Diabetic Neuropathy: In Search of a Treatment

Peripheral neuropathy, the most prevalent chronic complication of diabetes, critically contributes to increased pain and risk of amputations, lower physical functioning and daily living burden, reduced quality of life, increased health care costs, and high mortality risk. Although intensive glucose control was shown to delay the onset and progression of diabetic peripheral neuropathy (DPN) in patients with type 1 diabetes, similar evidence is not available for most patients who have type 2 diabetes (T2D). In addition, despite continuous research, a disease-modifying therapy to reverse human DPN is still not available. The mechanisms involved in DPN are complex, including but not limited to non-enzymatic glycation, polyol pathway activation, and oxidative and inflammatory stress. This makes finding a successful treatment extremely difficult.

In the seven articles that make up the thematic issue entitled “Diabetic Neuropathy: In Search of a Treatment,” “world-known” teams of investigators provided work that spans subjects including treatment for DPN, what we have learned from animal models, diabetic gastroenteropathy, treatment of painful DPN, omega-3 nutrition for diabetic sensorimotor polyneuropathy, exercise as a treatment of DPN, diagnostic tools and treatments in DPN, and cardiovascular autonomic neuropathy.

The Yorek laboratory has worked for many years, investigating possible treatments for diabetic vascular and neural complications in obese and diabetic rodent models. In this article, he reviews not only some of their past studies but also investigations from other laboratories. An extensive study of diabetic animal models has shown that the etiology of diabetic peripheral neuropathy is complex, with multiple mechanisms affecting neurons, Schwann cells, and the microvasculature, all contributing to the phenotypic nature of this common complication of diabetes. Moreover, animal studies have demonstrated that the mechanisms related to peripheral neuropathy occurring in type 1 and type 2 diabetes are likely different, with hyperglycemia being the primary factor for neuropathology in type 1 diabetes and contributing to a lesser extent in type 2 diabetes, where insulin resistance, hyperlipidemia, and other factors may have a greater role. Two of the earliest mechanisms described from animal studies as a cause of diabetic peripheral neuropathy were the activation of the aldose reductase pathway and increased non-enzymatic glycation. However, continuing research has identified numerous other potential factors that may contribute to diabetic peripheral neuropathy, including oxidative and inflammatory stress, dysregulation of protein kinase C and hexosamine pathways, and decreased neurotrophic support. In addition, recent studies have demonstrated that peripheral neuropathy-like symptoms are present in animal models representing pre-diabetes in the absence of hyperglycemia. Yorek concluded that this complexity complicates the identification of successful treatment of diabetic peripheral neuropathy and has likely been a factor in the poor outcome of translating successful treatments from animal studies to human clinical trials.

Autonomic neuropathy in diabetes is less researched than peripheral neuropathy. Autonomic neuropathy affects many organs in diabetes, including the gastrointestinal system. Diabetic gastroenteropathy affects every segment of the gastrointestinal tract and generates symptoms that may include nausea, early satiety, vomiting, abdominal pain, constipation, and diarrhea. Severe cases may be complicated by weight loss, dehydration, and electrolyte disturbances. The pathophysiology is complex, the diagnostics and treatment options are multidisciplinary, and there is generally a lack of evidence for the treatment options. The article by Meling et al. summarizes the pathophysiology and describes possible and expected symptoms and complications. Secondly, they present straightforward tools for diagnostics and summarize treatment options, including diet recommendations as well as pharmacological and non-pharmacological options. Lastly, they explore the multiple possibilities of novel treatment, looking at medications related to the pathophysiology of neuropathy, other manifestations of autonomic neuropathies, and symptomatic treatment for other gastrointestinal disorders. The goal of this article is to increase awareness and knowledge of diabetic gastroenteropathy and to provide better tools for the diagnosis and treatment.

Sloan, Alam, Selvarajah, and Solomon provide a review article relating to the treatment of painful diabetic neuropathy. This team is a leader in the field of clinical trials in the treatment of painful diabetic peripheral neuropathy (painful-DPN). Painful DPN is a highly prevalent and disabling condition, affecting up to one-third of patients with diabetes. This condition can have a profound impact, resulting in a low quality of life, disruption of employment, impaired sleep, and poor mental health with an excess of depression and anxiety. This article reviews the evidence for the treatment of painful DPN, including emerging treatment strategies such as novel compounds and stratification of patients according to individual characteristics (e.g., pain phenotype, neuroimaging, and genetics) to improve treatment responses. However, the statement that the recommended treatments based on expert international consensus for painful DPN have remained essentially unchanged for the last decade is disturbing and demonstrates how little we know about managing pain in this common complication of diabetes.

Nemenov and Premkumar provide a review article on mechanosensitive nociceptors in painful diabetic peripheral neuropathy. The cutaneous mechanisms that trigger spontaneous neuropathic pain in DPN are far from clear. They discuss the two types of nociceptors found within the epidermal and dermal skin layers that transmit pain from the periphery to the central nervous system. In DPN, dying-back of intra-epidermal nerve fibers leads to reduced pain sensitivity, but some patients complain of pain. Despite symptoms of pain, these patients have significantly increased pain thresholds when tested using traditional methods. The role of C mechanosensitive (CMI) fibers in painful neuropathies has not been fully explored. Data to be discussed will demonstrate that patients with painful DPN have increased Aδ fiber pain thresholds, while C-fiber thresholds...
are intact because, in these patients, CMi fibers are abnormally spontaneously active. This review discusses the role of CMi fibers in painful DPN.

Menon et al. discuss the potential role of omega-3 polyunsaturated fatty acids (PUFA) in the treatment of DPN. Omega-3 PUFA is an essential fatty acid with a vital role in a number of physiological processes, including neural health, membrane structure integrity, anti-inflammatory processes, and lipid metabolism. Identification of omega-3 PUFA-derived specialized pro-resolving mediators, namely resolvins, neuroprotectin, and maresins, which also favor nerve regeneration, have positioned omega-3 PUFA as a potential treatment option in DPN. Results from ongoing pre-clinical and clinical studies of the effect of omega-3 PUFA on nerve regeneration have been presented.

In the article by Singleton et al., evolving data concerning exercise as a promising treatment is discussed. Current literature on exercise treatment of metabolic syndrome neuropathy in humans and animal models has been reviewed in-depth, highlighting the diverse mechanisms by which exercise exerts beneficial effects and examining adherence limitations, safety aspects, modes, and dose of exercise. The takeaway message is that exercise should be considered as an integrative therapy that potently reduces cellular inflammatory state and improves distal axonal oxidative metabolism to ameliorate features of neuropathy in metabolic syndrome.

Bonhof, Herder, and Ziegler provide an overview of the current clinical aspects and recent advances in exploring local and systemic biomarkers of both distal symmetric sensorimotor polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN) assessed in human studies (such as biomarkers of inflammation and oxidative stress) to better understand the underlying pathophysiology and to improve early detection. Current therapeutic options for DSPN are as follows: (I) causal treatment, including lifestyle modification, optimal glycemic control, and multifactorial risk intervention; (II) pharmacotherapy derived from pathogenetic concepts; and (III) analgesic treatment against neuropathic pain. Recent advances in each category are discussed, including non-pharmacological approaches such as electrical stimulation. Finally, current therapeutic options for cardiovascular autonomic complications have been presented.

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