

Pathogenetic Treatment of Painful Diabetic Peripheral Neuropathy using an Evidence-Informed Bench-To-Bedside Translation on the Role of Diet and Nutrition

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Abstract

Background: Dyslipidemia and oxidative stress were shown to be pathogenetic mechanisms for developing diabetic peripheral neuropathy (DPN), which could be influenced, prevented, controlled or managed through dietary or nutritional interventions. **Objective:** To explore the evidence for pathological basis of diet and nutrition (DAN) in pathogenesis and treatment of DPN. **Methods:** A systematic review was performed using search terms 'diabetic neuropathy' with filters activated for subject category of 'Dietary Supplements' combined with another advanced search strategy including title terms "diet and nutrition" in PubMed, CINAHL and Google Scholar to identify studies published in English, with abstracts. The search was independently performed by two testers and consensus was adopted to solve disagreements in presence of third tester. A three-level scrutiny of obtained citations was done to identify relevant studies and descriptive synthesis was done to organize studies under bench and bedside evidence. **Results:** There were a total 15 bench studies and three bedside studies that provided evidence for DAN in DPN. Amongst the 15 bench studies on experimental DPN in rats, high fat diet (two studies) and fructose-rich diet (one study) had pathogenetic effect, while fish oil, E. officinalis fruit extract, glutathione, resveratrol, olive leaf extract, naringin, gastrodin, soy isoflavone genistein, and coenzyme Q10 (one study each) and cucumin (three studies) had therapeutic effect. There were no pathogenetic studies on humans and three bedside therapeutic studies were one each on Linolenic acid, Alpha-Lipoic acid and cannabis. **Conclusion:** There was limited bedside evidence from few studies which warrant future high quality clinical trials on efficacy of alpha lipoic acid, linolenic acid and cannabis-based extract in the management of DPN. The bench evidence had shown that fat-rich and fructose-rich diets had pathogenetic effects and cucumin had therapeutic effects on experimentally induced DPN in rats.

Keywords: Neuropathology; Neuropathogenesis; Pathogenetic neurorehabilitation; Neurometabolic syndrome; Diet and nutrition.

Introduction

Food is the source of energy for all life on

this planet.[1] Procuring food and satisfaction of hunger was considered as one among the important primary drives of human beings.[2] The quality and quantity of food determines the amount of energy input derived into the human body in order to maintain the energy balance between energy cost and energy expenditure.[3]

Diet is defined as the qualitative and

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quantitative method to organize the constituents of food, whilst nutrition denotes the composition and ensuing assimilation of various substances such as carbohydrates, proteins, fats, vitamins and minerals into the blood.[4] Although these terms were used interchangeably, diet is a common or colloquial term and nutrition is a therapeutic or clinical term.

Food intake directly and indirectly influences all bodily systems, through substance-specific and tissue-specific interactions that determine suitability or accommodation of a particular system.[5] Although ingestion, digestion and excretion of food occurs through the gastrointestinal system, energy delivery occurs to musculoskeletal, nervous and immunometabolic systems through transport of micronutrients and macronutrients through blood.[6]

Altered composition of nutrients absorbed from digested food alters the mechanical and biochemical properties of blood which acts as the transport medium, leading to blood-related hematopathologic abnormalities.[7] Hematopathologic consequences such as ischemia, hemorrhage and embolism immediately affect the blood vessels and capillaries and their smooth muscle layers which manifest as a micro- or macro-vascular condition or complication.[8] Common microvascular complication is such hematopathologic alterations of the vasa nervorum (blood vessels supplying peripheral nerves) leading to peripheral neuropathy in metabolic syndrome.[9]

Diabetes mellitus is the leading cause for peripheral neuropathy and peripheral neuropathy is the leading microvascular complication of diabetes leading to a chronic painful condition termed as diabetic peripheral neuropathy (DPN).[10] The role of vascular factors and metabolic interactions in DPN is well understood.[11,12] DPN bears a direct impact on patients' quality of life through its multidimensional symptoms and signs of pain, neurological dysfunction, mobility restriction, balance impairments and functional limitations thus acting as a huge public health burden.[13]

Pathogenetic evidence for developing DPN had established hyperglycemia,[14] glycation, polyol pathway, oxidative stress, vascular factors, growth factors, insulin-like growth factors, C-peptide, vasoendothelial growth factor, and immune mechanisms, all of which are dependent upon diet and nutrition.[15] Dyslipidemia was also shown to be an independent risk factor for developing DPN, which again could be prevented, controlled or managed through dietary interventions.[16]

Amongst the various pharmacological and non-pharmacological treatments available for DPN, varying degrees of success was reported in pain relief in these patients.[17] Useful treatment options for DPN include aldose reductase inhibitors, ACE inhibitors, lipid-lowering agents and alpha-lipoic acid (thioctic acid) supplementation.[18]

Oxidative stress also plays an important role in pathogenesis of DPN. Consensus recommendations widely suggested antioxidants such as alpha-lipoic acid together with other pharmacological agents such as tricyclic antidepressants (TCA), the selective serotonin and noradrenaline reuptake inhibitors (SNRIs), anticonvulsants, opiates, membrane stabilizers, and topical capsaicin for proven efficacy for painful DPN.[19]

Thus there is a need to evaluate the existing evidence base for pathogenesis and treatment of DPN through diet and nutrition so that subsequent attempts to evaluate their comparative efficacy could be made in order to establish the best suitable dietary supplementation. The objective of this paper was to explore the evidence for pathological basis of diet and nutrition in pathogenesis and treatment of DPN.

Methodology

A systematic review was performed using search terms “(neuropathy [Title] OR neuropathic [Title]) AND (pain [Title] OR painful [Title]) AND (diabetes [Title] OR diabetic [Title]) NOT autonomic [Title]” with

filters activated for subject category of 'Dietary Supplements' was combined with another advanced search strategy including terms "(diet [Title] OR dietary [Title] OR nutrition [Title] OR nutritional [Title])" in PubMed, CINAHL and Google Scholar to identify studies published in English, with abstracts. The search was independently performed by two testers and consensus was adopted to solve disagreements in presence of third tester. A three-level scrutiny of obtained citations based upon, title, abstract and full text content was done to identify relevant studies and descriptive data extraction and synthesis was done to organize studies under bench and bedside evidence for pathogenesis and treatment of DPN population with diet and nutrition (DAN).

Results

Of the 18 included studies in the final list of obtained articles, there were a total 15 bench studies and three bedside studies that provided evidence for DAN in DPN. Amongst the 15 bench studies on experimental DPN in rats, high fat diet (two studies) and fructose-rich diet (one study) had pathogenetic effect, while fish oil, *E. officinalis* fruit extract, glutathione, resveratrol, olive leaf extract, naringin, gastrodin, soy isoflavone genistein, and coenzyme Q10 (one study each) and cucumin (three studies) had therapeutic effect. There were no pathogenetic studies on humans and three bedside therapeutic studies were one each on Linolenic acid, Alpha-Lipoic acid and cannabis.

Experimental evidence- rat models of DPN

Pathogenetic effects

High-fat diet

Guilford *et al*[20] quantified neuropathic symptoms in diabetic mice fed a high-fat diet, and found that they developed dyslipidemia and a painful neuropathy (mechanical allodynia) instead of the insensate neuropathy (mechanical insensitivity). The high-fat diet-fed diabetic mice had slower sensory and motor

nerve conduction velocities compared to non-diabetic mice without worsening of thermal sensitivity.

Obrosova *et al*[21] evaluated neuro-pathogenetic changes to dietary interventions in Female C57BL6/J mice which were fed either a high-fat diet (HFD) or normal diet for 16 weeks and found that HFD-fed mice had motor and sensory nerve conduction deficits, tactile allodynia, and thermal hypoalgesia in the absence of intraepidermal nerve fiber loss or axonal atrophy.

Fructose-rich diet

Hotta *et al*[22] maintained Streptozotocin-diabetic rats on a 72% fructose diet for 4 weeks and found that Fructose feeding significantly influenced the development of impaired motor nerve conduction velocity in the diabetic rats and this effect was positively correlated with sorbitol accumulation in the sciatic nerves.

Therapeutic effects

Fish oil

Gerbi *et al*[23] assessed the preventive ability of a fish oil-rich diet (rich in n-3 fatty acids) on the DPN-related neurochemical abnormalities on Diabetic animals which were fed the standard rat chow either without supplementation or supplemented with either fish oil (DM, CM) or olive oil (DO, CO) at a daily dose of 0.5 g/kg for 8 weeks. Fish oil supplementation was found to change the fatty acid content of sciatic nerve membranes, decreasing C18:2(n-6) fatty acids and preventing the decreases of arachidonic acids and C18:1(n-9) fatty acids thus having beneficial effects on diabetes-induced alterations in sciatic nerve Na,K-ATPase activity and function.

E. officinalis fruit extract:

Kumar *et al*[24] investigated flavonoid rich fruit extract (ethyl acetate:methanol fraction) of *E. officinalis* (10 mg/kg), in type II diabetes (high fat diet fed) STZ-induced diabetic neuropathy in male Sprague-Dawley rats, and

found that *E. officinalis* extract (EOE) and quercetin reversed the changes in lipid peroxidation status and anti-oxidant enzymes (superoxide dismutase and catalase) levels observed in diabetic rats, with attenuation of diabetes-induced axonal degeneration.

Glutathione

Ueno *et al*[25] examined the effect of glutathione (GSH) on STZ-induced diabetic rats on the renal and neural functions when they were treated with 1 g/100 g GSH as a dietary supplement and found that GSH suppressed the urinary 8-hydroxy-2'-deoxyguanosine, a marker of oxidative stress and prevented the diabetes-induced increases in albumin and creatinine in urine.

Cucumin

Joshi *et al*[26] evaluated efficacy of self nano emulsifying drug delivery system (SNEDDS) curcumin formulation by measuring nerve function and sensorimotor perception along with inflammatory mediators (NF- κ B, IKK- α , COX-2, iNOS, TNF- β and IL-6). SNEDDS curcumin was found to be better in improving functional, behavioural and biochemical deficits in experimental diabetic neuropathy, when compared to naive curcumin.

Li *et al*[27] evaluated the effect of curcumin on STZ-induced DPN in 24 rats and compared them with 24 healthy control rats and found that Curcumin significantly attenuated the diabetes-induced allodynia and hyperalgesia and reduced the expression of both TNF- α and TNF- α receptor 1.

Sharma *et al*[28] explored the antinociceptive effect of 4-weeks curcumin on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) release and thermal hyperalgesia in streptozotocin induced diabetic mice and found that treatment with curcumin (15, 30 and 60 mg/kg body weight; p.o.) attenuated thermal hyperalgesia and the hot-plate latencies with inhibition of TNF-alpha and NO release in a dose dependent manner.

Resveratrol

Sharma *et al*[29] explored the antinociceptive effect of resveratrol, a polyphenolic phytoalexin, on thermal hyperalgesia, serum tumour necrosis factor-alpha (TNF-alpha) and whole brain nitric oxide (NO) release. Daily treatment with resveratrol (5, 10 and 20 mg/kg body weight; p.o.) for 4 weeks attenuated thermal hyperalgesia and also decreased the serum TNF-alpha levels and whole brain NO release in a dose-dependent manner.

Combination therapy

Cucumin + Resveratrol

Sharma *et al*[30] examine the effect of insulin and its combinations with resveratrol and curcumin on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) levels in streptozotocin (STZ) induced diabetic mice for 4-weeks and found that significantly attenuated thermal hyperalgesia and the hot-plate latencies, with inhibition of TNF-alpha and NO levels.

Olive (Olea europaea L.) leaf extract

Kaeidi *et al*[31] investigate the effects of olive leaf extract (OLE) on *in vitro* and *in vivo* models of diabetic pain neuropathy and found that OLE treatment (300 and 500 mg/kg per day) ameliorated hyperalgesia, inhibited caspase 3 activation and decreased Bax/Bcl2 ratio, with potent DPPH free radical scavenging capacity. The study results suggested that OLE inhibited high glucose-induced neural damage and suppressed diabetes-induced thermal hyperalgesia.

Naringin

Kandhare *et al*[32] evaluated the neuroprotective effect of 4-weeks treatment with naringin (40 and 80mg/kg) in streptozotocin (STZ) induced DPN rats and found dose-dependent attenuation of decrease in level of nociceptive threshold, endogenous antioxidants and membrane bound inorganic

phosphate enzyme, with decreases in the elevated levels of oxidative-nitrosative stress, inflammatory mediators as well as apoptosis in neural cells.

Gastrodin (phenolic glucoside)

Gastrodin was a main constituent of the Chinese herbal medicine *Gastrodia elata* Blume had been widely used as an anticonvulsant, sedative, and analgesic. Sun *et al*[33] investigated the role of gastrodin in an experimental rat model of STZ-induced PDN and to further explore the underlying cellular mechanisms and found that intraperitoneal administration of gastrodin effectively attenuated both the mechanical allodynia and thermal hyperalgesia induced by STZ injection.

Soy isoflavone genistein

Valsecchi *et al*[34] explored the ability of the soy isoflavone genistein in attenuating the STZ-induced DPN in rats and found that Genistein relieved diabetic peripheral painful neuropathy, reverted the proinflammatory cytokine and reactive oxygen species overproduction, and restored the nerve growth factor (NGF) content in diabetic sciatic nerve. Genistein was thus able to reverse allodynia, oxidative stress and inflammation, ameliorating NGF content and the vascular dysfunction in DPN.

Coenzyme Q10

Zhang *et al*[35] evaluated the prophylactic and antinociceptive effects of the antioxidant coenzyme Q10 (CoQ10) on diabetes-induced neuropathic pain in 56 mice with type 1 diabetes induced by streptozotocin and 20 normal mice. Low dose and long-term administration of CoQ10 not only prevented the development of neuropathic pain but also produced a dose-dependent inhibition of mechanical allodynia and thermal hyperalgesia in diabetic mice.

Clinical evidence- human studies

Therapeutic effects

Linolenic acid

Tao *et al*[36] investigated the association between dietary intake of polyunsaturated fatty acids (PUFAs) and DPN and found that dietary intake of linolenic acid was positively associated with lower odds of developing peripheral neuropathy.

Alpha-Lipoic acid

Ruessmann *et al*[37] evaluated switch-over from the pathogenetic treatment with alpha-lipoic acid to gabapentin in a retrospective cohort of 443 DPN patients and found that switching from long-term treatment with alpha-lipoic acid to central analgesic drugs such as gabapentin in painful diabetic neuropathy was associated with considerably higher rates of side effects, frequencies of outpatient visits, and daily costs of treatment.

Cannabis

Selvarajah *et al*[38] assessed the efficacy of Sativex, a cannabis-based medicinal extract, as adjuvant treatment in painful diabetic peripheral neuropathy (DPN) in their randomized controlled trial of 30 subjects who received daily Sativex or placebo and found no significant differences between groups on mean change of pain scores, with depression acting as a major confounder.

Discussion

This paper was aimed to explore the evidence for pathological basis of diet and nutrition in pathogenesis and treatment of DPN and the majority of evidence is only from the bench perspective that allows us to implicate DAN in the pathogenesis and treatment of DPN, but there is insufficient evidence from the perspective of bedside evidence.

The study findings mirror the earlier report of Halat and Dennehy [39] in their MeSH-based systematic review of MEDLINE database who found that herbs and botanical dietary supplementation (eg, evening primrose oil, alpha-lipoic acid, capsaicin) might improve symptoms of neuropathy without affecting glucose control.

McCarty [40] recommended use of low-fat, whole-food vegan diet together with regular daily walking exercise due to its positive effects on remission of neuropathic pain, glycemic control and improved blood rheology (decreased blood and plasma viscosity with reductions in hematocrit and in fibrinogen; and decreased white cell count with increased blood filterability) which in turn might reduce the risk for other major complications of diabetes - retinopathy, nephropathy, and macrovascular disease.

Mijnhout *et al* [41] identified five RCTs on effectiveness of alpha lipoic acid in their Systematic literature review of MEDLINE and EMBASE and provided grade A recommendation for alpha lipoic acid given intravenously at a dosage of 600 mg once daily over a period of three weeks leading to a significant and clinically relevant reduction in neuropathic pain.

Not only does dietary modification indicate pathogenetic and therapeutic effects on DPN population, but also early recognition and initiation of intensive enteral nutritional support was shown to effectively manage ensuing complications such as diabetic neuropathic cachexia. [42]

The selection of an adjuvant treatment is often based on patient comorbidities, cost and tolerability [43] and this should be kept by the treating clinician in mind. Understanding the pathogenesis of diabetic neuropathy may lead to the development of new treatments for preventing nerve damage and a better understanding of the mechanisms that modulate pain may lead to more effective relief of painful symptoms. [44]

Ziegler [45] explained four cornerstones for treatment of DPN as: “(1) multifactorial intervention aimed at (near)-normoglycaemia

and reduction in cardiovascular risk factors, (2) treatment based on pathogenetic mechanisms, (3) symptomatic treatment, and (4) avoidance of risk factors and complications.” Alpha-lipoic acid and epalrestat were opined to be the only available pathogenetic treatment options [46] keeping in mind the increasing number of new drugs in daily market, and individual patient tolerability prior to therapy selection and dosing. [47]

There were a few acceptable limitations of this study being narrative, without a meta-analysis, and the relatively lesser studies on pathogenesis in humans imply ethical issues in inducing DPN compared to animal models. Future studies should aim to answer pathogenetic mechanisms behind dietary and nutritional role in DPN along a multidisciplinary biopsychosocial framework. [48]

Conclusion

There was limited bedside evidence from few studies which warrant future high quality clinical trials on efficacy of alpha lipoic acid, linolenic acid and cannabis-based extract in the management of DPN. The bench evidence had shown that fat-rich and fructose-rich diets had pathogenetic effects, and cucumin had therapeutic effects on STZ-induced rat models of DPN.

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