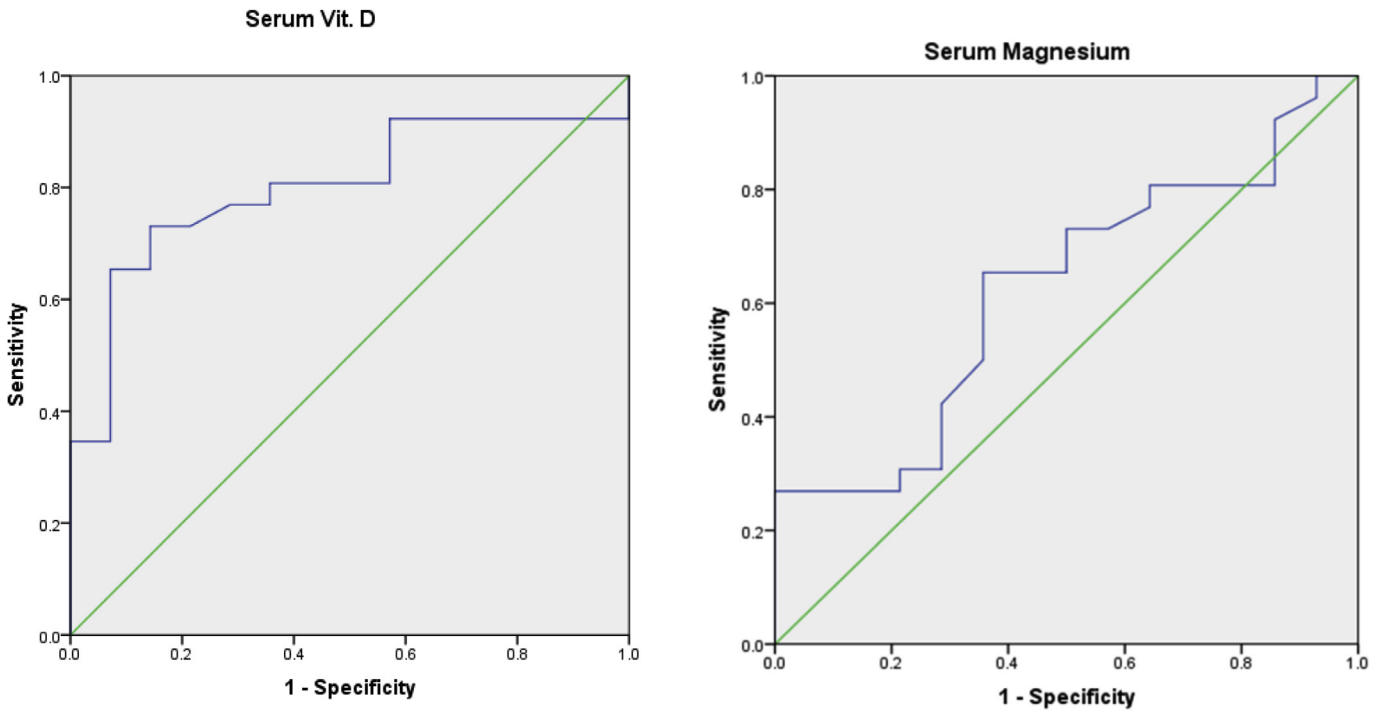

Fig. 1. Receiver operating characteristic curve(ROC) for baseline variations of Vit D and Mg+.

Table 6
Predictive characteristics of baseline variations of Vit D and Mg+.

Biomarkers	Opt. Cut of Value	Sensitivity	Specificity	AUC	95% CI of AUC
Vit D	12.5	0.77	0.71	0.80	0.66–0.94
Magnesium	0.85	0.65	0.64	0.62	0.44–0.80

5. Conclusion

The reduction in neuropathic pain was associated with the increase in serum Vit. D and Magnesium levels after four weeks which may be a good indicator of the role of LLLT in neurodegeneration. Further studies on surrogate markers may give new insights into the mechanism of action of Laser which may open the door to identify the most suitable marker for monitoring the therapy.

Declaration of interest

The authors report no conflicts of interest.

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