

Editorial

Diabetic Neuropathy: Is there a Pain Free Solution?

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Abstract

Peripheral neuropathy is the long-term and difficult to treat complication of diabetes that affects 50% of diabetic patients and interferes with the quality of life. Unfortunately, available medical treatment is relatively ineffective due to dependency and addiction. Emerging research indicates that moderate-to-vigorous physical activity provides health-related benefits. However, adequate research has not been accomplished to determine whether adults especially with Type 1 diabetes engaged in regular exercise show improvements in the progression of neuropathy. Emerging evidence suggest that the release of proinflammatory cytokines play an important role in development and persistence of pain. It is not fully explored whether moderate exercise reduces the release of proinflammatory cytokines thus improving the development of neuropathy. This article suggests that exercise may change the course of development of pain and release of these noxious cytokines, thus improving the painful neuropathy. More studies are necessary to define the mechanisms to establish novel treatments and provide a more useful and efficient way of management of pain.

Keywords: Diabetic Neuropathy; Type 1 and 2 diabetes; Proinflammatory; TNF α

Overview

The global diabetes crisis is predicted to rise to 439 million by the year 2030 and it would present a major health challenge. Both Type 1 and 2 diabetes impose increased risk of developing micro- and macro-vascular complications that lead to neurological dysfunction in diabetic patients, with a devastating impact on their quality of life and a challenge to the health care services worldwide [1]. Prolonged diabetes results in an altered composition of receptors and channels in the cell membrane, a change that might enhance the propensity of the neuron to fire, thereby leading to spontaneous pain and development of neuropathy. About 50 to 60 percent of the people with diabetes have some form of neuropathy which is extremely difficult to treat and more or less all these patients either experience burning pain or numbness in lower extremities. Due to loss of sensation, sores or wounds in the feet may become ulcerated or infected, if left unnoticed. Poor blood circulation increases the risk of foot surgery and amputation [2]. Since neuropathy is more likely to develop as the extent of diabetic condition progresses, the effectiveness of analgesic agents could be affected by modifications in the etiological and pathophysiological mechanisms during the course of the disease. Currently, available medical treatment is relatively ineffective due to a number of systemic side effects, dependency and addiction.

Present scenario

A growing body of evidence suggests that the release of proinflammatory cytokines plays an important role in the development and persistence of pain which is not well established in diabetic neuropathy. A number of neurotransmitters, receptors and nociceptor-related ion channels that are involved in the pain modulation could be a critical factor in determining the differences in pain susceptibility and development of neuropathy. Previous studies have shown that diabetic patients with painful neuropathy have

increased inflammatory cytokines in serum [3], which may appear to play a pathogenic role in the development of diabetic neuropathy. Not many studies have been done that focus on identification of locally produced inflammatory mediators in the skin and tibial nerve of the diabetic subjects. In the peripheral nerve, Schwann cells and perineurial cells are known to release cytokines and chemokines in response to nerve injury [4]. In patients, Tumor Necrosis Factor Alpha (TNF α) has been shown to act as a pain mediator in other neuropathic pain conditions, and nerve biopsies from patients with painful neuropathy show elevated levels of TNF- α expression, especially in Schwann cells [5]. Previous studies with diabetes suggest that the insulin therapy alone cannot suppress the production and/or activity of serum TNF α and that it also does not inhibit the development of chronic diabetic complications in mice [6]. Skin keratinocytes are major producers of pro-inflammatory cytokines like interleukin (IL)-1, -6, -8, and TNF and express a variety of cytokine receptors [7]. The ability to study the expression of inflammatory mediators in keratinocytes offers a possibility to investigate their role in the pathogenesis of diabetic neuropathy. Recent studies have established that altered Transient Receptor Potential Cation Channel (TRP)V1 expression and function contribute to diabetes-induced changes in thermal perception, and abnormal TRPV1 levels have been reported in skin nerve fibers in diabetic neuropathy [8]. Therefore, it is important to investigate whether early interruption of this neuroinflammatory cascade in the peripheral nervous system could prevent or delay nerve degeneration.

Exercise as a promising prospect

Emerging research indicates that moderate-to-vigorous physical activity provides health-related benefits. A number of studies have shown the beneficial effect of exercise in Type 2 diabetic animals. However, enough research has not been done to determine whether adults with Type 1 diabetes engaged in regular exercise show improvements in the development of painful neuropathy. Physical

exercise in combination with pharmacological intervention is now recognized as a cornerstone of treatment for the management of patients with Type 2 diabetes mellitus [9]. However, it is unclear how physical exercise prevents the development or progression of diabetic complications, including painful peripheral neuropathy [10]. Forced-exercise compared with voluntary exercise has been recently shown to selectively reduce ischemia and reperfusion injury in a rat stroke model and it has been also shown that it delays the onset of diabetes-associated neuropathic pain [11]. Treadmill training has been shown to accelerate hind limb motor function recovery in diabetic injured rats and to prevent morphometric alterations in proximal nerve portions in non-diabetic and diabetic injured rats [12]. Low-to-moderate swimming training for 8 weeks reduces thermal hyperalgesia in diabetic female Wistar rats [13]. Recent studies have shown that both chronic and acute exercises influence the phosphorylation and expression of components of the AMPK (AMP-activated protein kinase), AMPK serves as a master sensor of energy status. Exercise also improves GLUT4 (Glucose transporter type 4) trafficking in skeletal muscle that regulates glucose homeostasis in Type 2 model of diabetic rats [14]. However, the question remains unresolved that whether exercise protects against the development and progression of both Type 1 and Type 2 diabetic neuropathic complications and whether similar or different underlying neuroinflammatory mechanisms are involved in this process. More research needs to be carried out to understand the overall benefit of exercise, which may in turn provide an alternate route of treatment for painful neuropathy in diabetics by decreasing the use of pain medication and may provide a more useful and efficient way of pain management.

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