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Diabetic Neuropathy-A Mini-Review

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ABSTRACT

Diabetic neuropathy (DN) is a persistent complication of diabetes mellitus (DM). It affects approximately thirty to fifty percent of subjects who have this ailment. DM has become the most common causative factor of polyneuropathy in today's world. So much so that fifty percent of the neuropathies are linked to DM. It badly affects the quality of life (QOL) of those suffering from it. On top of it, Polyneuropathies cause chronic neuropathic pain, bringing depression, anxiety, and insomnia among its sufferers. Diabetic neuropathy is a painful and disabling condition that has huge costs in terms of deranged quality of life and financial repercussions linked to their treatment. Various painkillers have been tried in this regard with varying results. The aim of this review was to delve into various drug outcomes in this regard.

Keywords: Diabetic Neuropathy; Developments; Painkillers; Chronic Pain; Complications

Abbreviations: DN: Diabetic Neuropathy; DM: Diabetes Mellitus; QOL: Quality of Life; NET: Nerve Excitability Testing; NCS: Nerve Conduction Studies; NFL: Neurofilament Light Chain

Introduction

Diabetic neuropathy (DN) is a common complication of diabetes mellitus (DM). Its prevalence reaches up to fifty percent in subjects suffering from this ailment [1]. It is more prevalent in chronic DM and it has a negative impact on the quality of life (QOL) of those suffering from it. Polyneuropathies cause chronic neuropathic pain, which leads to heavy personality costs in terms of depression, anxiety, and insomnia among sufferers [1-3]. Diabetic neuropathies can be classified into generalized and focal/multifocal forms. The most common subtype of diabetic neuropathy is dependent on the length and manifests as a symmetrical sensory-motor peripheral polyneuropathy [4]. Its pathogenesis can be explained in a nutshell as a system of metabolic derangements, such as hyperglycemia, accelerated polyol flux, enhanced oxidative stress, and lipid alterations [4-8]. In recent criteria (Toronto consensus criteria) a framework for Diabetic Neuropathy diagnosis was formulated. Toronto consensus criteria took into account the combination of neuropathy symptoms and signs that could be confirmed using nerve conduction studies [7]. Nerve conduction studies are normal in small fiber neuropathy, so the most used diagnostic tool for small fiber neuropathy is a skin biopsy with the assessment of intraepidermal nerve fiber density [8,9]. A few of the recent developments regarding Diabetic Neurop-

athy include new biomarkers for early and accessible diagnosis, assessing metabolic risk factors, innovations in clinical trials relevant to painful diabetic neuropathy, genetic modifiers risk factors, and new therapeutic advancements.

Methods

We did a search on PubMed, and Medline database publications using: diabetic neuropathy, developments, painkillers, chronic pain, complications, and Pain control. The publications included were special communications, reviews, conference papers, books, and research studies regarding the subject matter over last twenty years.

Discussion

Diabetic polyneuropathy is can be defined as the occurrence of symmetrical, distal, and progressive degeneration of the sensorimotor and autonomic peripheral fibers, ascribable to metabolic and microvascular alterations due to chronic hyperglycemia [10-12]. More than four hundred million people suffer from diabetes mellitus globally [11-14]. Out of these, one-fourth fall prey to chronic painful diabetic neuropathy (PDN). Such kind of pain starts distally, and is remarkably unpleasant at night, and follows a proximal and symmetrical progression: discomfort starts in the toes, feet, then follows the ankles. It is a "burning" sensation accompanied by a feeling of tingling. Uncommonly, it may manifest as allodynia (sensitive to touch such as combing hair), wherein normal activities lead to pain [15,16]. It is a major challenge in the screening process for DPN that once a neuropathy becomes detectable by recently applied assessments; nerve injury is well-progressed and very difficult to reverse [17,18]. Hence, it is the need of the hour to formulate more sensitive biomarkers as screening and diagnostic tools and surrogate end-point measures [17]. There is a need for accurate diagnosis of various DPN types, especially small fiber neuropathy, which is vital for clinical trial design and to help find specified therapeutic interventions. There is a need for the development of minimally invasive and simplified biomarkers to facilitate diagnosis and design of clinical trials for disease prevention or timely intervention to slow their progression.

For example, Corneal confocal microscopy is a new noninvasive technique that can help in the detection and quantification of small nerve fiber loss in DPN and other forms of neuropathy [18,19]. A confocal laser scanning microscope noninvasively visualizes small-diameter unmyelinated axons in the cornea. Patients with DPN have reduced corneal nerve fiber density and length compared with normal controls [19]. More validation studies are required before corneal confocal microscopy can be used as an alternative measure of small-caliber nerve fiber loss. Nerve excitability testing (NET) is another test that may come up as an emerging experimental neurophysiological biomarker of early axonal dysfunction. NET calculates axonal firing thresholds in response to submaximal and supramaximal current given through noninvasive electrodes [20]. Thus it can act as a surrogate of axonal membrane dysfunction well before axonal damage really occurs and nerve conduction studies (NCS) findings are evident [21,22]. However, there are issues related to using of this technology such as requirements for specialist training , equipment and is not widely available. Moreover, NET is more reliable in motor nerves than sensory nerves , and it does not give information about the status of small fiber nerves. Hence, NET needs to be validated before it can be adopted as an alternative biomarker test for diabetic peripheral neuropathy [20-22]. Neurofilament light chain (NFL) protein, a marker of axonal degeneration, is another promising blood biomarker for diabetic neuropathy [23,24].

In addition to these, advanced imaging techniques manifest cortical changes that can be utilized as promising biomarkers in painful DPN. Various strategies have been tried so far to treat diabetic neuropathy. An expanding literature supports lifestyle-based therapies for patients with DPN and neuropathy in those who are in the prediabetes stage. Short-term exercise trials have shown improvement in gait and function in small sample size studies [25-32]. Studies regarding low-intensity exercises manifested enhanced quality of life and the resultant decrease in tingling sensations and pain [33]. Other studies relating to the effects of vitamin supplementation in diabetic neuropathy: oral alpha lipoic acid [32,33], vitamin E and D [34-37], and sodium channel blocker have mostly been inconclusive. In addition to these, few studies have explored possible role of neuromodulation as a therapeutic strategy for painful DPN [37,38].

Conclusion

Diabetic Neuropathy has a high prevalence associated with notable patient morbidity and heavy healthcare costs. There is a need for developing more effective treatment strategies. Sophisticated diagnostic criteria and categorization of specific pain subtypes will help formulate a better clinical trial design. Hence there is a need for developing biomarkers that prove to be promising in facilitating earlier diagnosis and formulating suitable clinical trials for such patients early in the course of the disease.

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