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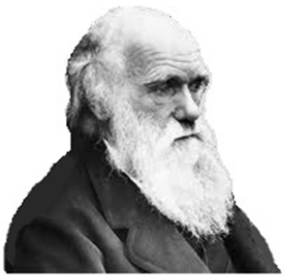

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Effectiveness of electrical stimulation and low-intensity laser therapy on diabetic neuropathy: A systematic review

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ABSTRACT

Diabetes mellitus (DM) is a group of metabolic diseases which typically presents with frequent urination, increased thirst, and increased hunger. DM may be classified into three main types: type I (insulin-dependent DM), type-II (non-insulin dependent DM), and type III (gestational DM). Diabetes is a group of diseases of global health significance, as 382 million people worldwide had diabetes in the year 2013, and this was projected to increase to an estimated 415 million in 2015. Damage to the nerves of the body (diabetic neuropathy) is the most common complication of diabetes. The signs and symptoms of diabetic neuropathy include numbness, diminished sensation, pain, etc. Various types of electrotherapy, such as transcutaneous electrical nerve stimulation (TENS), pulsed-dose electrical stimulation, frequency-modulated electromagnetic neural stimulation, have been reported effective in managing diabetic neuropathy. This study is a systematic review of the evidence to enable the determination of the effectiveness of electrical stimulation and low-intensity laser therapy (LILT), and also aid their recommendation if proven to be effective. The outcome of this study was that TENS and other forms of electrical stimulation reviewed in this study may be effective and safe non-pharmacological treatment modalities in relieving the symptoms associated with diabetic neuropathy. The effectiveness of LILT couldn't be determined due to the different parameters used to evaluate patients' outcome and limited number of studies. Authors recommend that further randomized

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controlled trials with similar methodological parameters and studies, with higher quality of evidences, are needed to establish the true effectiveness of these modalities in diabetic neuropathy.

***Keywords*:** Diabetes mellitus, diabetic neuropathy, electric stimulation, laser therapy

1. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases in which there is a high blood sugar level over a prolonged period (World Health Organization, 2014). Symptoms of high blood sugar include frequent urination (polyuria), increased thirst (polydipsia), and increased hunger (polyphagia). Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced (Shoback, 2011). Diabetes mellitus can be classified into three main types. Type I Diabetes mellitus (referred to as insulin-dependent diabetes mellitus) usually result from failure of the pancreas to produce enough insulin. The cause is unknown (World Health Organization, 2013). Type 2 DM (also referred to as non-insulin dependent Diabetes mellitus) begins with insulin resistance, a condition in which cells fail to respond to insulin properly (World Health Organization, 2013). In the course of the disease progression, lack of insulin may develop. The primary cause is excessive body weight and inadequate exercise (World Health Organization, 2013). Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood-sugar levels (World Health Organization, 2013).

According to the International Diabetes Federation, 382 million people worldwide had diabetes in the year 2013 (International Diabetes Federation, 2013). This was projected to increase to an estimated 415 million in 2015, with Type 2 Diabetes mellitus making up about 90% of the cases (International Diabetes Federation, 2015). The prevalence of diabetes in WHO African region was estimated in 2000 to be at 7.02 million people. Of these, about 0.702 million people had type 1 diabetes and 6.318 million had type 2 diabetes. In addition, close to 113,000 people died from diabetes related causes, 561,600 were permanently disabled, and 6,458,400 experienced temporary disability (World Health Organization, 2008; Kirigia, Sambo, Sambo, & Barry, 2009).

Complications of diabetes mellitus typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The foremost long-term complication of DM is damage to blood vessels. Diabetes doubles the risk of cardiovascular disease (Sarwar, *et al*., 2005) and about 75% of deaths in diabetics are due to coronary artery disease (O'Gara, *et al*., 2011). Diabetes can lead to other "macrovascular" diseases such as peripheral vascular diseases, stroke, etc. It can also lead to damage in small vessels, resulting in damage to the eyes, nerves, kidneys, etc. as their blood supply is affected. Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant (World Health Organization, 2014).

Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes (World Health Organization, 2014). It is defined as presence of symptoms and/or signs of peripheral nerve dysfunction in diabetes after exclusion of other

causes, which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infectious, immune mediated, neoplastic and secondary to other systemic illnesses (Bhadada, Sahay, V.P, & Agrawal, 2001). The signs and symptoms of diabetic peripheral neuropathy include numbness, diminished sensation, and/or pain. Painful symptoms, such as burning, pins and needles, shooting pain and hyperaesthesia, have also been reported (Galer, Gianas, & Jensen, 2000). Diabetes can affect the foot lending to diabetic foot ulcer which may be difficult to treat and sometimes requires amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness (World Health Organization, 2014).

Thomas (1973) classified diabetic neuropathy into two (2) based on anatomical characteristics which are diffuse and focal. He further sub-classified the Diffuse diabetic neuropathy into: Distal Symmetric Sensory Motor Polyneuropathy, Autonomic Neuropathy, Symmetric Proximal Lower limb Neuropathy (Amyotrophy), and the Focal diabetic neuropathy into: Cranial Neuropathy, Radiculopathy or Plexopathy, Entrapment Neuropathy and Asymmetric Lower limb Motor Neuropathy. The Distal Symmetrical Polyneuropathy (Ds Peripheral neuropathy) is the commonest clinical form of diabetic neuropathy affecting more than 90% of the patients (Tesfaye, Boulton, & Dickenson, 2013). Generally, Distal Symmetrical Polyneuropathy affects the toes and distal foot which slowly progresses proximally to affect the feet and legs in a stockings distribution (Tesfaye, Boulton, & Dickenson, 2013).

Painful diabetic neuropathy (PDN) can cause symptoms that last for years and severely impair quality of life and the painful diabetic neuropathy prevalence is 26.4% in diabetes. Peripheral neuropathy is a common complication of diabetes mellitus (Carrington, Abbott, Griffiths, Jackson, Johnson, & Kulkarni, 2001). Up to 36% of individuals with non-insulin-dependent diabetes mellitus are affected by this condition, which is believed to be progressive and irreversible (Harris, Eastman, & Cowie, 1993). Pain is usually the worst at night and may disrupt the patient's sleep (Jung and Pfeifer, 1986). Diabetic patients with Peripheral neuropathy may be unable to maintain their posture, as evidenced by their exaggerated body sway (Uccioli, Giacomini, & Monticone, 1995). Peripheral neuropathy is also a risk factor for foot ulcers, infection and even amputation (Cheer, Shearman, & Jude, 2009). Neuropathic ulcers frequently occur at the forefoot beneath the metatarsal heads (Boulton, Hardisty, Betts, Franks, Worth, & Ward, 1983). Peripheral neuropathy is associated with hyperextension of the metatarsophalangeal joints, clawing of the toes, and reduced plantar tissue thickness (Abouaesha, *et al*., 2001). This may increase foot pressure and lead to foot ulcers (Brink, 1995).

As the aetiology and pathogenesis of the painful symptoms induced by Peripheral neuropathy are poorly understood, medical treatment is largely symptomatic, it consist of analgesics, anticonvulsants, opioids and tricyclic antidepressants (Boulton, Malik, Arrezo, & Sosenko, 2004).

Physical therapy intervention includes exercise therapy, especially balance training which can be used for postural control (Matjacić and Zupan, 2006) Aerobic exercise training may prevent the onset, or modify the natural history of diabetic peripheral neuropathy (Balducci, Iacobellis, L., Di Biase, Calandriello, & Leonetti, 2006;). The pathogenesis appears to be multifactorial, and pathological changes in the endoneural capillaries appear to correlate with the severity of neuropathy (Malik, *et al*., 1989). Fisher, *et al*., 2007, endorse the notion that ischemia may be an important factor in the pathogenesis of diabetic neuropathies. He reported improvement in the nerve function after 24 weeks of moderate exercise training in patients with type II DM. The nerve function was assessed using neurophysiological parameters. Based on the suspected pathogenesis of ischemia, the treatment is focused on improving circulation and

oxygenation. Patients with diabetes may sometimes find it hard to perform their exercises and may therefore require other treatment. This is attributed to the numerous comorbidties of diabetes mellitus. One method is electrotherapy (Gilcreast, *et al*., 1998; Kaada, 1982; Jacobs, *et al*., 1988), which has been shown to enhance microcirculation and endoneural blood flow (Jacobs, *et al*., 1988). Electrotherapy could be effective in view of the impaired microcirculation in the peripheral nerves of patients with diabetic peripheral Neuropathy. Martin, *et al*., (1992) found electrical stimulation to exert an effect on the morphological and metabolic properties of paralysed muscles. Local release of neurotransmitters, such as serotonin (Walker, 1983), increased production of mitochondrial adenosine triphosphate (ATP) (Passarella, 1989), release of endorphins (Yamamoto, Ozaki, Iguchi, & Kinoshita, 1988), or anti-inflammatory effects (Ailioaie and Lupusoru-Ailioaie, 1999) may also trigger the analgesic effect of electrotherapy.

Electrotherapy is also involved via the activation of the dorsal column. The input of pain is interrupted by the inhibition of C fibres (thus interrupting/gating the input of pain) (Watkins and Koeze, 1993). Mima *et al*., (2004) registered a reduction in the excitability of the human motor cortex by the use of high-frequency transcutaneous electrical nerve stimulation (TENS); the outcome of this study shows that short-term TENS may have an inhibitory effect on both, the motor and sensory system. Various types of electrotherapy, such as transcutaneous electrical nerve stimulation (TENS) (Kumar and Marshall, 1997; Kumar, *et al*., 1998; Julka, *et al*., 1998; Alvaro, *et al*., 1999; Forst, *et al*., 2004), pulsed-dose electrical stimulation applied by stocking electrodes (Armstrong, *et al*., 1997; Oyibo, *et al*., 2004), pulsed (electro-) magnetic fields (Weintraub & Cole, 2004; Musaev, *et al*., 2003; Wróbel, *et al*., 2008; Weintraub, *et al*., 2009), static magnetic field therapy (Weintraub, *et al*., 2003), external muscle stimulation (Reichstein, *et al*., 2005; Klassen, *et al*., 2008; Humpert, *et al*., 2009) and frequency-modulated electromagnetic neural stimulation (FREMS) (Bosi, Conti, Vermigli, Cazzetta, & Peretti, 2005), have been reported, but to our knowledge have not been reviewed thus far. A systematic review of the evidence would enable the determination of the effectiveness of electrical stimulation and low-intensity laser therapy, and also aid their recommendation if proven to be effective. Therefore, the primary aim of this study was to systematically review the effectiveness of electrical stimulation and low-intensity laser therapy in relieving the symptoms associated with diabetic neuropathy.

2. METHDOLOGY - SEARCH STRATEGY

An electronic search of the following databases (from inception to February, 2017): PUBMED, SCIENCEDIRECT, PEDro, and COCHRANE LIBRARYwas done. The following keywords describing diabetic neuropathy was used: PAINFUL DIABETIC NEUROPATHY, PERIPHERAL DIABETIC NEUROPATHY, and DIABETIC NERVE DISEASE, DIABETIC NEUROPATHIES, DIABETIC ASYMMETRIC POLYNEUROPATHY, DIABETIC POLYNEUROPATHY combined with Electrical Stimulation; ELECTROSTIMULATION, TENS, TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION, ELECTROANALGESIA combined with, Low-Intensity Laser Therapy: LILT, LASER THERAPY, LASER, combined with Effect: EFFECTIVENESS, EFFICACY, IMPACT, EFFICIENCY and INFLUENCE. Included studies were protocol, clinical trials, retrospective study, prospective study, etc. The search was limited to English texts. The complete search strategy employed in PubMed, Cochrane library and Science direct is shown in **Table 1**.

Table 1. PubMed, Cochrane library and science direct search strategy

1.	Effect OR Efficacy OR Effectiveness OR Efficiency OR Impact OR Influence
2.	Electrical stimulation OR Transcutaneous Electrical Stimulation OR Electrotherapy OR Transdermal Electrostimulation OR Electric Stimulation OR Transcutaneous Electrical Nerve Stimulation OR Analgesic Cutaneous Electrostimulation OR Electroanalgesia OR Electrical Stimulation therapy OR Electrical Nerve Stimulation OR Cutaneous electrostimulation OR TENS
3.	Diabetic Neuropathy OR Diabetic Neuropathies OR Diabetic Polyneuropathy OR Diabetic Mellitus Complications OR Diabetic Mononeuropathy OR Peripheral Diabetic Neuropathy OR Asymmetric Diabetic Proximal Motor Neuropathy OR Diabetic Autonomic Neuropathy OR Painful Diabetic Neuropathy OR Diabetic Asymmetric PolyneuropathyOR Complications of Diabetes Mellitus.
4.	Low-Intensity Laser Therapy OR Laser Therapy OR LILT OR Low-Intensity Laser OR Low intensity Laser Therapy OR Laser.

Inclusion criteria

a) Articles published from inception to February, 2017
b) Types of studies that were included are Randomised control trials, pilot study, case study, retrospective study, etc., that evaluated electrical stimulation or low-intensity laser in the treatment of diabetic neuropathy
c) Population studies using human beings diagnosed with diabetic neuropathy
d) Articles written in English language
e) Invasive techniques such as spinal cord stimulation.

Exclusion criteria

a) Papers written in non-English language where translation cannot be arranged
b) Inclusion of subjects other diabetic neuropathy patients
c) Papers addressing other complications of diabetes mellitus
d) Papers without full text or abstract
e) Papers where other modalities were used.

Study selection and data extraction

The search produced a total of 2107 hits. Two investigators were assigned to one database. The titles and abstract of all articles identified using the search strategies were evaluated by eight investigators in duplicate. All abstracts that did not provide enough details of the inclusion and exclusion criteria were selected for full text evaluation. Further independent reviews of the full texts were also carried out by the investigators using the eligibility criteria

as the selection template. The disagreements that occurred among the reviewers were solved by consensus.

The main data extracted were number of patients, objectives of the study, interventions, type of the study, duration of treatment, and outcome measure used. The main outcomes extracted were pain relief and sensation improvement (**Table 2**).

The grading of the level of evidence of the articles was based on the grading system suggested by the evidence based medicine guidelines, adapted from the GRADE Working Group (42).

Table 2. Characteristics of studies reviewed

S/N	Author and date	Title of paper	Sample size	Objective of the study	Intervention	Types of study	Duration of study	Outcome measure	Results and conclusions	Level of evidence
1.	Najafi et al, 2013	A novel planter stimulation technology for improving protective sensation and postural control in patients with DPN	54	This study examined the effect of electrical Stimulation therapy on DPN patients' postural control as well as recovery of plantar sensation	Electrical stimulation provided via aqueous solution.	Double-blind, randomized study	6 weeks	Vibration perception threshold	This randomized pilot study provides preliminary data on the potential of electrical stimulation via aqueous solution to improve protective sensation and postural stability in DPN patients	C
2.	Gossrau, et al, 2011	The microcurrent transcutaneous electrical nerve stimulationin painful diabetic neuropathy: a randomized placebo-controlled study	41	To assess the effect of micro-TENS in reducing neuropathic pain in patients with PDN	micro-TENS	Single-blinded randomized controlled trial	4 weeks	Pain disability index	The pain reduction with the applied transcutaneous electrotherapy regimen is not superior to placebo	D

3.	4.	5.
Bosi, et al, 2005	Reinstein et al, 2005	Nabi et al, 2015
Effectiveness of frequency-modulated electromagnetic neural stimulation in the treatment of painful diabetic neuropathy	Effective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation	Comparison of transcutaneous electrical nerve stimulation and pulsed radiofrequency sympathectomy for treating painful DN
31	41	60
To evaluate the efficacy of frequency-modulated electromagnetic neural stimulation (FREMS) as a novel treatment for painful diabetic neuropathy	To compare the effects of high-frequency external muscle stimulation with those of TENS in patients with symptomatic distal symmetricalsensory polyneuropathy	To compare the efficacy of transcutaneous electrical nerve stimulation (TENS) and pulsed radiofrequency (PRF) lumbar sympathectomy in treating painful DPN.
FREMS	High-frequency external muscle stimulation and TENS	TENS; Pulsed Radiofrequency Treatments
Randomized, double-blinded, placebo-controlled	Randomized-controlled, prospective study	Clinical trial
3 weeks	3 days	3 months
Visual analogue scale	1-10 pain scale	NRS
FREMS is a safe and effective therapy for neuropathic pain in patients with diabetes	HF can ameliorate the discomfort and pain associated with DSP and suggests HF is more effective than TENS	Both TENS and PRF lumbar sympathectomyare promising pain relief treatments for painful DNP. However, PRF lumbar sympathectomy seems to have a superior efficacy.
C	D	B

6.	Hamza et al, 2000	Percutaneous electrical nerve stimulation of novel analgesic therapy for DN pain	50	To evaluate the use of percutaneous electrical nerve stimulation (PENS) in the management of patients with painful diabetic peripheral neuropathy	PENS	Cross over study	3 weeks	VAS/10	PENS is a useful non-pharmacological therapeutic modality for treating diabetic neuropathic pain	C
7.	Kumar and Marshall, 1997	Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrical stimulation	31	To evaluate the efficacy of transcutaneous electrotherapy for chronic painful peripheral neuropathy in patients with type 2 diabetes.	TENS	Randomized controlled	30mins daily times 4 weeks	0-5 Scale	A form of transcutaneous electrotherapy ameliorated the pain and discomfort associated with peripheral neuropathy. This novel modality offers a potential non-pharmacological treatment option.	B
8.	Kumar et al, 1998	Diabetes peripheral neuropathy: effectiveness of electrotherapy and anitriptyline symptomatic relief	26	To evaluate the efficacy of combining electrotherapy with amitriptyline for the management of chronic painful peripheral neuropathy in patients with type 2 diabetes.	Amitriptyline and transcutaneous electrotherapy	Randomized	12 weeks	0-5 scale(Analogue scale)	The clinical observations suggest that transcutaneous electrotherapy is effective in reducing the pain associated with peripheral neuropathy. This form of therapy may be a useful adjunctive modality when it is combined with a pharmacological agent, such as amitriptyline, to augment symptomatic relief.	B

9.	Julka et al, 1998	Beneficial effects of electrical stimulation on neuropathic symptoms in diabetes patients	34	To evaluate long-term effectiveness of electrotherapy administered by proprietary H-wave machine	Electrotherapy through H-wave machine	Randomized controlled	1.7 years	Analogue scale/10	The data suggested an effectiveness of electrotherapy in managing neuropathic pain as adjunct to analgesiscs	D
10.	Forst et al, 2004	Impact of low frequency transcutaneous electrical nerve stimulation on symptomatic DN using new solutarisdevice	19	To determine the impact of low frequency transcutaneous electrical nerve stimulation on symptomatic DN using new solutaris device	TENS through the Solutaris device	Double-blind, randomized study	12 weeks	New total symptom score NTSS and VAS sensory nerve threshold	The new TENS device “Salutaris” is a convenient non-pharmacological option for primary or adjuvant treatment of painful diabetic neuropathy	D
11.	Zinman et al, 2004	Low-intensity laser therapy for painful symptoms of diabetic sensorimotor polyneuropathy (DSP)	50	To determine whether LILT relieves pain of DSP	LILT	Randomized, double-blind, placebo-controlled study	4 weeks	VAS	The study results do not provide sufficient evidence to recommend this treatment for painful symptoms of DSP	C

12.	Kumar et al, 2015	Efficacy of low level laser therapy on painful diabetic peripheral neuropathy	19	To find the effect of low level laser therapy on painful diabetic peripheral neuropathy in Type 2 diabetes mellitus	Low level laser therapy	Pre-post observational study	10 days	VAS/10	Low level laser therapy was found to be effective in type 2 DM with peripheral neuropathy	D
13.	Peric, 2006	Influence of low-intensity laser therapy on spatial perception threshold and electroneurographic finding in patients with diabetic polyneuropathy	45	To analyse thye influence of LILT on spatial perception threshold (SPT) and electroneurographic finding in patients with diabetic polyneuropathy	LILT	Randomized, Placebo-controlled	12 weeks	Spatial perception threshold	There was significant decrease of SPT after LILT and indicated a favourable effect of this treatment in analysed patients with DPN	D
14.	Khasmeh et al, 2011	Diabetic distal symmetric polyneuropathy: effect of low-intensity laser therapy	107	To determine the effectiveness of LILT on DSP	LILT	Randomized controlled	3 weeks	Nerve conduction velocity	The study clearly demonstrated a significant positive effect of LILT on improvement of nerve conduction velocity on diabetic distal symmetric polyneuropathy	D

Data analysis

The data were analyzed by comparing the units of measurements used by the authors. The baseline data at the beginning of the study, before the intervention were compared to the outcome at the end of the study. For pain, the effectiveness of the intervention was determined

by an average reduction in pain score of all the subjects, between the baseline and the end of the study (**Figure 1**). The level of significance was set at 0.05.

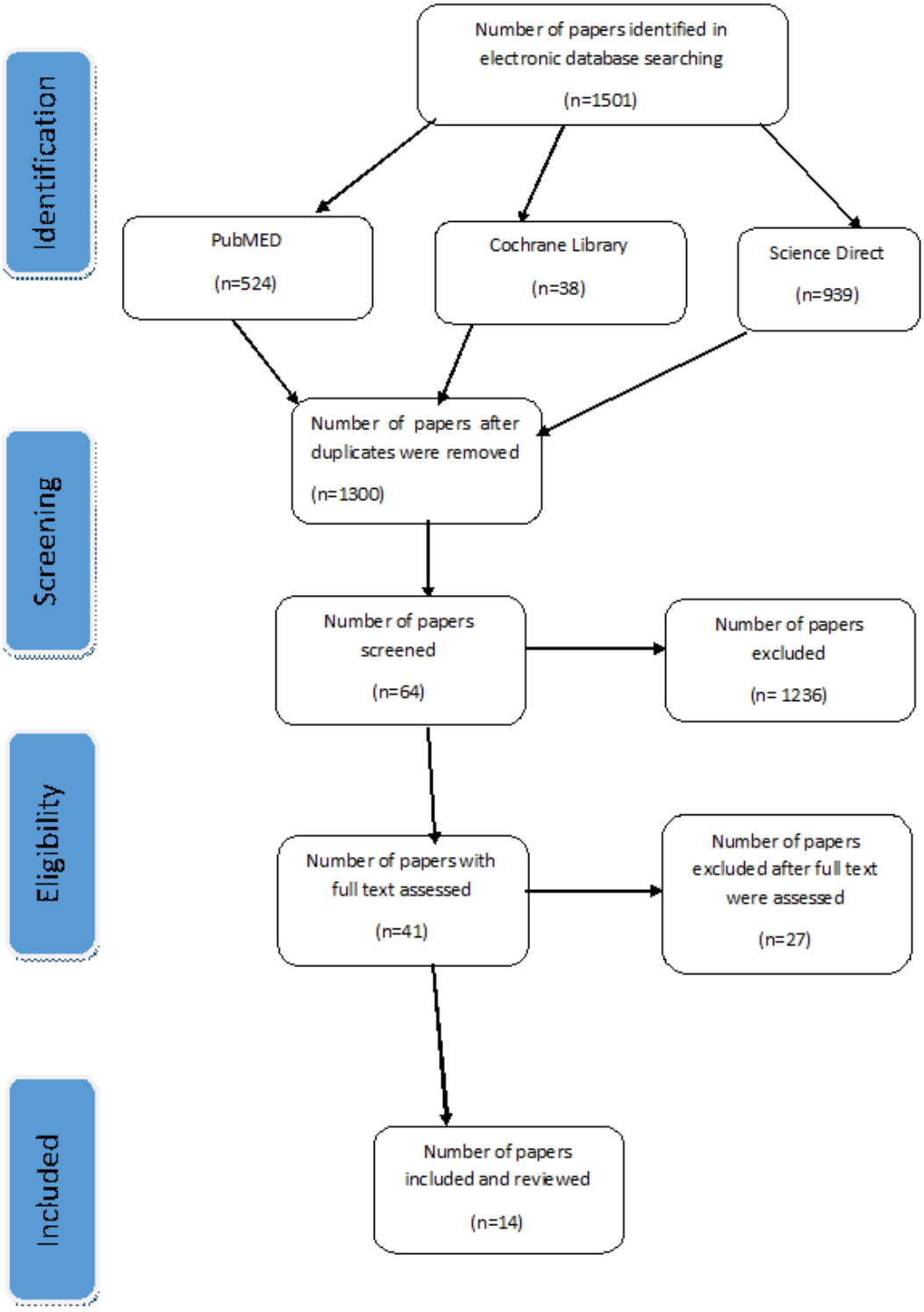

Figure 1. Schematic description of the systematic review process

3. RESULTS

The results of the search on PubMed, Cochrane library and Science direct are presented in Figure 1. One thousand five hundred and one studies were located on PubMed, Cochrane and Science direct, 201 of which were duplicates; of the studies left, 1199 were excluded by title and 37 for lack of abstracts; of the remaining 41, 27 studies that included surgical invasive spinal cord stimulation, written text in non-English language were excluded, thus left with 14 studies. Table 2 summarizes the characteristics of these studies.

Analysis of results

Four studies compared TENS versus placebo, one study compared FREMS versus placebo, one study compared TENS versus HF, one study used PENS versus placebo, one study compared TENS versus PRF, one study compared aqueous solution electrical stimulation versus placebo and one studies used TENS with no control group. Also, two studies compared LILT versus placebo and two studies used LILT with no control group.

Effects of electrical stimulation on Pain

Three of the studies that compared TENS and placebo utilized the Visual Analogue Scale (VAS). The studies by Kumar and Marshall (1997) and Kumar *et al*. (1998) used a five-point pain score. There was a significant reduction in pain from (3.17 to 1.44; $p < 0.01$) in the treatment group and (2.92 to 2.98; $p < 0.04$) in the control group in the study by Kumar and Marshall (1997) and reduction of (3.2 to 1.4; $p < 0.01$) in the treatment group and (2.8 to 1.9; $p < 0.01$) in the control group. The authors of both studies concluded that TENS is effective in reducing the pain associated with diabetic neuropathy. Also, in the study by Forst *et al*. (2004), there was a significant reduction in pain from (19.8 ± 5.0 to 14.4 ± 9.6; $p < 0.05$). The authors also concluded that TENS is an effective non-pharmacological treatment of painful diabetic neuropathy.

The study by Gossrau *et al*. (2011) concluded that TENS is not superior to placebo treatment as there was no significant difference in the group treated with microcurrent TENS and the placebo group because patients in the treatment group and those in the control group showed a pain reduction of 23% and 25%, respectively, on the Pain Disability Index (PDI).

The study by Hamza *et al*. (2002) compared PENS (Percutaneous Electrical Nerve Stimulation) group and control group, pain on the VAS score reduced from (6.2 ± 1.0) and (6.4 ± 0.9) to (2.5 ± 0.8) and (6.3 ± 1.1) in the treatment and control group, respectively. It was concluded that PENS is useful in the treatment of diabetic neuropathic pain.

The study by Bosi et al compared FREMS (Frequency-Modulated Electromagnetic Neural Stimulation) and placebo. The VAS daytime pain score reduced from reduced from (37.0 ± 5.3; $p < 0.01$) to (25.1 ± 4.2; $p < 0.01$) and the night time pain score decreased from (41.1 ± 5.20; $p < 0.01$) to (26.5 ± 3.9; $p < 0.01$). It was concluded that FREMS an effective therapy for neuropathic pain in patients with diabetes mellitus. Reinstein et al (2005) compared TENS and HF (High-frequency external muscle stimulation). Both treatment modalities led to a significant decrease in pain score between the baseline and the end of observation period, although the reduction was more pronounced in the HF group from, (7.0 ± 3.6 to 4.6 ± 3.4; $p < 0.005$) than in the TENS group from, (6.6 ± 3.2 to 5.4 ± 3.8; $p < 0.05$).

The authors concluded that both modalities are effective, however, HF is more effective than TENS. Nabi et al (2015) compared PRF (Pulsed Radiofrequency) and TENS.

The baseline pain score was compared with the pain score one week, one month and three months after treatment. Results from the TENS score revealed a reduction in pain score from 6.10 at the baseline to 3.96, 5.23 and 5.90 at the 1 week, 1 month 3 months after treatment follow-up, respectively ($p< 0.0001$). The study by Julka et al (1998), 41 (76%) patients reported a 44.0±4.0% subjective improvement in their neuropathic pain, there was also significant overall improvement on an analogue scale of 10 ($p < 0.01$).

Effect of electrical stimulation on sensation

The study by Forst et al (2004) investigated the effect of TENS at the threshold of sensory nerves (temperature, vibration, pain) in the lower limb compared to the control group. Although, there was no significant change in both groups, the authors reported a tendency toward an improvement in the patients' sensitivity to cold and heat and the heat pain perception threshold in the TENS group. Najafi (2015) et al evaluated the effect of electrical stimulation provided by aqueous solution, there was significant improvement in the Vibration Perception Threshold (VPT) score (-9.6 ±15.9 V; $p < 0.05$) relative to baseline in comparison to the control group (0.1±19.5 V) at the 6^{th} week of treatment. The difference was however not significant at follow-up visits. Also, in the study by Bosi et al (2005), the VPT decreased from (35.5±1.6 to 33.4±1.6; $p < 0.0001$). There was no significant change during treatment with placebo.

Effect of LILT on Pain.

The study by Zinman (2004) et al compared LILT (Low-Intensity Laser Therapy) and placebo. Results from the study showed a decrease in pain score from (7.1±1.9) in the LILT group to (5.8±1.7), (4.7±2.1), (5.2±2.2) at the 2^{nd}, 6^{th}, and 8^{th} week of treatment respectively. However, there was no statistical difference between the LILT group and the placebo group ($p = 0.07$). In the study by Kumar et al, there was a decrease in pain score from baseline (6.47±0.84) to (1.21± 0.78; $p <0.001$) after treatment with low-intensity laser.

Effect of LILT Sensation

The study by Kumar et al showed a decrease in VPT from (32.68±6.08 to 24.84±4.29; $p < 0.001$). In the study by Peric et al (2006), the Spatial Perception Thresholds (SPT) of the patients decreased from (5.25±1.11 to 4.87±0.90; $p < 0.01$).

Effect of LILT on nerve conduction test

Only one study; Khasmeh et al (2011), evaluated this. The subjects showed a significant increase in neural potential amplitudes ($p < 0.05$).

4. DISCUSSION

The study was conducted to determine the effectiveness of electrical stimulation and low-intensity laser therapy in patients with diabetic neuropathy. The results showed that various forms of electrical stimulation, especially TENS and low-intensity laser are effective non-

pharmacological treatment to relieve the symptoms associated with diabetic neuropathy as most of the studies demonstrated a pain alleviation and improvement in sensation.

Transcutaneous electrical nerve stimulation is the delivery of electricity across the intact surface of the skin to activate underlying nerves with the aim of providing symptomatic relief from various forms of pain, such as chronic pain due to diabetic peripheral neuropathy (Johnson and Bjordal, 2011). Its effect may be explained by the production of endogenous opioids and gate control mechanisms as several studies have demonstrated that low-frequency TENS increases the release of endogenous opioids (Sluka, et al., 1999; Kalra, et al., 2001). The mechanism by which LILT relieves pain is unknown. However, in case of neuropathic pain, the analgesic effects may be due to the local release of neurotransmitters such as serotonin (Walker, 1983), increased release of endorphins (Yamamoto, et al., 1988), increased mitochondrial ATP production (Passarella, 1989) or anti-inflammatory effects (Ailioaie and Lupusoru-Ailioaie, 1999). There was difficulty in performing a meta-analysis of all the articles in this systematic review since different methods were used to assess pain and sensation and different types of electrical stimulation were used. However, the reduction in pain and improvement in sensation when comparing the baseline measurement to the value after treatment and the conclusion from most of the studies were used to determine the effectiveness of the interventions.

The reviewed articles demonstrated the effect of TENS, four studies compared TENS with placebo and three out of these concluded that TENS is effective in reducing the pain associated with diabetic neuropathy. Also, there was improvement in pain in the study by Julka et al (1997) that evaluated TENS but with no control group. More recent literature has shown that both low- and high-frequency TENS reduces pain through the activation of opioid receptors. Low-frequency TENS activates mu opioid receptors, and high-frequency TENS activated delta opioids receptors (Chandran and Sluka, 2003).

The study by Reinstein et al (2005) compared TENS and HF but a meta-analysis could not be performed as it is the only included study that compared this. The study showed both forms of electrical stimulation to be effective but the patients treated with HF experienced more relief. Also, the study by Nabi et al (2015) compared PRF and TENS and there was significant pain relief in the patients treated with TENS. Other forms of electrical stimulation utilized were FREMS, PENS and aqueous electrical stimulation. The study by Bosi *et al*. (2005) that compared FREMS with placebo, demonstrated a decrease in pain before and after treatment in both, day-time and night-time pain score. Pain reduction was also seen in the patients that were treated with PENS in the study by Hamza *et al*. (2000). This reduction did not occur in the placebo group.

There was improvement in sensation in the patients treated with FREMS in the study by Bosi *et al*. (2005) as there was a significant decrease in the vibration perception threshold. The study by Najafi *et al*. (2013), which evaluated the effect of aqueous electrical stimulation showed a similar outcome. Use of vibration perception threshold is a simple way of detecting large-fibre dysfunction, thus identifying individuals with diabetes at risk of ulceration (Boulton, *et al*., 2005; Tesfaye, *et al*., 2010). A previous study has shown VPT to be a sensitive measure of peripheral neuropathy. However, there was no improvement in sensory nerve threshold in the study by Forst *et al*. (2004), but the authors reported a tendency toward an improvement in the patients' sensitivity to cold and heat and the heat pain perception threshold in the TENS group.

Four studies evaluated the effective of LILT on symptoms associated with diabetic neuropathy and in three out of these, there was significant improvement. The study by Kumar

et al. (2015) compared LILT and placebo, and there was a significant pain relief and decrease in VPT. The authors concluded that LILT is effective in patients with Type 2 Diabetes mellitus with peripheral neuropathy. Low-level laser therapy has been used to manage nerve injuries and other pathologies of the nerve because it holds the potential to induce a bio-stimulation effect on the nervous system (Leonard, *et al*., 2004; Zinman, *et al*., 2004). Low-intensity laser therapy was also demonstrated to improve nerve conduction velocity in the study by Khasmeh *et al*. (2011). Nerve conduction study (NCS) has been considered the gold standard for diagnosis of neuropathy, and is correlated with the disease severity (Schroder, *et al*., 2007). The study by Zinman *et al*. (2015) showed to significant improvement in pain relief in patients treated with low-intensity laser although the authors reported that an encouraging trend was observed. Considering the diverse methodological differences and different parameters used to evaluate patients' outcome to treatment with LILT, it was difficult to determine the effectiveness of LILT in patients with diabetic neuropathy.

5. CONCLUSION

Transcutaneous electrical nerve stimulation and other forms of electrical stimulation reviewed in this study may be effective and safe non-pharmacological treatment modalities in relieving the symptoms associated with diabetic neuropathy. The effectiveness of LILT cannot be determined due to the different parameters used to evaluate patients' outcome and limited number of studies.

Recommendation

Further randomized controlled trials with similar methodological parameters and studies with higher quality of evidences are needed to establish the true effectiveness of these modalities in diabetic neuropathy.

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