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INTEGRATIVE NEUROMUSCULAR MEDICINE: NEUROPATHY AND NEUROPATHIC PAIN: CONSIDER THE ALTERNATIVES

JULIE ROWIN, MD

Wellness and Integrative Neurology, Advanced Pain and Anesthesia Consultants, Centers for Pain Management, Westchester, Illinois, USA

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ABSTRACT: Complementary and alternative treatment modalities are commonly utilized by patients for neuropathy and neuropathic pain due to perceived lack of benefit from conventional medical treatment. As the association between metabolic syndrome and neuropathy is increasingly recognized, diet and lifestyle interventions are becoming important components in the management of neuropathy. Progress in the understanding of the gut–immune interaction highlights the role the gut microbiome and inflammation plays in the modulation of neuropathy and neuropathic pain. Evidence for nutritional interventions, exercise, supplements, acupuncture, and mindfulness-based practices in the treatment of neuropathic pain is encouraging. This article reviews the available evidence to support the safe use of complementary and alternative treatments for commonly encountered conditions associated with neuropathy and neuropathic pain.

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Over the past century, acquired inflammatory and metabolic diseases have surpassed infectious diseases as the primary cause of morbidity and mortality, particularly in the Western world.[1] Altered regulation of gene expression (epigenetics) rather than monogenic mutations underlies the majority of risk factors responsible for disease. Diet, exercise, smoking, alcohol, medications, psychological stress, and toxic exposures are examples of known causes for epigenetic changes.[2] The majority of chronic disease in the USA is strongly associated with diet and lifestyle, and the pain epidemic is no exception.[3] Due to growing opioid overuse and the less-than-ideal perceived efficacy of currently available treatments for neuropathic pain, utilizing evidence-based lifestyle and alternative approaches in the treatment of neuropathy and neuropathic pain is not only gaining popularity but is clearly warranted.[4]

Complementary and alternative medicine (CAM) modalities, such as diet, acupuncture, nutrients, herbs, and mind–body medicine, are commonly utilized in the treatment of pain.[5] This monograph outlines the literature in support of the safe use of lifestyle and CAM approaches to the treatment of neuropathic pain and peripheral neuropathy focusing on diet, exercise, and nutraceuticals. It does not cover the diagnosis, clinical presentations, evaluations, and causes of neuropathy or pharmacological treatment, as exhaustive reviews can be found elsewhere.[6–10] This is a tool to enhance the practitioner's knowledge of CAM treatments and the current state of evidence supporting their use for neuropathy and neuropathic pain as well as an aid to implementing these strategies to improve patient outcomes.

In the integrative treatment model, the paradigm has shifted from a disease-based model to a wellness- and prevention-based model, or lifestyle medicine.[11] Also, rather than single interventions, multimodal therapy—including nutritional, physical activity, mind–body, and acupuncture approaches—is often applied simultaneously alongside pharmacology-based therapies. The goal of integrative medicine is to promote healthier lifestyles through education and communication to support behavioral change, recognizing that the majority of chronic disease is secondary to low-grade inflammation, a dysregulated stress axis, and metabolic dysfunction, all of which can be addressed through lifestyle modifications.[11,12] This approach may be utilized as first-line management, adjunctive therapy, or when conventional treatment with pharmaceuticals and surgeries have failed. Neuropathy and neuropathic pain are particularly well-suited to the integrative medicine model.

THE METABOLIC SYNDROME AND NEUROPATHY

Forty-three percent of Americans over the age of 60 are reported to have metabolic syndrome.[13] This is the term given to a cluster of 5 cardiovascular risk factors including abdominal obesity, insulin resistance, hypertension, hypertriglyceridemia, or other dyslipidemia. Although diabetes mellitus and insulin resistance are commonly associated with painful sensory neuropathy, approximately one-third of presenting neuropathy is considered idiopathic.[14] Growing evidence suggests that a significant subset of idiopathic neuropathy may be

Additional supporting information may be found in the online version of this article.

Abbreviations: ALA, alpha-lipoic acid; ALC, acetyl-L-carnitine; CAM, complementary and alternative medicine; CIPN, chemotherapy-induced peripheral neuropathy; CRP, C-reactive protein; CTS, carpal tunnel syndrome; EFA, essential fatty acids; GALT, gut-associated lymphoid tissue; GLA, gamma-linolenic acid; GMP, Good Manufacturing Process; Hb, hemoglobin; IENFD, intraepidermal nerve fiber density; Ig, immunoglobulin; IL, interleukin; RCT, randomized, controlled trial; SCFA, short-chain fatty acid; VAS, visual analog scale

Key words: complementary; integrative; neuropathic pain; neuropathy; treatment

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Correspondence to: J. Rowin; e-mail: jrowin@apacgroupe.com

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associated with metabolic syndrome and therefore diet- and lifestyle-related.[15,16]

This idea originally sprang from the clinical observation of patients with idiopathic neuropathy with recurring phenotypic characteristics such as obesity, dyslipidemia, and hypertension, without having overt diabetes. In type 1 diabetes, hypertension, smoking, obesity, and elevated serum triglycerides are independent risk factors for neuropathy.[17] A careful case–control study of idiopathic polyneuropathy showed significantly higher triglyceride, but not glucose, concentrations in patients compared with control subjects.[18] Another study showed that 55% of all patients with idiopathic chronic axonal polyneuropathy, compared with 34% of controls, met the criteria for metabolic syndrome, defined as meeting 3 or more of the following: impaired glucose tolerance; hypertension; abdominal obesity; reduced high-density lipoprotein cholesterol; or hypertriglyceridemia.[16] In particular, abdominal obesity and hypertension were more prevalent in patients with idiopathic neuropathy than in control subjects in this study.[16] Also, the prevalence of polyneuropathy is high in obese individuals without diabetes or prediabetes.[19] Increased triglycerides are independently associated with neuropathy progression in diabetes type 1, irrespective of glycemic control,[20] and glycemic control has only a marginal effect on preventing neuropathy in type 2 diabetes, suggesting other factors are at play.[21]

It has also been suggested that metabolic syndrome–associated neuropathy and diabetic neuropathy may have common etiologies.[22] Reported mechanisms linking chronic systemic metabolic inflammation to neuronal injury include fatty deposition in the nerves, mitochondrial dysfunction, extracellular protein glycation, and oxidative stress.[22] Current management of those with diabetic neuropathy concentrates on the control of the diabetes and symptomatic analgesia for control of neuropathic pain. However, emerging data support the concept that additional management of metabolic syndrome will lead to better outcomes.[19,20]

THE MICROBIOME, GUT HEALTH, AND SYSTEMIC INFLAMMATION

There are substantial data supporting the connection between diet, microbiome health, and systemic disease, including diabetes and metabolic syndrome.[3,23–30] The standard American diet (calorie-dense, low in fiber, high in red meat, refined grains, sugar, and chemical additives), increased use of antibiotics and proton-pump inhibitors, lack of physical exercise, and increased levels of perceived stress have all been linked to alterations in the gut microbiome and declining health.[26,27,30–33] The integrity of the intestinal barrier is critical to the health of the gut microbiome, and alterations in this barrier have been linked to the development of multiple diseases, including inflammatory, autoimmune, metabolic, neurodegenerative, and neoplastic ones.[29,30,34–36] Commonly used food additives and chemicals used in food processing, such as sugars, artificial sweeteners, salt, emulsifiers, surfactants, organic solvents, gluten, microbial transglutaminase, and nanoparticles, are abundant in the Western diet and have been linked to intestinal tight junction leakage, altered gut microbiota, and glucose intolerance.[33,37,38]

In recent years, it has become clear that inflammation is a key factor leading to obesity, metabolic syndrome, and type 2 diabetes.[39] There is also evidence linking increased intestinal permeability, activation of inflammatory signaling, and the risk for diabetes types 1 and 2.[40,41] Also, because only a single layer of epithelial cells separates the luminal contents of the intestine from the immune cells in the lamina propria, increased intestinal permeability can have a direct effect on immune effector cells.[42] Environmental factors—including gastrointestinal infections, medications (antibiotics), and most importantly diet—can influence the pathogenesis of autoimmune, inflammatory, and metabolic conditions such as diabetes, both systemically and in part by modifying the T-regulatory/T-effector cell balance in the gut-associated lymphoid tissue.[35,42–45] Factors that support gut barrier integrity, such as anti-inflammatory diets, prebiotics, probiotics, fiber, and short-chain fatty acids (SCFAs), have been protective in animal models of multiple neurological and metabolic diseases through mechanisms that decrease systemic inflammation[29,42,44–46] (Fig. 1).

MEDICATION-INDUCED NUTRIENT DEPLETION AND NEUROPATHY

To complicate matters, medications commonly used for treatment of diet- and lifestyle-related conditions may contribute to neuropathy (Fig. 2).[39,47–52] Some medications, such as proton-pump inhibitors, H2 blockers, and metformin, are associated with reduced absorption of B vitamins.[49,51–54] Drug-induced nutrient depletion is more common than has been previously acknowledged.[55] For those of older age, there is often a concomitant use of medications that contribute to nutrient depletion in addition to having a decreased ability to absorb vitamin B_{12} due to reduced stomach acid.[56] Therefore, neuropathy that is assumed to be "diabetic" may in fact be at least partially secondary to B_{12} deficiency.[51,52] Furthermore, statin medication (often used for patients with metabolic syndrome and dyslipidemia) is associated with an increased risk of diabetes.[57,58]

LIFESTYLE INTERVENTIONS FOR NEUROPATHY

Despite knowledge that diet and lifestyle modifications may significantly improve a patient's health, and in many cases are shown to be superior to medical treatment to prevent obesity and diabetes,[59] many physicians report skepticism regarding their

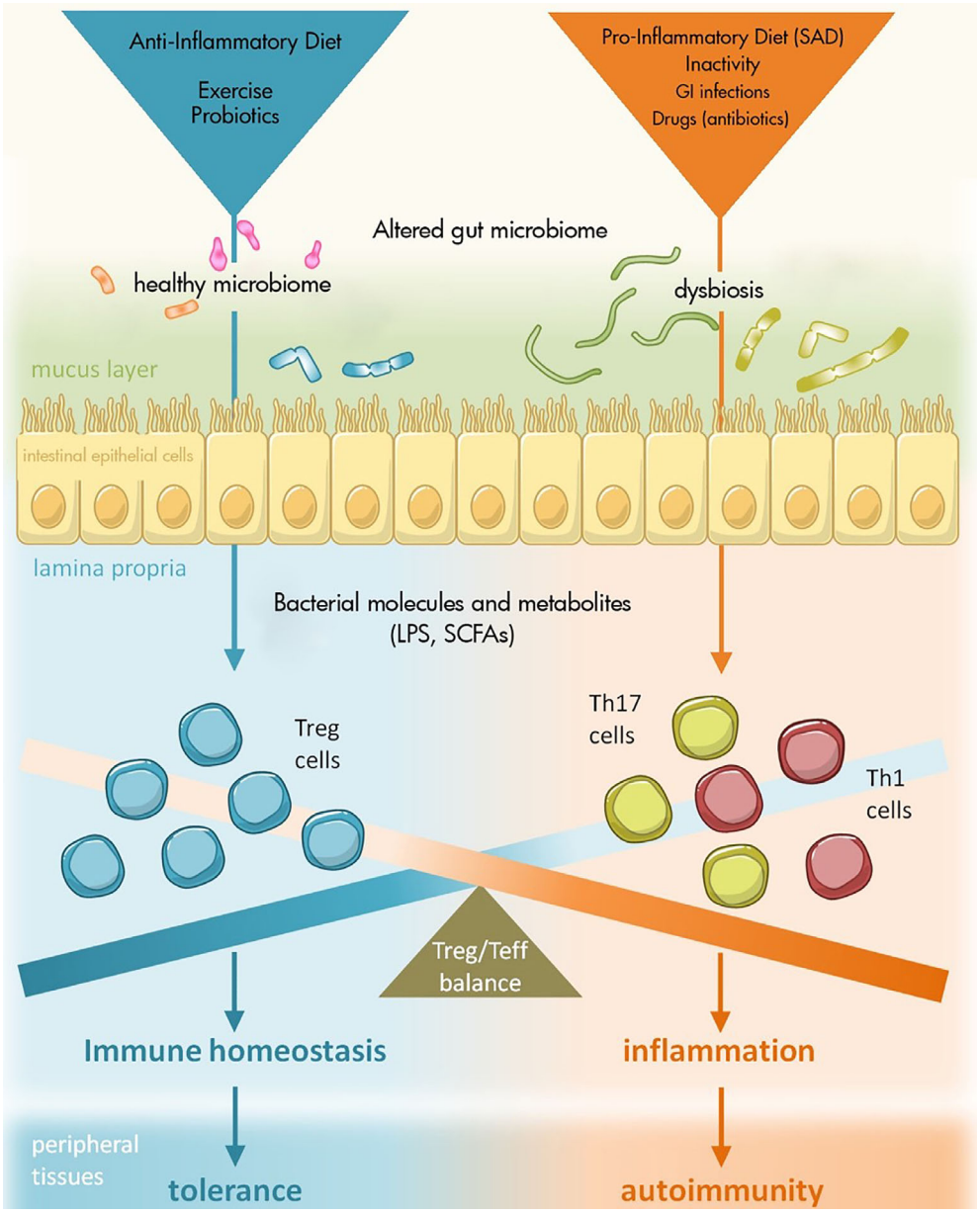

FIGURE 1. A schematic diagram depicting the potential influences on the gut that may lead to systemic immune activation. The systemic innate immune system is intimately connected to the gut microbiota and its metabolic products. Various factors can contribute to the development and maintenance of a dysbiotic microbiota. In addition to genetics, gut microbiota are influenced by lifestyle factors, including diet, exercise, and toxin exposure, as well as probiotics, antibiotics, and enteric infections.[29] GI, gastrointestinal; LPS, lipopolysaccharide; SCFA, short-chain fatty acid; Teff, effector T cells; Th1 and Th17, T helper 1 and 17 cells, respectively; Treg, regulatory T cell. [Color figure can be viewed at wileyonlinelibrary.com]

patient's ability to make the necessary behavioral changes and cite time constraints and lack of nutritional training as barriers.[60,61] Although there is a realistic concern that compliance with diet and lifestyle changes is challenging for patients, evidence suggests that a strong physician–patient relationship and structured individual guidance by a professional dietician, nurse, or health coach can enhance compliance.[62,63]

Nutritional Intervention. In the face of clear recommendations from the U.S. Department of Agriculture, U.S. Department of Health and Human Services, and National Cancer Institute supporting adequate daily intake of fruits and vegetables to prevent many chronic diseases, the majority of Americans do not meet their nutrient requirements[64,65] (Table 1). Also, adequate fiber intake, essential for production of SCFAs and protective to the intestinal colonocytes and beneficial gut bacteria, is lacking in the USA.[66] Plant-based and Mediterranean diets rich in olive oil and nuts—in contrast to a low-fat diet—have been shown to be anti-inflammatory and beneficial in the treatment and prevention of diabetes and metabolic syndrome in at-risk individuals,[67–70] and diet and lifestyle modifications are more beneficial in preventing diabetes than metformin in individuals with impaired glucose tolerance.[59,71]

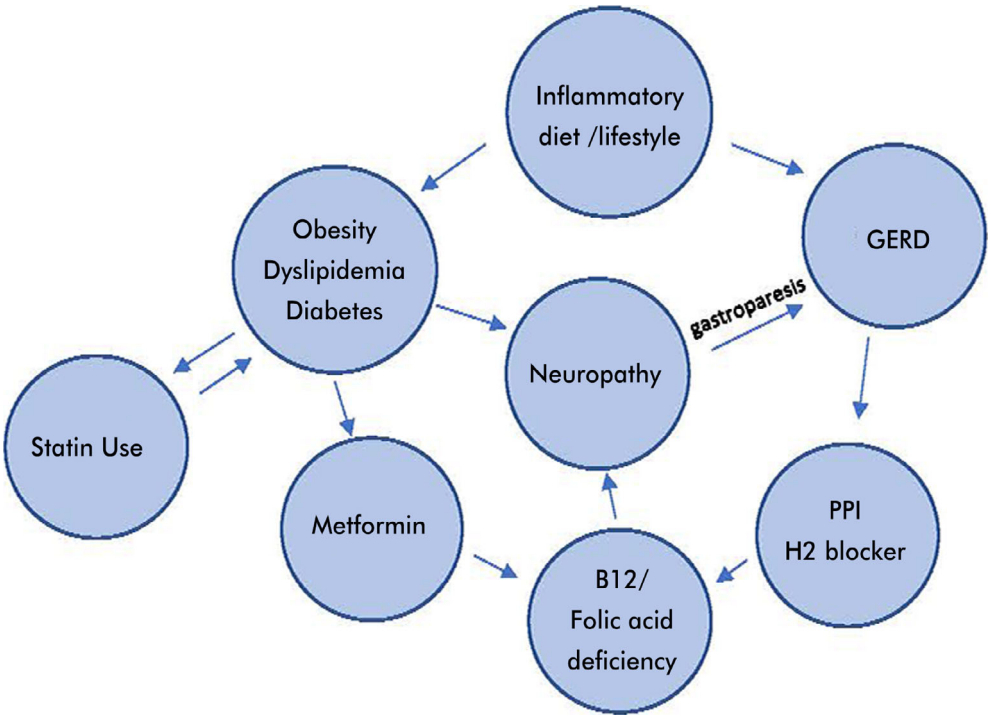

FIGURE 2. Potential neuropathy cascade.[52] GERD, gastroesophageal reflux disease; PPI, proton-pump inhibitor. [Color figure can be viewed at wileyonlinelibrary.com]

To address these dietary imbalances, the present author uses nutritional plans developed by the Institute for Functional Medicine[72] including foods to support an anti-inflammatory, neuroprotective milieu, utilizing whole foods with a high phytonutrient density, low glycemic load, protective antioxidants, and high-quality dietary fats along with the option of being free of gluten (see Fig. S1A and B in the Supplementary Material online). Because of the abundance of literature in support of a cardiometabolic/Mediterranean-type diet for improved outcomes in a variety of conditions, including diabetes, prediabetes, and metabolic syndrome,[68,70,73] this approach is a reasonable first-line nutritional intervention for the treatment of diabetic and metabolic syndrome–associated neuropathy (see Fig. S1A online). However, the author's experience favors a 3–5-week trial of an anti-inflammatory elimination diet, which, in addition to the benefits of a Mediterranean-type diet, is void of common inflammatory foods (gluten, diary, sugar, corn, and soy) and chemical additives and processing, which are known to disrupt intestinal barrier function and contribute to glucose intolerance[33,74] (see Fig. S1B online). High-histamine foods, nightshade vegetables, and fermented foods can be removed on an

Table 1. Comparison of nutritional plans

Category	Standard American diet	Mediterranean/ cardiometabolic diet	Anti-inflammatory/elimination diet
Vegetables and fruits	Few	High consumption	High consumption, large diversity, variety of colors to increase phytonutrients
Protein source	Red meat, dairy	Fish, legumes, nuts	Plant-based sources; nuts, seeds, non–soy-based legumes and wild-caught fatty fish, some lean animal protein
Carbohydrates	Refined carbohydrates; high-fructose corn syrup, added sugar, fewer whole grains	Whole grains	High-fiber, reduced refined carbohydrates, gluten-free whole grains
Dairy	High-fat dairy sources	Low-fat dairy, yogurt	Dairy alternatives
Fats	Solid added fats such as butter and sour cream	Olive oil and olives	Olive oil, olives, coconut oil, avocados, nuts, omega-3 rich fatty fish, flax, walnuts; avoidance of soybean, cottonseed, peanut, and corn oil
Other	Added-sugar beverages, processed foods	Moderate red wine	Spices: turmeric, garlic, ginger, and other anti-inflammatory herbs and spices; green tea and prebiotic and probiotic (fermented) vegetables
Cultural	Eating on the run/overeating	Highly social and connected experiences	Mindful eating approach: quality over quantity

Modified from "Anti-Inflammatory Diet in Clinical Practice: A Review."[74]

as-needed basis if symptoms suggest sensitivity to these foods.

Celiac Neuropathy and Nonceliac Gluten-Sensitivity Neuropathy. Extraintestinal manifestations of celiac disease include various forms of neuropathy, with length-dependent sensorimotor polyneuropathy and sensory ganglionopathy being the most common.[75] Neuropathy is the second most common neurological manifestation of celiac disease after gluten ataxia.[76] It has also been argued that gluten sensitivity (i.e., wheat or gluten sensitivity) in the absence of enteropathy or endomysial or tissue transglutaminase antibodies may be a distinct syndrome, although this is somewhat controversial. Nonetheless, gluten sensitivity in the absence of diagnosed celiac disease is becoming increasingly recognized and has been confirmed, with a placebo-controlled trial demonstrating the existence of gluten sensitivity by food challenge.[77] Patients with gluten neuropathy consequently may not necessarily have associated enteropathy or meet the diagnostic criteria for celiac disease, and gluten neuropathy should be considered in the setting of unexplained or "idiopathic" neuropathy.

The presence of serologic evidence of gluten sensitivity (immunoglobulin A [IgA] or IgG to anti-gliadin antibodies) is a useful diagnostic clue,[78] but may not always be present in patients with gluten sensitivity.[77] Pain is prevalent in gluten neuropathy, and a strict gluten-free diet is associated with reduced risk of neuropathic pain in patients with gluten sensitivity associated neuropathy.[78] Thus, it is reasonable to conclude that some idiopathic neuropathies may be secondary to nonceliac gluten sensitivity and may show improvement with dietary modifications in the absence of these antibodies. A trial of gluten elimination in these patients is a relatively straightforward and risk-free intervention that may yield both diagnostic and therapeutic benefit. As shown in Figure 3, a 3–5-week or longer trial of a gluten-free elimination diet may be indicated in patients with a neuropathy of undetermined origin. If improvement is noted, then lifetime removal of gluten from the diet is recommended.

Therapeutic Exercise for Neuropathy. Long-term inactivity has been shown to be proinflammatory, as indicated by elevated circulating levels of inflammatory markers such as tumor necrosis factor and C-reactive protein (CRP).[79] The chronic pro-inflammatory state produced by a sedentary lifestyle has been associated with the development of insulin resistance.[80] Conversely, the effects of exercise are anti-inflammatory and include reduction of visceral fat, increased production and release of anti-inflammatory cytokines from muscle, reduced expression of Toll-like receptors on monocytes and macrophages, and increased T-regulatory cells both in circulation and in adipose tissue.[79,81]

Perhaps the best evidence in favor of exercise for treatment and prevention of diabetic and metabolic syndrome–associated neuropathy comes from studies of cutaneous reinnervation capacity in patients with metabolic syndrome and diabetes.[82–84] Intraepidermal nerve fiber density (IENFD) is reduced in metabolic syndrome and diabetes with and without clinical neuropathy.[85] Six months of combined supervised aerobic and resistance training exercise has shown improved cutaneous nerve regeneration capacity in patients with metabolic syndrome using the capsaicin axotomy model.[82] Also, 1 year of exercise increased IENFD in diabetes patients without neuropathy[83] and in those with impaired glucose tolerance with neuropathy,[85] indicating that cutaneous nerve disease in unmyelinated axons is potentially reversible. This improvement was associated with improved body mass index, oral glucose tolerance test, serum cholesterol, and quantitative sudomotor axon reflex test.[85] One randomized, controlled trial (RCT) in diabetic patients showed that long-term aerobic exercise training (4 hours/week at 50%–85% maximal heart rate) is able to prevent the onset and modify the natural history of diabetic polyneuropathy.[86] Taken together, physical activity provides a strong and natural anti-inflammatory strategy with few side effects and should be recommended for patients with neuropathy whenever possible.

DIETARY SUPPLEMENTS

Regulation. It is important to understand how to recommend use of supplements, because, as discussed in what follows, there are useful, well-tolerated supplements with evidence showing therapeutic benefit in neuropathy and neuropathic pain. Historically, physicians have avoided recommending dietary supplements and herbs due to the lack of rigorous federal regulatory oversight of these compounds as well as potential interactions with pharmaceutical agents. These are important concerns. Good Manufacturing Process (GMP) certification of all dietary supplement manufacturing facilities is required by the U.S. Food and Drug Administration. At the minimum, recommended dietary supplement companies should have their facility GMP registered by NSF International, an independent global health and safety organization. It is important to explain the value of safety and quality assurance to the patient and, if possible, recommend a specific product. Consumers can search GMP-registered manufacturers[87] and NSF finished product or ingredient certification.[88] There are also natural medicine databases available to assist with the identification of interactions, effectiveness, and nutrient depletion associated with natural medicines and pharmaceuticals.

Alpha-Lipoic Acid. Alpha-lipoic acid (ALA; Table 2, and Table S1 online) has been extensively studied and utilized in Europe for treatment of diabetic

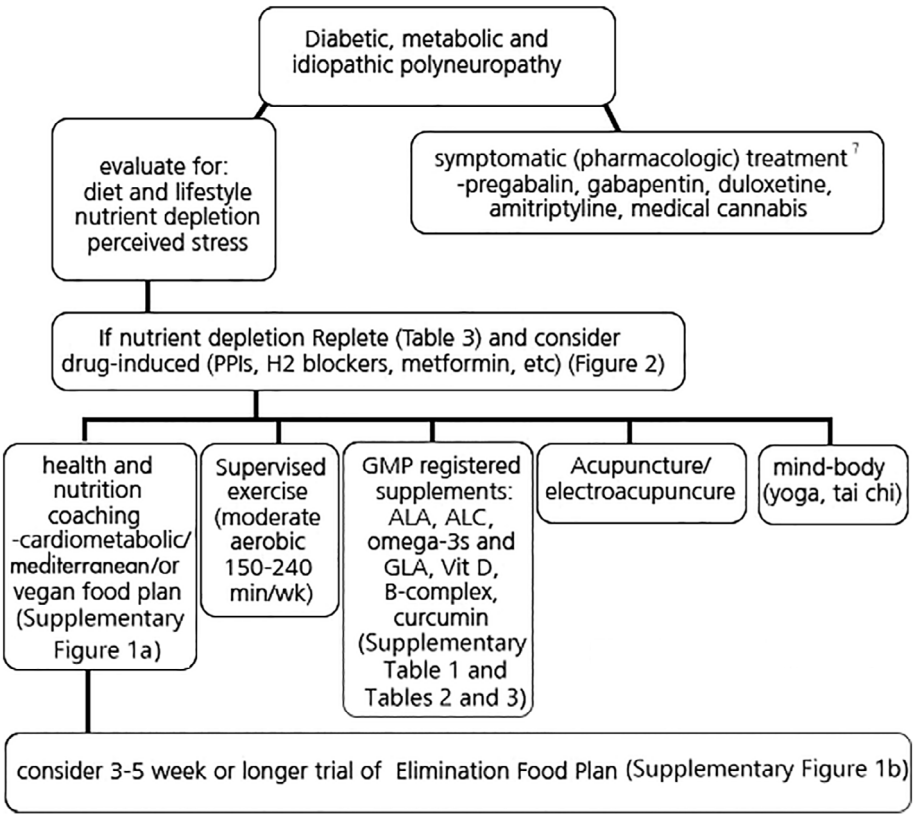

FIGURE 3. Integrative treatment algorithm for diabetic, metabolic, and idiopathic polyneuropathy. ALA, alpha-lipoic acid; ALC, acetyl-L-carnitine; GLA, gamma-linolenic acid; GMP, good manufacturing processes; PPI, proton-pump inhibitor.

neuropathy.[89–93] Treatment with ALA reduces oxidative stress and proinflammatory markers and improves endothelial function in patients with metabolic syndrome and animal models of diabetic neuropathy.[94,95] Short-term treatment with the intravenous (IV) form, not available in the USA, at a dose of 600 mg/day IV for 3 weeks, has been shown to reduce pain, burning paresthesias, and numbness in diabetic neuropathy.[96] After 5 weeks of oral treatment, patients demonstrated improvement in multiple measures of neuropathy symptoms.[91] After 4 years of treatment with ALA, neuropathy impairment score, including muscular weakness, improved in the treatment group and worsened in the placebo group.[90] There was no change in nerve conduction studies (NCSs) compared with placebo over the long term. The side-effect profile of oral ALA is favorable; however, there have been reports of nausea, vomiting, and vertigo.[91]

Acetyl-L-Carnitine. Acetyl-L-carnitine (ALC; Table 2, and Table S1 online) is an effective dietary supplement for diabetic neuropathy, as shown in RCTs.[97–99] ALC is vital for normal mitochondrial function and is known to be deficient in diabetes.[100] ALC potentiates nerve growth factor actions and promotes peripheral nerve regeneration and nerve conduction in animal models.[101] In studies of chronic diabetic neuropathy, patients treated with an ALC dose of 500–1,000 mg 3 times daily showed significant improvements on the visual analog scale (VAS) for pain as well as in vibration perception in both the fingers and toes; in addition, morphometric analyses of sural nerve biopsies showed increases in nerve fiber numbers and regenerating nerve fiber clusters at 52 weeks.[97]

An RCT of ALC demonstrated pain reduction in antiretroviral (HIV) neuropathy[102] (see Table S1 online). There is mixed evidence for ALC in chemotherapy-induced peripheral neuropathy (CIPN). Two RCTs showed reduced severity of neuropathy symptoms[103] and incidence of severe neuropathy[104] when patients

Table 2. Complementary and alternative medicine treatments with evidence for neuroprotection in diabetic neuropathy

Treatment	Recommended dose	References
ALA	600–1,800 mg/day in divided doses	90, 92
ALC	500–1,000 mg 3 times daily	97, 98
GLA (as evening primrose oil)	360–480 mg/day	110, 111
Omega-3 fatty acids (fish oil)	EPA 1,000–2,000 mg/day and DHA 500–1,000 mg/day	109
Active B-complex	L-methylfolate, pyridoxal 5'-phosphate, methylcobalamin (Metanx)	125, 126
Exercise	Moderate aerobic exercise 150–240 min/week (50%–85% maximal heart rate)	84, 86

ALA, alpha-lipoic acid; ALC, acetyl-L-carnitine; GLA, gamma-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

were treated with ALC during chemotherapy. These trials involved patients receiving sagopilone or a mixed population receiving ALC with chemotherapy. One RCT of breast cancer patients treated with taxone showed more severe neuropathy in the treatment group, and thus ALC is not recommended in this patient population.[105]

Dietary Essential Fatty Acids and Cholesterol. Myelin sheaths are comprised of 70% lipids.[106] Essential fatty acids (EFAs) must be supplied by the diet, and EFAs and cholesterol are required for myelin formation and function.[106] Omega-3 fatty acids (alpha-linolenic, docosahexaenoic acid, and eicosapentaenoic acid) added to the diet have been shown to decrease proinflammatory cytokines.[107] Omega-3 fatty acids have been found to be protective against paclitaxel-induced peripheral neuropathy in a double-blind, placebo-controlled trial.[108] An open-label pilot study of 12 months of seal oil omega-3 improved corneal nerve fiber length measured by *in-vivo* corneal confocal microscopy in patients with type 1 diabetes and sensorimotor polyneuropathy[109] (see Table S1 online).

One large and 1 small double-blind RCT of 360–480 mg gamma-linolenic acid (GLA), given as evening primrose oil, improved NCS results and sensory threshold measurements in patients with mild diabetic neuropathy[110,111] (Table 2, and Table S1 online). The response was better in patients with better diabetic control, that is, lower hemoglobin A_{1c} (HbA_{1c}). Evening primrose oil is a rich source of the omega-6 EFA linoleic acid and GLA, which are essential components of myelin and neuronal cell membranes. In diabetes, the first step in metabolism of linolenic acid to GLA is impaired, so these results support the view that one factor contributing to diabetic neuropathy is reduced linoleic acid metabolites.[112] There is also animal-model evidence to suggest that GLA supports remyelination.[113]

Curcumin. Curcumin (see Table S1 online), a natural phenol, is the principal curcuminoid of turmeric root. It is one of the most widely used and researched natural medicines for pain. Curcumin has been shown to lower oxidative stress, pain, and inflammation, and to have neuroprotective effects.[114] It has demonstrated antinociceptive activity in rat models of diabetes-, alcohol-, and chemotherapy-induced neuropathic pain.[115–117] Human studies of curcumin in neuropathy are lacking, but 1 larger RCT showed improved VAS for pain in an add-on study using a nonsteroidal anti-inflammatory drug ± ALA ±400 mg of twice-daily curcumin and piperine (often used in combination with curcumin to increase its bioavailability).[118]

Vitamin D. Several recent observational studies have demonstrated an association between low vitamin D levels and the presence and severity of type 2 diabetic neuropathy. Vitamin D deficiency has been shown to be an independent risk factor for diabetic neuropathy.[119] Proinflammatory cytokines are thought to play a role in the pathogenesis of diabetic neuropathy, and 25-hydroxyvitamin D may regulate inflammatory mediators interleukin-13 (IL-13) and IL-17 in diabetes and diabetic neuropathy, suggesting that vitamin D deficiency may be a modifiable risk factor.[120] One nonrandomized and 2 open-label trials demonstrated that treatment with vitamin D_3 improved pain levels in patients with diabetic neuropathy.[121–123] In addition, patients with vitamin D deficiency and myeloma receiving bortezomib and/or thalidomide were more likely to develop severe peripheral neuropathy than those patients with normal vitamin D levels[124] (see Table S1 online).

B Vitamins. *B-Complex Vitamins.* Vitamins B_1 (thiamine), B_6 (pyridoxine), B_{12} (cobalamin), and folate play an important role in the pathogenesis of neuropathy in deficiency syndromes such as alcoholism, pernicious anemia, and isoniazid-induced pyridoxine deficiency as well as malabsorption syndromes (e.g., atrophic gastritis, gastric bypass).[56] There is clinical trial evidence supporting the use of B vitamins in diabetic neuropathy (specifically the metabolically active forms, i.e., L methyl-folate, methylcobalamin, and pyridoxal-5-phosphate, or Metanx [Alfasigma USA, Covington, Louisiana]) despite absence of evidence for deficiency states.[125–127] Metanx has been shown in small, blinded clinical trials to increase epidermal nerve fiber density and 2-point discrimination in diabetic neuropathy.[125,126] Pyridoxal-5-phosphate and methylcobalamin are cofactors to peripheral nerve functions impaired in type 2 diabetes. Cobalamin facilitates myelinogenesis and nerve regeneration.[127] Methyl-folate has been shown to improve endothelial function in type 2 diabetes.[126] A vitamin B complex was evaluated in the prevention of CIPN in an RCT. There was a trend indicating that B-complex vitamins may reduce the onset and severity of CIPN[128] (see Table S1 online).

Benfotiamine: Vitamin B_1. Diabetic patients are subject to vitamin B_1 deficiency due to an increase in renal clearance.[129] Benfotiamine (see Table S1 online) is a lipid-soluble derivative of vitamin B_1 (thiamine) and has a significantly higher bioavailability than the water-soluble counterpart. Studies have shown that benfotiamine reduces markers of endothelial dysfunction and oxidative stress and advanced glycation end-products in individuals with type 2 diabetes.[130] Symptomatic improvement, particularly improvement of pain, with benfotiamine in diabetic neuropathy may be seen as early as 6 weeks and is most significant at doses of 600 mg/day.[131,132] An RCT of alcoholic neuropathy patients showed benfotiamine to be superior to placebo and B-complex in treating pain and neurological deficits.[133]

Methylcobalamin: Vitamin B_{12}. Standard reference ranges for vitamin B_{12} in the USA (lower limit of normal is 200 pg/ml) are generally much lower than the reference ranges used in other countries (e.g., in Japan the lower limit of normal is 500 pg/ml).[135] Serum B_{12} assays are not standardized, and there is no universally agreed-upon cut-off level to define deficiency.[136] It is recommended that if patients are in the low normal range, less than 400 pg/ml, and methylmalonic acid and/or homocysteine levels are elevated, then supplementation should be initiated.[56] Vitamin B_{12} deficiency is relatively common in the USA, particularly in older individuals when absorption declines and long-term use of medications increases, and in persons with a predominantly plant-based diet. Methylcobalamin is an analog of cobalamin (B_{12}) and is necessary for the maintenance of the peripheral nervous system. Cobalamin is an important cofactor of Methyltetrahydrofolate (MTHF)-homocysteine-methyltransferase whereby homocysteine is converted to methionine, and methionine is involved in the biosynthesis of lecithin, which is necessary for myelination and nerve regeneration. Methylcobalamin has been shown to promote nerve regeneration after peripheral nerve injury in animal models.[137] Despite normal serum B_{12} levels, a double-blind RCT of methylcobalamin 500 mg 3 times daily in diabetic neuropathy showed statistically significant improvement in neuropathy symptom scores, including tightness, numbness, cramps, fatigue, weakness, and autonomic symptoms, but no changes in NCS findings at 4 months.[127]

Pyridoxal-5'-Phosphate: Vitamin B_6. Sustained very high doses of vitamin B_6 can cause severe toxic sensory ataxic neuropathy (ganglionopathy). Doses exceeding 200 mg/day, and probably much higher in most cases, seem to be required for toxicity.[138] There is little evidence to suggest, however, that B_6 intoxication causes predominantly sensory or sensorimotor axonal polyneuropathy.[139] Thus, vitamin B_6 deficiency occurs in at-risk populations and leads to neurological complications, including neuropathy.[14] Doses in the range of 25 mg/day to 50 mg twice daily are adequate and safe to treat deficiency states.[140] The highly bioavailable form, pyridoxal-5'-phosphate (P-5-P), is the preferred form to use as supplement. Individuals at risk for deficiency include those on a predominantly plant-based diet or with poor nutritional status (i.e., alcoholics), recipients of gastric bypass surgery, or those taking isoniazid or other pyridoxine antagonists. In the general population, elevated levels appear to be more common than abnormally low levels, but it is important to measure fasting vitamin B levels as transient elevations occur after ingestion of water-soluble vitamins.[141] It is also important to note that low levels of circulating B_6 are linked to elevation of the inflammatory marker CRP and increased risk of cardiovascular disease independent of homocysteine levels.[142,143] Higher vitamin B_6 intake has been linked to protection against inflammation.[144] Therefore, appropriate dietary counseling to include foods high in B_6 and/or B_6 supplementation is indicated, because vitamin B_6 is a cofactor for greater than 100 enzymes and is specifically required for production of cytokines and other regulators of chronic inflammation.

MOVEMENT-BASED THERAPIES

Tai Chi. Tai chi chuan is a traditional Chinese martial art practiced for many centuries that consists of deep diaphragmatic breathing and relaxation with slow, gentle movements and postures. Twelve weeks of tai chi (1 hour, 3 times per week) improved fasting blood glucose, insulin resistance, HbA_{1c}, balance, and Total Symptom Score in diabetic neuropathy in 2 controlled trials.[145,146] In addition, tai chi increased circulating numbers of regulatory T cells and increased the ratio of T helper to T suppressor cells (CD4:CD8 ratio) in diabetic patients.[147] Two uncontrolled trials of tai chi showed improved results for 6-minute walk test, timed-up-and-go test, leg strength, and plantar sensation in a heterogeneous neuropathy population.[148,149]

Yoga. Yoga has been shown to be beneficial in neurological disorders, pain, and diabetes in multiple studies, but RCTs in neuropathy have been rare.[150] The practice of yogic postures for carpal tunnel syndrome (CTS) has been shown to be superior to splinting or no intervention in 1 RCT showing improved pain and grip strength in the treatment group.[151] Another study randomized 120 diabetic patients to 6 months of a comprehensive yogic breathing program in addition to standard therapy of diet and exercise. The treatment group showed significantly improved postprandial glucose (but not fasting or HbA_{1c}) and quality-of-life measurements and improved cardiac autonomic function.[152]

ACUPUNCTURE

A systematic review and meta-analysis of acupuncture for the treatment of peripheral neuropathy evaluated 15 studies, including 13 RCTs and 2 follow-up studies to RCTs evaluating acupuncture for neuropathy secondary to diabetes, Bell's palsy, CTS, HIV, and idiopathic neuropathy[153] (see Table S1 online). Most studies originated in China and the USA, with the majority of RCTs showing benefit of acupuncture or acupuncture plus usual medical care over sham acupuncture or usual medical care alone for diabetic neuropathy and CTS.[153] One of 2 well-designed RCTs of acupuncture for Bell's palsy showed improvement compared with standard medical treatment, and in the other RCT, all groups, including the control group, had high improvement rates, resulting in a negative study. The discrepancy was thought to be due to the heterogeneous but generally favorable prognosis of this condition.[153] The current

Table 3. Recommended dietary supplement doses

Blood test (fasting)	Dietary supplement intervention[162]	Comment
Plasma vitamin B_6	P-5-P 20–50 mg/day maximum (may be neurotoxic at >200 mg/day)	Use whole food, whole food vitamins or bioavailable, methylated B_{12}, and MTHF and P-5-P; the preference is to avoid folic acid, cyanocobalamin, and pyridoxine
Vitamin B_{12}	Methylcobalamin 1 mg/day by mouth or IM/SC weekly for 1 month, then monthly in malabsorptive states	
Homocysteine	Methylcobalamin/methylfolate/P-5-P	
RBC folate	Methylfolate 0.8–5.0 mg	
RBC thiamine pyrophosphate	Benfotiamine 150–300 mg twice daily	
25-hydroxyvitamin D	Vitamin D_3	Dose to target level
Vitamin E, alpha-tocopherol	Mixed tocopherols and tocotrienols 800 IU	
Insulin	ALA, *N*-acetylcysteine 500–1,500 mg, berberine 300–500 mg 3 times daily, cinnamon one-quarter teaspoon, or metformin	Low-glycemic/anti-inflammatory diet
Hemoglobin A_{1c}		
Fasting glucose		
Omega-6:omega-3 ratio	DHA 1 g, EPA 0.5–1 g	
hs-CRP	Curcumin	

ALA, alpha-lipoic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; hs-CRP, high-sensitivity C-reactive protein; IM/SC, intramuscular/subcutaneous; MTHF, methyltetrahydrofolate; P-5-P, pyridoxal-5-phosphate; RBC, red blood cell.

state of evidence also shows that acupuncture may be beneficial in HIV neuropathy, but further study is needed in this condition as well as in idiopathic neuropathy and CIPN.

The promising acupuncture studies in diabetic neuropathy and CTS involved acupuncture points that were located near to the affected peripheral nerves, suggesting a direct effect on underlying nerve and perineural tissues. Electroacupuncture, in which a small electric current is passed between pairs of acupuncture needles, is also often utilized to treat pain, including neuropathic pain. In 2017, Maeda and colleagues[154] showed that there is somatotopically distinct neuroplasticity after acupuncture therapy, and the improvement noted in NCSs after acupuncture for CTS is associated with enhanced neuroplasticity in the primary somatosensory cortex.[155]

CANNABINOIDS

RCTs involving cannabinoids and cannabis have demonstrated effective analgesia in various patient populations with chronic neuropathic pain refractory to other treatments[155–161] (see Table S1 online). Due to changes in the legalization of cannabis and the growing use of medical cannabis for chronic pain syndromes, it is important to consider cannabinoid medicine as part of an integrative medicine approach.

SUMMARY OF AN INTEGRATIVE MEDICINE APPROACH TO NEUROPATHY

An integrative approach to painful neuropathy involves a detailed lifestyle history, including dietary history, activity level, toxic exposure, family history, social connections, perceived stressors, medical history, medications, and supplement use, in addition to over-the-counter medications and medications that may lead to nutrient depletion and potentially contribute to neuropathy (Fig. 2). Laboratory analysis will include evaluation of nutritional status (see Table 3 for nutraceutical and dietary interventions) as well as the etiology of neuropathy.[6] In addition to symptomatic pharmaceutically based treatment (described in detail elsewhere),[9] lifestyle management is central to treatment of diabetic, prediabetic, metabolic syndrome–associated, and idiopathic neuropathy. Detailed nutritional counseling and education is ongoing and generally includes a diet low in glycemic load and high in micronutrient, phytonutrient, fiber, and healthy fats, as shown in Table 3 and in Figure S1A online (low-carbohydrate Mediterranean-type diet), with the option of a 3–5-week trial of an elimination diet (preferred) that is void of common inflammatory foods such as gluten, dairy, sugar, corn and soy, packaged processed foods, hydrogenated/trans fats, refined grains, and chemical additives (Table 1 and Fig. 3, and Fig. S1B online). If symptoms are improved on the elimination diet, then foods are systematically added back (except for packaged processed foods, refined grains, hydrogenated/trans fats, and sugar) into the diet every few days while monitoring for return or worsening of symptoms. If symptoms recur or worsen, then elimination of the foods (e.g., gluten) is recommended for more extensive periods depending on the severity of the recurrence. This is best achieved by working with a nutritionist experienced in functional medicine. Laboratory tests that should provide insight into a patient's dietary changes within 1 month include insulin sensitivity, high-sensitivity CRP, triglycerides, and homocysteine levels.

Whenever possible, a supervised exercise program should be initiated, including at least 150 minutes of moderate aerobic exercise per week. Not uncommonly, adherence to this kind of nutritional and lifestyle change will allow for discontinuation of medications such as proton pump inhibitors or H2 blockers and,

with time, some patients may no longer require metformin or cholesterol-lowering agents.

Nutraceutical-based treatment should be based on available evidence to support neuroprotection and nerve regenerative capacity (Table 2) as well as to optimize nutritional status (Table 3). Supplements are not a replacement for lifestyle change nor are the benefits as great in the author's experience.

If pain is suboptimally controlled with the aforementioned measures, then acupuncture or electroacupuncture may be used as an add-on therapy. Tai chi or yoga may be beneficial, particularly if levels of perceived stress are high or if balance is impaired. For refractory patients, medical cannabis is a viable consideration.

CONCLUSIONS

Poor diet quality and lack of physical exercise contribute to the development of dysbiosis and chronic systemic inflammation, and there is accumulating evidence that these factors contribute to the development of prediabetic, diabetic, and metabolic syndrome–associated neuropathies. An integrative medicine approach, including diet, exercise, supplementation, acupuncture, and movement-based therapies, offers additional treatment modalities that may lead to improved patient outcomes in peripheral neuropathy.

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