Introduction
At present, diabetes and its associate complications are owed global health burden and risk to silent death. In 2015, WHO estimated diabetes killed 1.6 million people globally and expected to double within 10 years [1]. The number of people with diabetes worldwide was estimated in 2011 were 366 million and is expected to rise to 522 million in 2030 [2]. The estimated worldwide prevalence of diabetes in 2010 was 6.4% and this value is predicted to rise to around 7.7% in 2030 [3]. The highest prevalence of diabetes in adult population noted in North America 7.9% followed by Europe 7.8% and South America 5.6% [4]. The top ten countries with diabetes population are China, India, USA, Brazil, Russian Federation, Mexico, Indonesia, Germany and Egypt [5].

Diabetic peripheral neuropathy
Diabetic peripheral neuropathy (DPN) is the most common and troublesome complication of diabetes leading to great morbidity and resulting in a huge economic burden for diabetes care. DPN was defined by the presence of at least two of the following three characteristics: (a) pain, paresthesias, or numbness; (b) absence of tendon reflexes; (c) abnormal malleolar vibration perception threshold. Diabetic patients due to DPN have 12 times higher risk of amputations when compared with non-diabetic subjects [6]. The exact prevalence of DPN is not known and reports vary from 10-90% in diabetic patients depending on the criteria and methods used to define neuropathy [7]. In United States, about 60-70% of people with diabetes have some form of DPN. People with diabetes can develop nerve problems at any time, but risk rises with age and longer duration of diabetes. The highest rates of DPN are among people who have had diabetes for at least 25 years [8].

Mechanisms involved in DPN
Mechanisms involved behind DPN are persistent hyperglycemia, microvascular insufficiency, oxidative and nitrosative stress, defective neurotrophism, and autoimmune nerve destruction are the important factors of DPN. Peripheral nerve conduction velocities (NCV) are considered one of the most sensitive indices of the severity of neuropathy in DPN. Control of hyperglycemia is only the best treatment exists for DPN. Besides glucose lowering therapy, antidepressants, anticonvulsants, opioid analgesics, anti arrhythmics, and NMDA receptor antagonists are commonly used, though all these drugs have adverse actions. Recent researches are focused on the development of neurotrophic factor (NTF), nitrate sprays and topical capsaicin for the treatment of DPN.

Keywords: Diabetes; Diabetic peripheral neuropathy; Nerve conduction velocity; Neurotrophic factors; Nitrate sprays; Topical capsaicin

Abstract
Diabetes poses neurological damages and result in diabetic peripheral neuropathy (DPN). The prevalence of DPN varies from 10-90%. The persistent hyperglycemia, microvascular insufficiency, oxidative and nitrosative stress, defective neurotrophism, and autoimmune nerve destruction are the important factors of DPN. Peripheral nerve conduction velocities (NCV) are considered one of the most sensitive indices of the severity of neuropathy in DPN. Control of hyperglycemia is only the best treatment exists for DPN. Besides glucose lowering therapy, antidepressants, anticonvulsants, opioid analgesics, anti arrhythmics, and NMDA receptor antagonists are commonly used, though all these drugs have adverse actions. Recent researches are focused on the development of neurotrophic factor (NTFs), nitrate sprays and topical capsaicin for the treatment of DPN.

Keywords: Diabetes; Diabetic peripheral neuropathy; Nerve conduction velocity; Neurotrophic factors; Nitrate sprays; Topical capsaicin

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Submission: October 31, 2017; Published: January 24, 2018
diabetic complications, including DPN [14]. Moreover, a nitric oxide deficit and increased oxygen free radical activity are responsible for microvascular damage and hypoxia [15]. In diabetes, myo-inositol deficiency is observed in the nerves, resulting from the inhibition of the sodium-dependent uptake of myo-inositol and severe changes to the polyol pathway [16]. It has also been suggested the involvement of proinflammatory factors derived from activated microglia in diabetes-induced allodynia and the involvement of the p38-MAPK pathway in diabetes-induced hyperalgesia [17,18]. There are also reports implicating the release of pro-inflammatory cytokines from glia and immune cells for neuropathic pain of different origins [19].

**Diagnosis of DPN**

However, the progression of DPN can be reduced by early detection and intervention [20]. Nerve conduction studies, primarily nerve conduction velocities (NCV) are considered one of the most sensitive indices of the severity of neuropathy. Nerve conduction tests are used to localize lesions and to describe the type and severity of the patho physiological process, including alterations in function that are not recognized clinically [21]. In Type 2 diabetic patients decreased NCV is probably one of the earliest neuropathic abnormalities. NCV in DPN gradually decreases at a steady rate of approximately 1m/s/year and it show a correlation with the duration of diabetes [22].

**Treatment in DPN**

A large number of randomized clinical trials have been conducted to assess the efficacy of various therapeutic agents, but the results have been disappointing, most probably due to the complexity of mechanisms involved in its pathogenesis [23]. Therefore, till date no effective treatment exists for DPN, other than the control of hyperglycemia [24,25]. Besides glucose lowering therapy, antidepressants (amitriptyline, imipramine and desipramine), [26] anticonvulsants (gabapentin), [27] opioid analogues (morpine), [28] antiarrhythmics (mesilatine) and NMDA receptor antagonists (ketamine and dextromethorphan) [29] are commonly used, but all have adverse drug reactions.

**Target of research in DPN**

Peripheral nerves have the ability to regenerate axons, as long as the nerve cell itself has not died. The injuries of nerve cells are able to be avoided by treatment before its permanent damage. One promising area of research focuses on a class of molecules called neurotrophic factors (NTFs). NTFs are help to maintain normal function in mature nerve cells and some stimulate axon regeneration [30]. On the contrary, new topical drug for DPN target (i) either to improve microvascular endothelial function for enhancing the vasodilatory capacities and blood flows, (ii) or analgesic and anaesthetic actions on sensory nerve endings to block the pain signals to brain, (iii) or eventually supply or to generate NTFs to prevent, control and repair neuronal damage without any or minimum systemic health hazards. Two major classes of topical test drug now developing for the use of DPN are Nitrate sprays and Capsaicin [31].

**Topical nitrate sprays:** Nitrate spray is commercially available as isosorbide dinitrate or glyceryl trinitrate. Both isosorbide dinitrate as well as glyceryl trinitrate act as potent nitric oxide donor and have similar pharmacological activity compared to endothelial derived relaxing factor-a nitric oxide dependent enzyme with vasodilator capacity. The basis of nitrate spray use is based on the theory that impaired nitric oxide generation which is involve in the progression of pathogenesis of DPN [32-35].

**Topical capsaicin:** Capsaicin is commercially available as 0.025%, 0.075%, and 0.1% creams. Topical capsaicin has shown analgesic benefits in postherpetic neuralgia, painful polyneuropathies including DPN. Capsaicin causes reversible depletion of substance P from the sensory nerve endings by activity of vanillloid-receptor and possibly through a reversible decrease in the number of epidermal nerve fibre. FDA approved 8% Capsaicin patch for postherpetic neuralgia. A major adverse effect is a burning discomfort potentially leading to poor patient adherence.

**Conclusion**

DPN is most common complication of diabetes that can be result early, if hyperglycemia is not properly controlled. Substantial evidences supports that only early detection and diagnosis can resist DPN from major neuronal damage. Therapeutic treatments for DPN are limited. Besides oral therapy, topical agents are now also showed effectiveness in the management of pain in DPN with minimum side effects.

**References**

1. WHO Fact sheets.


