CAN LOW-LEVEL LASER THERAPY HAVE AN IMPACT FOR SMALL FIBER NEUROPATHY?

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In addition to reviewing diagnostic testing for small fiber neuropathy and current treatments, these authors discuss recent study results for low-level laser therapy.

Podiatry Today, Issue Number: Volume 24 - Issue 6 - June 2011

CASE STUDY

Diabetic neuropathy is the most common diabetes-related comorbidity. Diabetic neuropathy impacts between 60 to 70 percent of all patients with diabetes. The burden to treat this disorder will only intensify as current trends predict that more than 360 million individuals worldwide will be diagnosed with diabetes by the year 2030.[1,2]

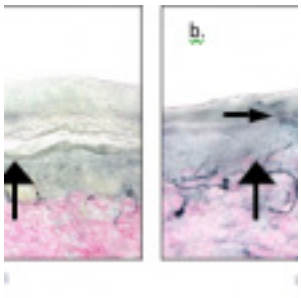
Neuropathy can have serious detrimental effects on a patient's quality of life. Patients with diabetic neuropathy have a 1.7-fold greater risk of amputation and a 25 to 50 percent higher mortality rate in comparison to those diabetic patients without neuropathy.[3] Neuropathy of the lower extremity is tightly coupled with the development of pain or discomfort, restricted activity, and foot ulcers.

One would determine the classification of neuropathy by the fiber type that is directly affected. Small fiber neuropathy (SFN) is one prevalent form of neuropathy that affects small fiber sensory neurons.[4] Small fiber neuropathy results from nerve ischemia, direct effects of hyperglycemia on neurons and intracellular metabolic modulations that impair nerve function.5 Small fiber neurons are cytoplasmic extensions of the dorsal root ganglion neurons that innervate skin and visceral organs, and are responsible for the transmission of thermonociceptive stimuli. Small fibers include myelinated A-∂ fibers and unmyelinated C fibers. Somatic fibers innervate the skin and voluntary muscles whereas autonomic fibers innervate cardiac and smooth muscles.[6] Ischemia-induced small-fiber nerve degeneration results in clinical symptoms including pain or discomfort, numbness, and loss of temperature sensation.[4,5,7]

In addition to vascular deficiencies, researchers have reported perivascular inflammation involving macrophages and T cells, and believe this promotes further nerve degeneration.[8]

KEYS TO THE CLINICAL PRESENTATION OF SMALL FIBER NEUROPATHY

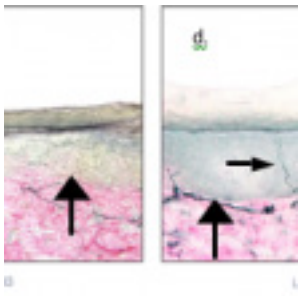
The clinical manifestation of neuropathic pain is derived from the degeneration of large diameter or small diameter sensory nerves. Large fiber sensory nerves or large fibers are responsible for the transmission of proprioception and vibration sensation.[9] Large fiber disruption commonly leads to paresthesias, muscle weakness, impaired balance and absent or reduced tendon reflexes.[4] Clinical examination using electrodiagnostics, including electromyography (EMG) and nerve conduction velocity studies, help classify the type of neuropathy. Physicians may use EMG to evaluate the extent of axon degeneration by assessing sensory action potential amplitudes and intervention.[7] Demyelinating neuropathy consistently presents with decreased nerve conduction velocity, prolonged terminal latency, temporal dispersion and blocked conduction.[9]



The clinical presentation of individuals with small fiber neuropathy includes pain, paresthesias, loss of two-point discrimination, loss of thermal perception, xerosis and sometimes diminished Achilles deep tendon reflex and loss of the superficial reflexes.[10] The diagnosis of small fiber neuropathy with traditional methods including nerve conduction studies is difficult as small fibers are undetectable. Therefore, the diagnosis of small fiber neuropathy often occurs as a result of positive sensory symptoms.[11]

Patients often complain that they have a feeling of a band around their foot or describe a sensation of wearing a tight sock even when barefoot. Pain can be constant or can occur at certain times, such as when they are in bed. Often, innocuous contact can become quite painful. This may include the wearing of shoes or irritation from sheets while in bed. However, positive sensory symptoms are not associated with only small fiber neuropathy as pain is also a common symptom of large fiber disorders.

Patients with small fiber neuropathy may also present with negative symptoms including numbness, tightness and coldness.[12] Generally, a patient's symptoms are initially localized to the digits and plantar aspect of the foot but over time can spread proximally to the distal third of the leg. Often, the patient will start to complain of dysesthesia in his or her hands. This generally occurs after involvement of the lower leg.



In addition to the involvement of small somatic nerve fibers, researchers have also reported involvement of small autonomic fibers.[12] Autonomic symptoms can include modulation of sweating, skin discoloration, dry eyes and mouth, or facial flushing. Vascular dysregulation is a common occurrence with small fiber neuropathy and can manifest with localized edema and/or color and temperature changes in the lower extremities.[13] Skin can become atrophic, thin and anhidrotic because innervating small fibers influence keratinocyte proliferation and thickness of the epidermis.[14-17] Widespread autonomic involvement can have generalized distribution involving the gastrointestinal system, erectile dysfunction and cardiovascular and peripheral vascular involvement.[12,18] Furthermore, small fiber neuropathy is associated with the onset of retinopathy. The diverse clinical presentation of small fiber neuropathy requires an interdisciplinary approach to effectively treat this disorder.

All patients should have a detailed history and physical examination. This is especially true for patients with small fiber neuropathy. Questions regarding onset, progression, distribution and characteristics of symptoms all provide clues to the etiology. One should review the patient's medical history and question him or her on family history, medications and possible toxic exposures. A comprehensive lower extremity evaluation should include vascular, neurologic, musculoskeletal and dermatologic examinations. However, even with the most comprehensive evaluation, the results are sometimes normal. Therefore, an effective therapeutic strategy may not be apparent when the underlying etiologies are undeterminable.

PERTINENT INSIGHTS ON THE DIAGNOSTIC WORKUP

In the majority of cases, small fiber neuropathy is commonly linked to an underlying disorder that may include diabetes mellitus, impaired glucose tolerance, vasculitis, Sjogren's syndrome, systemic lupus erythematous and numerous other conditions. However, the exact pathogenesis of small fiber neuropathy remains elusive. There is evidence for immune-mediated pathology in which pro-inflammatory cytokines such tumor-necrosis factor-μ (TNF-μ) provoke and sustain neuropathic pain.[19-21] Oxidative stress has also been implicated in the pathogenesis of small fiber neuropathy.[22-24] Nutritional deficits, alcohol, smoking and toxins, such as mercury, arsenic, and lead, can all contribute. For some patients, small fiber neuropathy may be idiopathic with a poorly understood pathogenesis.

Depending on the history and physical examination, the following laboratory studies may be indicated: complete blood count, comprehensive metabolic panel, lipid panel, blood urea nitrogen, creatinine, electrolytes, thyroid stimulating hormone, free thyroxine (T4), antinuclear antibody, extractable nuclear antigens, angiotensin-converting enzyme, serum and urine immunofixation tests, hemoglobin A1c, serum B-1, B-6, B-12, and folate levels, vitamin E, and erythrocyte sedimentation rate. If you have a strong index of suspicion, you can pursue heavy metal testing as well.

One would only utilize EMG and nerve conduction

velocity studies to ascertain the presence of large fiber neuropathy because of the inability to measure the action potentials of small fibers. Electromyography is a test that measures the response of muscle to nerve stimulation. Since small fiber nerves generally do not innervate neuromuscular junctions, this test is usually normal with small fiber involvement unless there is combined small and large fiber neuropathy.[6]

Neurodiagnostic pathology techniques are emerging as the gold standard for the diagnosis of small fiber neuropathy. Intraepidermal nerve fiber density is consistently reduced in individuals with neuropathy.[25,26] Immunohistochemical use of an antibody against protein gene product 9.5 yields a high quality analysis of unmediated epidermal nerve endings.[6]

Physicians have used this approach to identify reduced nerve fiber density in both the dermis and epidermis in patients with neuropathy. It allows one to quantify and compare nerve fiber loss and degeneration to an established normal range for the lower leg and the foot. One can repeat this procedure at appropriate intervals to monitor small fiber nerve loss.

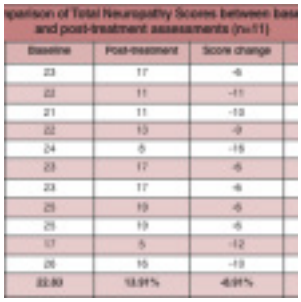
Serial biopsies are advantageous for staging the severity of neuropathy and determining the effectiveness of any neuromodulation therapy. One can obtain biopsies from the dorsum of the foot and the distal third of the lateral aspect of the lower leg. Physicians can obtain a skin punch biopsy with aseptic techniques by utilizing a local anesthetic and a 3 mm punch biopsy instrument.

CURRENT AND EMERGING TREATMENTS FOR SMALL FIBER NEUROPATHY

Once you make the diagnosis of small fiber neuropathy, there are several treatment options to consider. Historically, physicians have directed treatment toward controlling pain. Pharmacological treatment has included the use of antidepressants, anticonvulsants, sodium channel blockers and opioid analgesics. Various studies have shown that these modalities have some effect in controlling neuropathic pain, but they have side effects that one must monitor.

In addition, clinicians have used local anesthetic patches, local anti-inflammatory neuromodulation agents in transdermal gels, physical therapy, acupuncture and various forms of relaxation techniques including biofeedback.

More recently, physicians have utilized a nutraceutical approach with promising results. Metanx (Pamlab, LLC) is a prescription nutraceutical, which contains bioavailable forms of L-methylfolate (2.8 mg), pyridoxal 5'-phosphate (25 mg) and methylcobalamin (2 mg) that have been shown to have a positive response in small fiber neuropathy.[27] Early preliminary studies have shown regrowth of small nerve fibers after several months of treatment. There are very few adverse effects when utilizing the nutraceutical approach.



Overall though, therapeutic options for SFN are limited with most therapies attempting to address the underlying immune-mediated aspects. The use of simple analgesics, anticonvulsants or antidepressants does not address the important etiologies of SFN, which include ischemia and nerve degeneration. An effective therapeutic approach would promote angiogenesis, downregulate inflammation and induce small fiber nerve regeneration.

A therapy with such promise is low-level laser therapy (LLLT). Researchers have shown that low-level laser therapy promotes: central and peripheral neuron repair; suppression of cyclooxygenase-2 (COX-2); enhancement of peripheral endogenous opioids; upregulation of vascular endothelial growth factor (VEGF); angiogenesis; collagen synthesis and decorin expression during tendon and ligament repair; reduction in fibrosis, suppression of conduction along unmyelinated C fibers; and inhibition of histamine release.[28-54]

Low-level laser therapy is an emerging technology to help treat and control pain in the lower extremities. Researchers have shown that low-level laser irradiation can have a positive response for tissues that exhibit microvascular compromise and

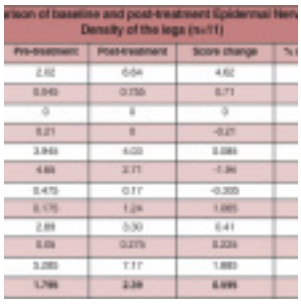
become anoxic secondary to metabolic injury with resulting microvascular inflammation, oxidative injury, and mitochondrial dysfunction. Authors have demonstrated that the more recently developed 17.5 mW 635 nm laser has a positive response on cell membranes, mitochondria and damaged neurologic structures. Lasers of low intensity initiate analgesic, anti-inflammatory and biostimulatory effects, resulting in an increase in local microcirculation and increased healing.[55-57] Increasing microcirculation induces an essential function in the tissue repair process and in pain control. This process allows increases in oxygenation and nutritional supply to tissues. This process allows for the expulsion of metabolic byproducts, which may contribute to pain.

A CLOSER LOOK AT THE MECHANISM OF ACTION OF LOW-LEVEL LASER THERAPY

Lasers deliver light in a highly concentrated manner defined by a high degree of spatial and temporal coherence. Lasers involve high-intensity photo-bio stimulation of a medium, which can be a gas, liquid, crystal, dye or semiconductor, resulting in the emission of photons.

The two major categories of laser therapy are class IV and class III, which are differentiated according to output power. Low-level laser therapy is a class III laser and requires only a discrete amount of output intensity or energy (5-500 mW) to yield a clinical response. Power reveals a biphasic dose-response in which higher intensities impede rather than facilitate a cellular and clinical response.[58] Low-level lasers operate within the principles of bioorganic photochemistry, a discipline of science that explores the interaction between photons and biochemical pathways in cells.

The clinical utility of low-level laser therapy is derived from the ability to modulate cellular metabolism and influence a diverse array of intracellular biochemical cascades that directly affect cellular behavior and function.



The biological effect of coherent laser irradiation on cells is termed photobiomodulation. All light is radiation energy that is measured in discrete units called photons and its effect on cellular components is mediated by biological photo-acceptor molecules that are found in a variety of cellular components throughout the human body.

Two cellular components in particular that have been identified are cytochrome c oxidase, which is part of the electron transport chain of mitochondria, and porphyrins, which are found in the eukaryotic cell membrane.

Cytochrome c oxidase is a multi-component membrane protein, which contains a binuclear copper center (CuA) and a heme binuclear center (a3-CuB). Cytochrome c oxidase facilitates the transfer of electrons from cytochrome c to oxygen, driving oxidative phosphorylation.[59,60] Researchers believe low-level laser stimulation of cytochrome c oxidase accelerates the transfer rate of electrons and makes more electrons available for the reduction of dioxygen.[61-69] Functional changes in the terminal enzyme increase the membrane potential and proton gradient, changing mitochondrial optical properties and increasing the rate of ADP/ATP exchange.[70,71]

The combination of upregulation of ATP and upregulation of reactive oxygen species directly affect secondary reactions that regulate gene expression, protein and growth factor synthesis, cell proliferation, and many other cellular properties. Upregulation of ATP is coupled to the production of reactive oxygen species, which can affect the intracellular redox state. Sensitization of primary afferent nociceptors is aggravated by TNF-μ and other pro-inflammatory cytokines.[72] Synthesis of pro-inflammatory cytokines such as TNF-μ occurs via the inducible enzyme COX-2, which catalyzes the formation of prostaglandin H2 from arachidonic acid.[68] Both prostaglandin E2 (PGE2) and prostacyclin promote pain by stimulating the pain-producing mechanism of bradykinin and other autacoids.[71-73]

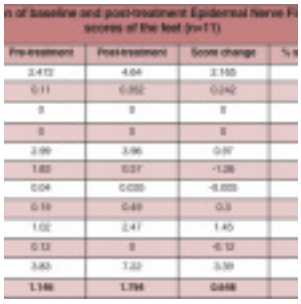
Several classes of non-opioid analgesics act as specific inhibitors of COX-2 and prevent eicosanoid formation.[74-78] *In vitro* and *in vivo* studies have shown that laser therapy reduces PGE2, interleukin-1μ and TNF-μ by inhibiting COX-2.[55-57] One hypothesis is that laser therapy influences the intracellular redox state by modulating the transcription factor nuclear factor kappa B, which undergoes phosphorylation and ubiquitination, and promotes proteolytic degradation of IKB-a under oxidative stress. A shift in the intracellular redox state may affect the cascade responsible for regulating COX-2 expression, thereby suppressing the synthesis of pro-inflammatory cytokines.

Researchers have shown that low-level laser therapy upregulates VEGF, which promotes neovascularization.[54] Enhanced microcirculation may contribute to the stabilization of cell metabolism by increasing cellular nutrient and oxygen concentrations.

WHAT ONE SMALL STUDY REVEALS ABOUT LLLT FOR PATIENTS WITH SMALL FIBER NEUROPATHY

Although histological evidence of the effectiveness of low-level laser therapy is rather extensive, clinical evidence with well-defined laser parameters is inconsistent. Therefore, we developed a study to assess the efficacy of low-level laser therapy at 635nm with an output intensity of 17.5 mW to promote small fiber nerve regeneration and reduce the symptoms associated with small fiber neuropathy. Recent reports have validated skin biopsy as an accurate method for quantitative assessment of intraepidermal nerve fiber density.[57,79] Accordingly, we obtained skin biopsies before and after treatment with low-level laser therapy in order to document nerve regeneration in regions presenting with skin denervation.

Eleven patients diagnosed with small fiber neuropathy via epidermal nerve fiber density testing underwent 12 low-level laser therapy treatments (10 minutes per extremity) three times a week for four weeks. Study participants received treatment from a multiple-diode low-level laser scanning device that emits divergent 635-nm laser light from each diode, generating 17.5mW of output intensity the Erchonia® ML Scanner.



Study authors directed the diodes at the common peroneal nerve at the fibular neck, the posterior tibial nerve at the medial ankle, the deep peroneal nerve at the dorsum of the foot, the superficial peroneal nerve at the anterolateral ankle and the plantar aspect of the foot. The treatment protocol included epidermal nerve fiber density testing before and after laser treatment.

In addition, we utilized the Total Neuropathy Score-reduced (TNSr) to objectively evaluate each patient's response to laser therapy. The Total Neuropathy Score-reduced is a combination of subjective questions and physical examination results, and gives a score ranging from 0 to 44 with a higher score representing worse neuropathic pain (see "Measuring Patient Response To Laser Therapy With The Total Neuropathy Score-Reduced"). We quantified both the percent increase in epidermal nerve fiber density in the foot and the leg, and the change in the TNSr. In addition, we asked patients to quantify their overall improvement in neuropathic pain as a percent improvement. (See the table "How Patients Were Asked To Quantify Their Improvement In Neuropathic Pain.")

The average Total Neuropathy Score (TNS) for patients at baseline was 22.83 with a range between 17 to 26. In comparison to baseline, the average post-treatment TNS exhibited a significant decrease of 8.91 points or 40.05 percent with a range between 24.00 and 70.59 percent. (See the table "Comparison of Total Neuropathy Scores Between Baseline And Post-Treatment Assessment.")

Assessment of epidermal nerve fiber density of the legs showed a change in the average epidermal nerve fiber density of 0.595 points or 33.15 percent between baseline and post-treatment evaluation points (see the table "Comparison Of Baseline And Post-Treatment Epidermal Nerve Fiber Density Of The Legs"). The average change observed between baseline and post-treatment epidermal nerve fiber density testing was not statistically significant. However, seven of the 11 patients demonstrated an increase in epidermal nerve fiber density of the legs from baseline with a range in percent improvement between 2.15 percent and 1578 percent.

Assessment of epidermal nerve fiber density of the feet showed an average change between baseline and post-treatment evaluation periods of 0.648 points or 56.54 percent. This change was not statistically significant. However, a majority of participants (6 of 11) revealed an improvement in epidermal nerve fiber density of the feet with a range between 32.44 percent and 220 percent. (See the table "Comparison of Baseline And Post-Treatment Epidermal Nerve Fiber Density Scores Of The Feet.")

We have included figures showing actual histological specimens of a 65-year-old study patient before and after laser therapy. As one can see in figures a and c, at the start of the study, the patient has very few small fiber nerves that cross the basement membrane into the epidermis. The epidermal nerve fiber density before laser therapy for this patient was significantly

less than the normal range, resulting in a diagnosis of small fiber neuropathy. In figures b and d, after laser therapy, there has been a significant increase in the number of small fibers penetrating into the epidermis and the calculated epidermal nerve fiber density increased to the normal range.

For each participant in the study, we reported an improvement in the overall perceived pain rating. Study participants exhibited an average improvement in neuropathic pain of 75 percent.

IN CONCLUSION

The data acquired from this prospective, non-randomized, non-controlled study demonstrates the potential utility of low-level laser therapy. These data show a clinically meaningful outcome for the treatment of neuropathic pain without an adverse event. However, a placebo-controlled, randomized, double-blind, multi-centered clinical investigation is warranted in order to elucidate the complete efficacy of this therapeutic approach. Furthermore, it would be important to enroll study participants who demonstrate similar baseline epidermal nerve fiber density of the legs and feet in order to appropriately quantify any improvement produced by low-level laser therapy.

Perhaps the variance in baseline epidermal nerve fiber density of the legs and feet we observed in study participants contributed to the failure to achieve statistically significant post-treatment improvements. Another possibility is that for some participants, we may have prematurely acquired the post-treatment biopsy to assess epidermal nerve fiber density of the legs and feet. We obtained all the post-laser biopsies immediately after the final laser treatment. In retrospect, waiting six to eight weeks after treatment may be preferable as the effects of the laser may not be immediate. It is our belief that waiting several weeks after the final laser application would allow the acute effects of the laser to transpire and promote an observable improvement in epidermal nerve fiber density.

Treatments for small fiber neuropathy have been pharmaceutical in nature and have produced varying success rates. Low-level laser therapy is a non-invasive, low-risk treatment that we have shown to be effective in increasing the density of small fiber nerves in the epidermis in some patients. When one assesses the results collectively, these data demonstrate improvements at the micro- and macroscopic levels as a majority of participants exhibited improvements in epidermal nerve fiber density of the feet and legs along with each patient revealing improvements in the Total Neuropathy Score along with perceived pain.

This multidimensional study attempted to assess neuropathic pain from multiple perspectives in order to successfully quantify and qualify the utility of low-level laser therapy. Given that we observed improvements across all study outcome measures, continuous investigation of this application is necessary.

There is clearly a great need for quality research to evaluate the effects of low-level laser therapy on patients with small fiber neuropathy. The limitations of this study include a small patient population and the lack of a control group. Ideally, we would like to initiate a large cohort, double-blind, randomized control trial with a sham laser and a rigid protocol of how many laser treatments each patient receives and a more clearly defined schedule for the timing of the biopsies.

We chose to present these findings as preliminary data because the patient response to the laser therapy was so promising. Given that low-level laser therapy is non-invasive and has no reported side effects, it is a very low-risk treatment option for patients with small fiber neuropathy. Patients are reporting a decrease in their neuropathy symptoms and, in some cases, are regenerating the small fiber nerves in the epidermis.

Dr. Zang is the founder of the Arizona Institute of Footcare Physicians and is in private practice in Mesa, Az. He is a Fellow of the American College of Foot and Ankle Surgeons, and is a Diplomate of the American Board of Podiatric Surgery. Dr. Zang is an Adjunct Professor of Surgery at Midwestern University in Glendale, Az.

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