



The Potential Role of Fatty Acids in Treating Diabetic Neuropathy

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Abstract

Purpose of review This review will summarize recent findings of the effect of supplemental fatty acids, with an emphasis on omega-3 polyunsaturated fatty acids, as a treatment for diabetic peripheral neuropathy.

Recent findings Pre-clinical studies have provided evidence that treating diabetic rodents with δ linolenic acid (omega-6 18:3) and to a greater extent with eicosapentaenoic and docosahexaenoic acids (omega-3 20:5 and 22:6, respectively) improve and even reverse vascular and neural deficits. Additional studies have shown resolvins, metabolites of eicosapentaenoic and docosahexaenoic acids, can induce neurite outgrowth in neuron cultures and that treating type 1 or type 2 diabetic mice with resolvin D1 or E1 provides benefit for peripheral neuropathy similar to fish oil.

Summary Omega-3 polyunsaturated fatty acids derived from fish oil and their derivatives have anti-inflammatory properties and could provide benefit for diabetic peripheral neuropathy. However, clinical trials are needed to determine whether this statement is true.

Keywords Diabetic peripheral neuropathy · Omega-3 polyunsaturated fatty acids · Omega-6 polyunsaturated fatty acids · Resolvin · Inflammatory stress · Oxidative stress

Introduction

Peripheral neuropathy is the most common of diabetic complications affecting about 50% of subjects with either type 1 or type 2 diabetes [1•, 2•, 3•]. It drastically reduces the quality of life and is the leading cause of non-trauma related amputations of lower limbs [4, 5]. The 5-year survival rate for patients after non-trauma related amputation is estimated at less than 50% [4]. About 25% of subjects with diabetic neuropathy experience pain and treatments exist to help alleviate this symptom; however, there is no treatment for repair of nerve damage other than good glycemic control, which only delays its progression in

subjects with type 1 diabetes and has little impact in subjects with type 2 diabetes [2•, 5–8]. The mechanisms responsible for diabetic neuropathy and potential treatments have been the subject of intense research for many years. Studies with animal models have identified a wide range of therapeutic targets for treatment of diabetic peripheral neuropathy, but translation to human subjects has not been successful [1•, 9, 10•, 11, 12•, 13–19]. There are many explanations that may account for the lack of success in discovering a treatment(s) for diabetic neuropathy [20, 21•]. Nonetheless, the severity of this problem necessitates a continued pursuit for a treatment. In this review, article study of the potential role for dietary fatty acids as a contributor as well as a treatment for diabetic peripheral neuropathy will be presented with an emphasis on omega-3 polyunsaturated fatty acids commonly found in fish oil and other cold water marine mammals.

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Dietary Lipid Contribution to Peripheral Neuropathy

Abnormal lipid metabolism or excess lipids have been associated with a wide variety of diseases including diabetic neuropathy. High-fat diets consisting primarily of saturated fat derived from lard have been used to induce dietary obesity in rodent models. Studies from my laboratory has shown that

feeding rodents a high-fat diet causes a slowing of sensory nerve conduction velocity, decrease in intraepidermal and corneal nerve fibers, and abnormal sensory nerve perception as indicated by increased thermal latency and reduced cornea sensitivity and in rats vascular dysfunction in epineurial arterioles of the sciatic nerve [22–26]. Interestingly, we have not been able to detect a slowing of motor nerve conduction velocity in rodents fed a high-fat diet unless they have been on such a diet for almost a year. This suggests that there may be a difference in the pathogenesis caused by excess saturated fats in the diet on large and small or myelinated and un-myelinated nerve fibers. Other laboratories have reported similar events overall when feeding rodents a high fat/Western diet. Obrosova et al. demonstrated that female C57Bl6/J mice fed a high-fat diet for 16 weeks developed obesity, increased plasma free fatty acid and insulin levels, and impaired glucose tolerance [27]. In these studies, they found a slowing of both motor and sensory nerve conduction velocities, tactile allodynia, and thermal hypoalgesia in the absence of intraepidermal nerve fiber loss or axonal atrophy. Two other studies using C57Bl6/J mice fed a high-fat diet for 14–16 weeks found impaired glucose tolerance and reduction in motor and sensory nerve conduction velocity and decreased intraepidermal nerve fiber density [28, 29]. In addition, in the study by Hinder et al. [28], they demonstrated that reversing the diet of high-fat fed mice to a normal diet for 6 weeks improved metabolic parameters and nerve function. We performed a similar reversal study in high-fat fed Sprague-Dawley rats and obtained mixed results [22]. Rats were fed a high-fat diet for 12 weeks and then a normal diet for 12 weeks. Reversing the diet improved glucose utilization and steatosis but only marginally improved neuropathology. We concluded that more extensive treatment or a longer duration is required to reverse peripheral neuropathy in obese rats. In another study, Ozay et al. [30] fed male Wistar rats a high-fat diet for 12 weeks and reported that nerve fiber diameter and thickness of the myelin sheath were significantly lower in the high-fat fed rats.

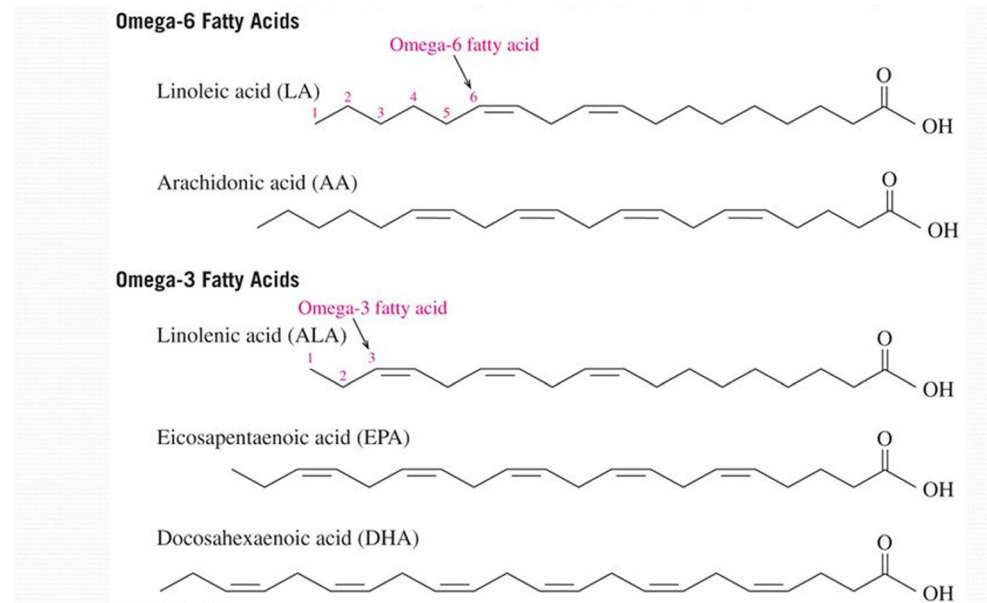
Besides animal studies, there is evidence that suggests development of neuropathy in human subjects with impaired glucose tolerance and metabolic syndrome [31]. Early onset of neuropathy in patients with pre-diabetes is frequently reported to be a burning pain and allodynia and loss of small myelinated A δ fibers or unmyelinated C fibers [28]. In the general population, the prevalence of neuropathy in prediabetes is intermediate and milder between overt diabetes and subjects with normoglycemia [32]. Above results have led to studies examining the effect of lipid lowering on diabetic neuropathy. In type 2 diabetic mice, treatment with fenofibrate ameliorated endothelial and neural damage by activating the peroxisome proliferative-activated receptor- α [33]. Studies with fenofibrate were shown to lower levels of atypical sphingolipids, which have been linked to inherited forms of sensory neuropathy, in plasma of dyslipidemic patients, and

the authors proposed that this could be a novel approach to prevent/treat diabetic neuropathy [34]. Fenofibrate has also been shown to improve microvascular complications in human subjects with type 2 diabetes [35]. A study by Davis et al. using a large observational cohort, termed the Freemantle Diabetes Study, suggested that the use of statins or a fibrate may slow the progression of neuropathy in patients with type 2 diabetes [36]. In a multi-center study referred to as the Fenofibrate and Event-Lowering in Diabetes (FIELD) study conducted using 9795 patients with type 2 diabetes randomized to placebo or fenofibrate reported a significantly lower rate of non-traumatic amputations in the fenofibrate-treated group [37]. A randomized trial enrolled 10,251 participants with type 2 diabetes and targeted to receive either intensive or standard treatment for glycemia (target glycosylated hemoglobin level, < 6.0 or 7.0 to 7.9%, respectively) and also for dyslipidemia (160 mg daily of fenofibrate plus simvastatin or placebo plus simvastatin) or for systolic blood pressure control (target, < 120 or < 140 mmHg). A subgroup of 2856 participants was evaluated for the effects of these interventions at 4 years on the progression of diabetic retinopathy by three or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale. It was found that intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive blood-pressure control, reduced the rate of progression of diabetic retinopathy [38]. Overall, a number of clinical studies have led investigators and clinicians to conclude that hyperglycemia is not the only factor contributing to diabetic neuropathy, particularly in patients with type 2 diabetes, and that components of the metabolic syndrome, such as dyslipidemia, obesity, insulin resistance, and cardiovascular risk factors including hypertension, may also have a contributing role [39, 40]. For reasons that are not entirely clear, lipid lowering drugs are not commonly recognized as a treatment for diabetic neuropathy.

Lipids as Potential Therapy for Peripheral Neuropathy?

Lipids have many roles in the mammalian system ranging from structural components of membranes to signaling molecules. In the section above, we have seen that in excess lipids in the form of saturated fatty acids can contribute to development and progression of peripheral neuropathy. However, is it possible that lipids could also have a role in the treatment of peripheral neuropathy? Besides saturated fatty acids, which have no double bonds, fatty acids may also have a single double bond with oleic acid (18:1) being the most common fatty acid of this class or they may have multiple double bonds and referred to as polyunsaturated fatty acids. There are two classes of polyunsaturated fatty acids commonly referred to as omega-6 or omega-3 (Fig. 1). Omega-6 fatty acids (also referred to as ω -6 fatty acids or n-6 fatty acids) are a family of

Fig.1 Structure of the primary omega-6 and omega-3 polyunsaturated fatty acids



polyunsaturated fatty acids that have in common a final carbon-carbon double bond in the n-6 position, that is, the sixth bond, counting from the methyl end. Linoleic acid (18:2) is the shortest-chained omega-6 fatty acid, and arachidonic acid (20:4) is the most common and important for synthesis of signaling molecules. Both omega-6 and omega-3 are categorized as essential fatty acids because the human body is unable to synthesize them. In omega-3 fatty acids (also referred to as ω -3 fatty acids or n-3 fatty acids), the first double bond is between the third and fourth carbon atoms from the methyl end of the carbon chain. The three primary omega-3 fatty acids involved in human physiology are α -linolenic acid (18:3), found in plant oils, and eicosapentaenoic acid (20:5) and docosahexaenoic acid (22:6), both commonly found in fish/marine oils.

Mammals synthesize the longer chain polyunsaturated fatty acids from linoleic acid and α -linolenic acid, which are the two precursors of omega-6 and omega-3 fatty acid families provided by the diet [41]. Specific enzymes, desaturases and elongases, are involved in this pathway, but the conversion of precursors to long chain polyunsaturated fatty acids is generally low in humans. In addition, diabetes impairs the desaturases activities [41, 42]. Consequently, the decrease in bioavailability of polyunsaturated fatty acids affects the fatty acid composition of membrane phospholipids and signaling pathways [41]. The National Health and Nutrition Examination Survey (NHANES) reported that the mean dietary intake of γ -linolenic acid (18:3, omega-6) was significantly lower among adults with peripheral neuropathy compared to those patients without peripheral neural neuropathy [43]. This suggests that increasing the intake of polyunsaturated fatty acids may be an effective treatment to delay or prevent development of diabetic peripheral neuropathy.

Omega-6 and omega-3 polyunsaturated fatty acids have been tested pre-clinically as a potential treatment for diabetic peripheral neuropathy. The effect of γ -linolenic acid or evening primrose oil (natural oil enriched in γ -linolenic acid) on neuropathy was first examined nearly 30 years ago in diabetic animal models. Tomlinson et al. reported that treating type 1 diabetic rats with evening primrose oil prevented completely the development of motor nerve conduction deficit [44]. Cameron et al. also reported that treating type 1 diabetic rats with Efamol Marine for 2 months increased plasma levels of γ -linolenic acid and prevented nerve conduction velocity deficits and improved nerve hypoxia [45]. Other investigators have conducted similar experiments and have shown that treating diabetic rats with γ -linolenic acid improved neuropathy and membrane composition of the sciatic nerve and Na⁺, K⁺ ATPase activity [46, 47]. Investigators have also examined the effect on diabetic neuropathy in pre-clinical studies of the combination of γ -linolenic acid and α -lipoic acid. α -Lipoic acid is an antioxidant that is available over the counter. Two groups reported that a lipoic acid/ γ -linolenic acid conjugate was effective against multiple indices of experimental diabetic neuropathy [48, 49]. Both groups reported that the combination of α -lipoic acid and γ -linolenic acid was more effective than monotherapy in improving electrophysiological and neurochemical endpoints. Investigators have also examined the combined effect of α -lipoic acid and evening primrose oil on diabetic neuropathy [50, 51]. These studies have demonstrated that this combination was effective at treating diabetes-induced changes in enteric nerves of the rat ileum and improving endoneurial blood flow. Two clinical studies have examined the effect of γ -linolenic acid on human diabetic peripheral neuropathy. Jamal and Carmichael studied 22 patients with distal diabetic polyneuropathy using a double-blind,

placebo-controlled study design to assess the effect of dietary supplementation of γ -linolenic acid on their neuropathy [52]. Patients received capsules containing 360 mg of γ -linolenic acid or indistinguishable placebo daily for 6 months. Compared to the placebo group, the patients on γ -linolenic acid showed a significant improvement in neuropathy symptom scores as well as a number of electrophysiology endpoints [52]. In the γ -Linolenic Acid Multicenter Trial, 111 patients with mild diabetic neuropathy were randomized into a double-blind, placebo-controlled study using γ -linolenic acid at a dose of 480 mg per day [53]. The investigation included 16 parameters and at the end of the study the response to γ -linolenic acid was more favorable to placebo for 13 parameters and statistically significant. Overall, these studies would suggest that γ -linolenic acid with or without α -lipoic acid could be an effective treatment for diabetic peripheral neuropathy. However, the use of γ -linolenic acid has not been an accepted therapeutic approach.

Fish oil has been the most common source for omega-3 polyunsaturated fatty acids and is enriched in eicosapentaenoic and docosahexaenoic acids. Docosahexaenoic acid is the most abundant omega-3 polyunsaturated fatty acid in the mammalian brain and retina, and up to 60% of all fatty acids esterified in neuronal plasma membrane phospholipids at the sn-2 position of the glycerol moiety consist of docosahexaenoic acid [54, 55]. Even though the brain has a high concentration of docosahexaenoic acid, it has a limited capacity to synthesize it from α -linolenic acid suggesting that docosahexaenoic acid required by the brain is taken up from the circulation [54].

Work from my laboratory has demonstrated that enriching the diet of chronic diabetic mice or rats with menhaden (fish) oil can not only slow progression of diabetic peripheral neuropathy as determined by protection of motor and sensory nerve conduction velocity and prevention of thermal hypoalgesia but also can stimulate reversal and repopulation of sensory nerves in the skin and cornea [22, 56–59, 60•, 61]. Different cellular properties and functions may be altered when cells are enriched in long chain polyunsaturated fatty acids such as membrane fluidity, which may alter carrier-mediated transport, the properties of certain membrane-bound enzymes, binding to the insulin and opiate receptors, phagocytosis, endocytosis, depolarization-dependent exocytosis, immunologic and chemotherapeutic cytotoxicity, prostaglandin production, and cell growth [62]. However, in our studies with menhaden oil we have attributed the beneficial effects on diabetic peripheral neuropathy to the reduction of oxidative and inflammatory stress and the neuroprotective properties of resolvins [63]. Focusing on oxidative stress and inflammation as a therapeutic target for diabetic peripheral neuropathy is not novel since other studies have also concluded that these pathways to be important [10•, 64, 65].

Other laboratories besides our own have reported favorable results when treating diabetic rodents with omega-3

polyunsaturated fatty acids for neuropathy related endpoints. Gerbi et al. reported that fish oil supplementation prevented decrease in Na⁺, K⁺ ATPase activity in the sciatic nerve, diabetes-induced slowing of nerve conduction velocity, and neuroanatomical changes in rats [66]. Julu reported that eicosapentaenoic acid prevented slowing of nerve conduction velocity in streptozotocin-induced diabetic rats [67]. Two recent studies have suggested that treatment with fish oils may also be beneficial in preventing painful diabetic neuropathy. Heng et al. reported that dietary supplementation of docosahexaenoic acid inhibited mechanical allodynia and thermal hyperalgesia by decreasing the excitability of dorsal root ganglions [68]. Li et al. reported that supplementing the diet of diabetic rats with fish oil prevented mechanical allodynia and thermal hyperalgesia by blocking nuclear factor- κ B-mediated inflammatory pathways [69].

In a clinical study conducted over 20 years ago, Okuda et al. reported that treating patients with type 2 diabetes with a new, highly purified, ethyl esterification product from natural eicosapentaenoic acid improved the clinical symptom (coldness, numbness) as well as the vibration perception threshold sense of the lower extremities [70]. They also reported a significant decrease of serum triglycerides and significant decrease of the excretion of albumin in urine. They concluded that omega-3 polyunsaturated fatty acids have significant beneficial effects on diabetic neuropathy and serum lipids as well as other diabetic complications such as nephropathy. In a more recent study, Lewis et al. reported that treating 40 type 1 diabetic patients with omega-3 polyunsaturated fatty acids derived from seal oil for 1 year increased corneal nerve fiber length by 29% but did not change nerve conduction or sensory function [71••]. These are encouraging results since studies in the last few years have promoted changes in corneal nerve fiber density as a potential early marker for diabetic neuropathy [72–74]. It will be interesting to see if a longer treatment phase may lead to improvement in other neurological deficits.

As mentioned above, the focus of our studies of the potential mechanism for the effect of eicosapentaenoic and docosahexaenoic acids on diabetic peripheral neuropathy has been on the effect of resolvins. Resolvins are oxygenated metabolites of eicosapentaenoic acid (E series resolvins) and docosahexaenoic acid (D series resolvins) and are generated through series of reactions that include the enzyme 15-lipoxygenase-1. Docosahexaenoic acid can also be converted into neuroprotectin-1. Eicosapentaenoic and docosahexaenoic acids are excellent substrates for 15-lipoxygenase-1, and resolvins formation is elevated by consuming increased amounts of eicosapentaenoic and docosahexaenoic acids as occurs when increasing intake of fish oils [75, 76]. It has been shown that regeneration of corneal nerves damaged by refractive surgery can be increased by treatment with docosahexaenoic acid through synthesis of neuroprotectin-1 [77, 78]. This group also reported that neuroprotectin-1 increases neurite outgrowth from

trigeminal ganglia neurons from Swiss Webster mice [77]. Robson, et al. reported that omega-3 fatty acids promote neurite outgrowth from dorsal root ganglia neurons, and the effect of docosahexaenoic acid was still prominent in neurons from aged animals [79]. We have obtained similar results when we treated dorsal root ganglion with resolvin D1 [58]. In a recent study, we used exogenous injections of resolvin D1, E1, and methyl esters of resolvins D1 or D2 and compared their effect to dietary enrichment with menhaden oil on neuropathic endpoints in type 2 diabetic mice [80]. As stated above, we have previously demonstrated in both type 1 and type 2 diabetic mice that endogenous treatment with daily injections of resolvin D1 was able to improve many endpoints associated with diabetic peripheral neuropathy [58, 60••]. The improvement observed with treatment of resolvin D1 was similar to the improvement we obtained through enriching the diet with menhaden oil [58, 60••]. Resolvin D1 levels in serum was also found to increase in the mice treated with diet enriched in menhaden oil [58, 60••]. In our most recent study, we were interested in comparing the effect of resolvin D1, derived from docosahexaenoic acid, to resolvin E1, derived from eicosapentaenoic acid, on neuropathic endpoints as well as to determine if the methyl ester analogues of resolvins D1 or D2 are more potent than resolvin D1 due to a reported longer circulatory half-life for these analogues [80•]. Results from this study indicated that untreated diabetic mice had mechanical allodynia, were thermal hypoalgesic, and had reduced motor and sensory nerve conduction velocities, and innervation of the cornea and skin was decreased. Treating diabetic mice with daily injections of resolvin D1 or E1 improved these neurological endpoints similar to dietary treatment with menhaden. However, treating the diabetic mice with the methyl esters of resolvins D1 or D2 was generally less potent than menhaden oil or resolvins D1 or E1. The two important findings from this study were that resolvins derived from eicosapentaenoic acid or docosahexaenoic acid were equally effective in improving neuropathy and that methyl esters of resolvins D1 or D2 even

though they may have longer half-lives were not as efficacious as resolvin D1. Overall, this study provided further support for omega-3 polyunsaturated fatty acids derived from fish oil via in part due to their metabolites could be an effective treatment for diabetic neuropathy. Resolvins as mediators of inflammation have been shown to have multiple effects on other tissues as previously reviewed [81••].

In another study, previously unreported, we examined the effect of resolvin D1 and menhaden oil on diabetic neuropathy in female C57Bl6/J mice. We had previously demonstrated that inducing type 2 diabetes through a combination of high-fat diet and streptozotocin and the development of peripheral neuropathy is similar for male and female C57Bl6/J mice [82]. In this study, after 6 weeks of diabetes, female mice were treated for 8 weeks with menhaden (fish) oil enriched diet or with daily injections of resolvin D1. Afterwards, multiple neuropathies related endpoints were examined (Table 1). Diabetic mice were hyperglycemic compared to control mice and treatment with menhaden oil or resolvin D1 did not improve blood glucose levels. Motor and sensory nerve conduction velocity was significantly decreased by diabetes and both were significantly improved with treatment. Intraepidermal nerve fiber and corneal nerve fiber densities were significantly decreased in diabetic mice and improved with the menhaden oil-enriched diet or exogenous resolvin treatment. Two behavioral studies were performed relating to sensory nerve sensitivity. Diabetic female mice demonstrated latency to a thermal challenge and greater sensitivity to a mechanical force. Both of these endpoints were significantly improved with menhaden oil or resolvin D1 treatments. This study further demonstrated that fish oil is an effective treatment for multiple endpoints related to diabetic neuropathy and that the beneficial effects are not gender specific.

If the pro-resolving lipid mediators of eicosapentaenoic acid and docosahexaenoic acid are potential treatments for peripheral diabetic neuropathy, then discovering means to

Table 1 Effect of menhaden oil dietary enrichment or daily treatment with resolvin D1 of diabetic female mice on fasting blood glucose, motor and sensory nerve conduction velocity (MNCV/SNCV), intraepidermal

nerve fiber density (IENF), cornea nerve fiber length, thermal nociception, and mechanical allodynia

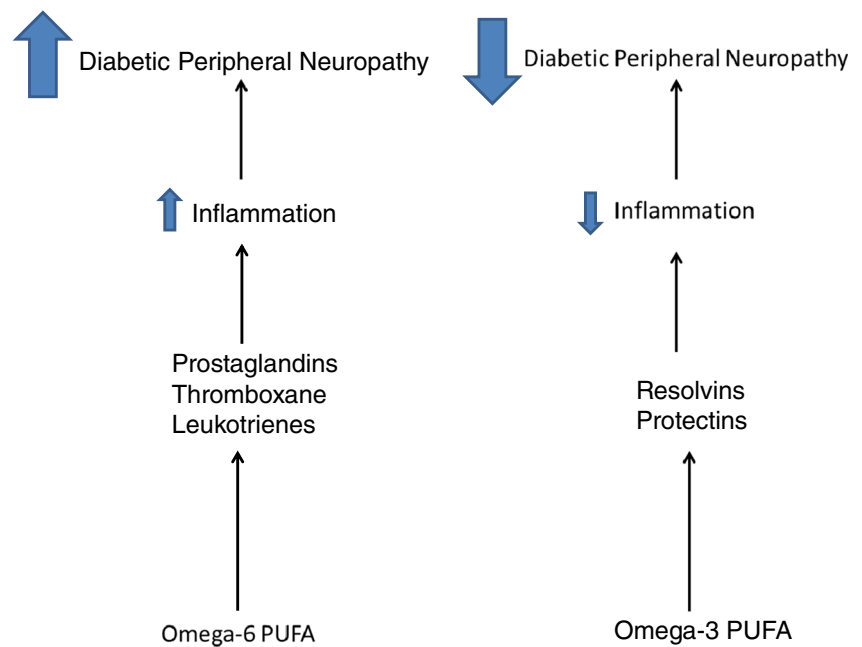
Determination	Control	Diabetic	Diabetic + menhaden oil	Diabetic + resolvin D1
Fasting blood glucose (mg/dl)	204 ± 7	407 ± 25 ^a	343 ± 30 ^a	375 ± 31 ^a
MNCV (m/s)	34.9 ± 1.3	21.9 ± 0.9 ^a	31.9 ± 1.2 ^b	31.3 ± 1.4 ^b
SNCV (m/s)	17.9 ± 0.2	15.0 ± 0.5 ^a	17.9 ± 0.2 ^b	18.2 ± 0.3 ^b
IENF (profiles/mm)	24.9 ± 0.5	15.7 ± 0.3 ^a	21.5 ± 0.4 ^{a,b}	20.8 ± 0.3 ^{a,b}
Corneal nerve fiber length (mm/mm ²)	2.00 ± 0.11	0.93 ± 0.07 ^a	1.81 ± 0.15 ^b	1.70 ± 0.14 ^b
Thermal nociception (s)	4.94 ± 0.07	7.25 ± 0.13 ^a	5.41 ± 0.16 ^b	5.87 ± 0.14 ^{a,b}
Mechanical allodynia (g)	2.82 ± 0.08	1.15 ± 0.03 ^a	1.82 ± 0.09 ^{a,b}	1.69 ± 0.10 ^{a,b}

Data are presented as the mean ± S.E.M

^a $P < 0.05$ compared to control

^b $P < 0.05$ compared to diabetic. Number of experimental animals for each group was 15

Fig. 2 Effect of omega-6 and omega-3 PUFA on diabetic peripheral neuropathy



naturally increase their production *in vivo* may promote greater benefits. Aspirin is one compound that has been reported to increase the production of resolvins [83]. However, aspirin has side effects that make it undesirable for long term clinical use. Another compound with aspirin-like properties that has been reported to provide beneficial effects in obesity and diabetes by targeting established chronic inflammatory signaling and reducing insulin resistance is salsalate; aspirin and salsalate *in vivo* are metabolized to salicylate [83]. Salsalate activates brown adipose tissue in high-fat fed mice and improves glucose tolerance [84]. In human subjects with diabetes, salsalate improved insulin resistance and the lipid, lipoprotein, and apoprotein profile of insulin-resistant individuals who were overweight or obese [85–88]. Based upon studies utilizing salsalate, one group concluded that targeting inflammation and nuclear factor- κ B may be a viable therapeutic approach for treating type 2 diabetes [89]. We recently completed a study designed to examine the efficacy of fish oil with or without salsalate on vascular and neural complications using a type 2 diabetic rat model [90]. Four weeks after the onset of hyperglycemia diabetic rats were treated via the diet with three different amounts of menhaden oil (10, 25, or 45% kcal) with or without salsalate for 12 weeks. Afterwards, vascular reactivity of epineurial arterioles and neuropathy-related endpoints were examined. The addition of salsalate to high-fat diets enriched with 10 or 25% kcal of menhaden oil protected vascular reactivity to acetylcholine and calcium gene-related peptide, motor and sensory nerve conduction velocity, thermal nociception, intraepidermal nerve fiber density, and cornea sensitivity to a greater extent than 10 or 25% menhaden oil alone. Vascular and neural function was maximally protected with diet containing 45% kcal as menhaden oil and adding

salsalate did not provide any additional benefit. Salsalate alone in the high-fat diet of diabetic rats provided minimal protection/improvement of vascular and neural dysfunction. Adding salsalate to the menhaden oil enriched diets increased serum levels of resolvins D1. These studies imply that dietary salsalate in combination with lower amounts of menhaden oil can provide greater benefit toward diabetes-induced vascular and neural impairment than menhaden oil alone. Currently, a phase 2/3 human clinical trial evaluating salsalate for diabetic neuropathy is ongoing (NCT NCT02936843).

Conclusion

Diabetic peripheral neuropathy is a complex condition with multiple etiologies that can be influenced by lipids in a negative or positive manner (Fig. 2). Generally, saturated fatty acids and omega-6 polyunsaturated fatty acids negatively impact nerve function especially in obesity where abnormal adipose tissues and liver likely contribute to oxidative and inflammatory stress. The role of abnormal liver function in peripheral neuropathy is another interesting area that has been understudied. Recent studies in human subjects have linked non-alcoholic fatty liver disease with diabetes complications including chronic vascular complications and peripheral neuropathy [91–94]. Our rodent studies have provided similar evidence [22]. In our studies, we found that partially substituting oleic acid for saturated fatty acids did not provide any benefit to nerve function. This was not surprising since there was little change in the fatty acid profile of serum or tissues under this condition. However, partial replacement of saturated fatty acids derived from lard with omega-3 polyunsaturated fatty acids (derived from fish oil) in

the diet of type 2 diabetic rats did improve vascular reactivity of epineurial arterioles of the sciatic nerve and neuropathy. We found that linoleic acid (omega-6 polyunsaturated fatty acid derived from safflower oil) was pro-inflammatory and aggravated vascular and neural function. However, enriching the diet of type 2 diabetic rats with δ linolenic acid (omega-6 polyunsaturated fatty acid derived from evening primrose oil) provided some benefit for vascular and neural function, although the greatest benefit was obtained when the diet was enriched with menhaden (fish) oil a source for the omega-3 eicosapentaenoic and docosahexaenoic acids. Enriching the diet with α -linolenic acid (omega-3 polyunsaturated fatty acid derived from flaxseed oil) also improved vascular and neural function, but it was not as efficacious as menhaden oil. The pre-clinical studies performed to date are insufficient and do not provide definitive proof that fish oil should be a recommended treatment for diabetic peripheral neuropathy. Future properly designed clinical studies are needed to determine whether fish oil can provide relief for peripheral neuropathy in human diabetic patients. Furthermore, fish oil treatment could only be one component of a successful treatment for diabetic peripheral neuropathy. Due to the multiple etiologies associated with diabetic neuropathy, the most effective treatment may be a combination of compounds that target these different mechanisms.

Compliance with Ethics Standards

Conflict of Interest The author has no conflicts of interest to declare. The studies reported in this article from the author's laboratory were supported by grants from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Rehabilitation Research and Development [RX000889-06] and by the National Institute of Diabetes and Digestive and Kidney Diseases [DK107339-03] from NIH.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institution guidelines).

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