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Pathophysiology and Pharmacotherapeutics of Diabetic Neuropathy: A Review

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Abstract **Review Article**

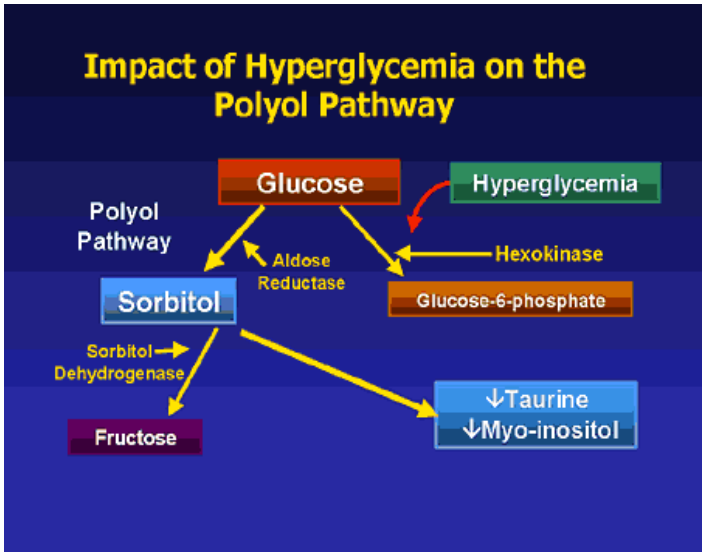
Diabetic neuropathy affects most of the patients with type I & II diabetes. Peripheral neuropathy has devastating consequences resulting in charcot joints and its related complications. American diabetes association helps to classify different type of diabetic neuropathies into groups trying to make some sense of out it for future work. There are number of cellular mechanisms that have been proposed as cause of the neuropathy including polyol pathway, advanced glycosylation end products, oxidative stress, hypoxia theory and other factors. All these have been discussed in some detail in the coming paragraphs. A number of add-on modalities have been discussed in literature to help diagnose diabetic peripheral neuropathy. Understanding the cellular mechanism of diabetic neuropathy can help come up with best therapeutic agents which may be able to arrest that cellular events behind diabetic neuropathy helping to stop it at early stages. A number of medicines are in use to treat diabetic peripheral neuropathy once it is set, however prevention of such cellular changes using medicines or by controlling glucose levels seems to be the future area of work trying to improve outcomes of this devastating illness. Most of the current recommendations for treating established diabetic neuropathy are based on comparing effects of these drugs against placebos in reducing the symptoms of diabetic peripheral neuropathy. This review article tries to find a connection between cellular mechanisms for diabetic peripheral neuropathy with available pharmacotherapeutics and defines areas for future work of pharmacological industry to help find definitive treatment and if possible definitive prevention for diabetic peripheral neuropathy.

Keywords: Diabetic peripheral neuropathy (DPN), type I & II diabetes, glucose levels.

BACKGROUND

8.3% of the global population (382 million adults) have diabetes and this figure is likely to rise to more than 592 million by 2035. Investment in effective diabetes prevention and management has become paramount to fight this global epidemic [1]. Neuropathy affects about 50% to 60% [2] of patients with type 1 and type 2 diabetes. Peripheral neuropathy has devastating consequences including repeated falls in elderly and the consequences that follow from them [2]. In limbs, loss of proximal muscle strength is strongly associated with the severity of peripheral neuropathy [3]. 43% of diabetic patients presenting with erectile dysfunction have been found to have autonomic neuropathy [4]. A comprehensive classification of diabetic neuropathy originally proposed by Thomas and then modified by American diabetes association (shown below) indicates the widespread effect of neuropathy on the body [5, 6].

Generalized symmetrical	**Focal and multifocal neuropathy**
Acute Sensory	Cranial
Chronic sensorimotor	Truncal
Autonomic (cardiovascular, gastrointestinal, genitourinary)	Focal limb
	Proximal motor (amyotrophy)
	Co-existing chronic demyelinating polyneuropathy



Pathophysiology

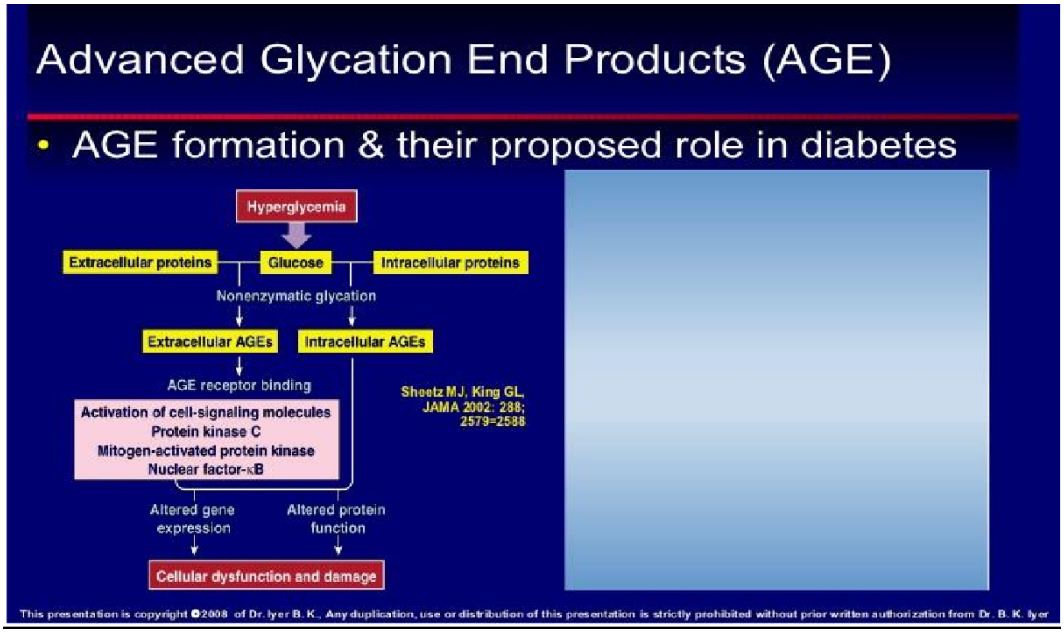
Diabetic peripheral neuropathy (DPN) affects autonomic as well as somatic peripheral nerves. Due to the ubiquity of autonomic innervation in the body, diabetic autonomic neuropathy causes a plethora of symptoms and signs. It impacts upon cardiovascular, urogenital, gastrointestinal, pupillomotor, thermoregulatory, and sudomotor systems [7]. What follows is the mechanisms through which diabetic complications, specifically neuropathy, can be caused.

1. Polyol Pathway

High serum glucose levels in diabetes leads to high intracellular glucose in nerves, which in turn causes saturation of the normal glycolytic pathway. The extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase [8]. Accumulation of sorbitol and fructose leads to lower nerve myoinositol, decreased membrane Na^+/K^+ - ATPase activity, impaired axonal transport, and ultimately structural breakdown of nerves. This leads to abnormal signal transmission across the nerves. This mechanism is targeted by the use of aldose reductase inhibitors (ARIs), in order to improve nerve conduction [9].

2. Advanced Glycation End Products (Age)

High glucose level leads to non-enzymatic formation of advanced glycation end-products (AGEs). It not only modifies myelin, but also tubulin, neurofilament and actin. Modification of these cytoskeletal proteins lead to axonal atrophy, degeneration and impaired axonal transport, while glycation of laminin results in malfunctioning regenerative activity [10, 11].



3. Oxidative Stress

Excess free oxidised radicals production in diabetes may be detrimental via a number of pathways which are not fully understood. There could be direct damage to blood vessels leading to nerve ischemia and facilitation of AGE reactions. Despite the incomplete understanding of these processes, use of the antioxidant alpha-lipoic acid may hold promise for improving neuropathic symptoms [12-14].

4. Hypoxia Theory

According to the hypoxia theory, the nerves of patients with diabetes develop ischaemia because of inflammation in the blood vessles of the endoneurium, perineurium and epineurium [17]. Reduced endoneurial oxygen levels seem to relate with reduced motor conduction velocity, myoinositol content, axoplasmic transport, sodium–potassium ATPase activity and oxygen utilization in sciatic nerves of diabetic rats [18]. Additionally, functional abnormalities, for example increased permeability to radioiodinated albumin [19], have been reported in new blood vessels that develop in a diabetic milieu. Such abnormalities may lead to local ischaemia and excess release of endothelin, a potential vasoconstrictor, and nitric oxide. Therefore, raised levels of endothelin have been reported in patients with diabetes. Endothelin receptors are found on the vasa nervorum and, in diabetes, endothelin vasoconstriction produces prolonged neural ischaemia resulting in infarction [18].

These different theories are not mutually exclusive and, rather, are complementary to each other [20]. Nitric oxide acts as the potential bridge between the metabolic and vascular theories [21]. Initially, the excess rise in nitric oxide levels may lead to dilatation of blood vessels but, subsequently, this action fails as it is altered by AGEs and also because the vessels probably become resistant as well [19].

5. Other Factors

These disturbed biochemical processes lead to altered gene expressions, altered cellular phenotypes, changes in cell physiology relating to endoskeletal structure or cellular transport, reduction in neurotrophins and finally nerve ischemia [15]. Clinical trials of the best-studied neurotrophin, human recombinant nerve growth factor, were not encouraging. With future refinements, however, pharmacologic intervention targeting one or more of these mechanisms are likely to be successful. In the case of focal or asymmetrical diabetic neuropathy syndromes, vascular injury or autoimmunity may play more important roles [16].

Diagnostics

Traditionally diagnostic modalities that may be considered to diagnose diabetic peripheral neuropathy are electromyography, nerve conduction velocity testing, electrophysiologic studies, magnetic resonance imaging, computed tomography (including single-photon emission computed tomography), nuclear imaging, doppler imaging, microdialysis, electrocardiography and nerve and skin biopsy. A recent meta analysis investigating the association of raised serum homocysteine levels with development of DPN has found that increased serum levels of homocysteine might be an important risk factor for development of neuropathy and may be used as a marker for new therapeutic approaches [22].

A recent study involving ultrasound and electrophysiology studies on 44 diabetic and 55 control patients, in an attempt to find a radiological early diagnosis of diabetic peripheral neuropathy, has concluded that increase in cross sectional area of a nerve on ultrasound at non compression sites implies early detection of morphological changes of diabetic peripheral neuropathy even with normal electrophysiology [23].

Pharmacotherapeutics

A large number of pharmacological treatments have been effective in diabetic neuropathy (see table A), only two (duloxetine and pregabalin) are approved for the treatment of neuropathic pain in diabetes by both the Food and Drugs Administration of the United States and the European Medicines Agency. All these are symptomatic treatments only [24].

Most of the randomised controlled trials on pharmacological agents used to treat diabetic peripheral neuropathy have compared a pharmacological agent against placebo, rather than compared these agents against each other. Unless direct head-to-head comparison is made, the relative merits of the given drugs cannot be determined. Guidelines based on meta-analysis and systematic reviews determine the order of recommendation by comparing need to treat or odds ratio for achievement 30%, 50% or moderate pain relief taking adverse effects into account among classes of agents or individual agents. Recently, network meta-analysis (also called multiple treatment comparison meta-analysis) using the Bayesian Markov chain Monte Carlo method (Table 1) has been introduced to provide estimates of effect sizes for all possible pairwise comparisons regardless of whether or not they have been directly compared in randomized controlled trials [25].

Table 1: Courtesy of Tesfay *et al*., 2011 [24]

Lifestyle, metabolic control and pharmacological treatment approaches for painful diabetic peripheral neuropathy showing some of the commonly prescribed treatments

- Physiological glucose control (HbA1c 6–7%)
- Lifestyle modification (diet, exercise)
- Management of cardiovascular risk factors
- Tricyclic anti-depressants
  - Amitriptyline 25–75 mg/day
  - Imipramine 25–75 mg/day
- Serotonin noradrenalin re-uptake inhibitors
  - Duloxetine 60–120 mg/day (indicated for painful diabetic peripheral neuropathy by US Food and Drug Administration and European Medicines Agency)
  - Venlafaxine 150–225 mg/day
- Anti-convulsant
  - Gabapentin 900–3600 mg/day
  - Pregabalin 300–600 mg/day (indicated for painful diabetic peripheral neuropathy by US Food and Drug Administration and European Medicines Agency)
  - Carbamazepine 200–800 mg/day Topiramate 25–100 mg/day
- Opiates
  - Tramadol 200–400 mg/day
  - Oxycodone 20–80 mg/day
  - Morphine sulfate sustained-release 20–80 mg/day
- Capsaicin cream
  - (0.075%) Applied sparingly three to four times per day

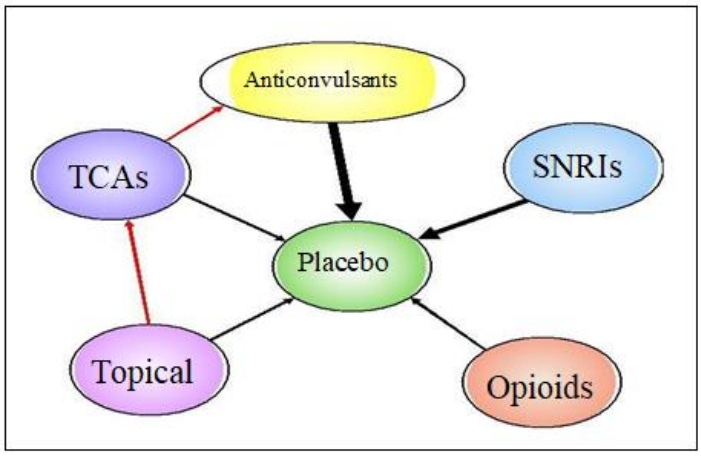


Figure 1: Example of network of randomized controlled trials evaluating painful diabetic neuropathy (Courtesy of Yasuda H 2015 [25])

Figure 1, is a diagrammatic representation of a network of randomized controlled trials evaluating painful diabetic neuropathy. The width of the lines is proportional to the number of trials for that comparison. The missing links between active interventions reflect the scarcity of direct comparisons [26].

Griebeler *et al*., [27] carried out a systematic review with the umbrella approach (systematic review of systematic reviews) and network meta-analysis to summarize and evaluate evidence from randomized controlled trials, thereby enabling comparison of the relative effectiveness of all included interventions among analgesics. Multiple treatment comparisons simultaneously include both direct and indirect evidence. Indirect and multiple treatment comparisons assume that relevant trials are similar enough in essential features, such as patient characteristics, definitions, and measurements of outcomes and risk of bias in the studies, to be combined. Their network meta-analysis showed that serotonin–norepinephrine reuptake inhibitors, topical capsaicin, TCA, and anticonvulsants all resulted in larger and significant reduction compared with placebo for short-term (within 3 months) pain

control [28]. However, opioids, ARIs, dextromethorphan, mexiletine and lacosamide did not show a statistically significant difference from placebo, the latter classes of agents have been ranked as second or third line in the guidelines [24, 29]. The comparative analysis between classes of agents showed that serotonin–norepinephrine reuptake inhibitors were more effective than anticonvulsants, but not more effective than tricyclic antidepressants. In addition, the comparison between individual agents showed that serotonin–nor-epinephrine reuptake inhibitors, venlafaxine and duloxetine, were significantly superior to pregabalin in pain relief [28].

Table 2: Comparative analgesic effect of serotonin–norepinephrine reuptake inhibitors by class

Class and comparator	SMD from direct comparisons (95% CI)	SMD from network meta-analyses (95% CI)†
Placebo	-2.10 (-3.41 to -0.79)*	-1.36 (-1.77 to -0.95)*
Opioids		-0.92 (-1.72 to -0.09)*
Aldose reductase inhibitors		-1.02 (-2.85 to 0.75)
Anticonvulsants	-0.34 (-0.63 to -0.05)*	-0.69 (-1.17 to -0.21)*
Lacosamide		-1.06 (-2.71 to 0.53)
Topical Capsaicin		-0.45 (-1.36 to 0.49)
Tricyclic antidepressants	-0.25 (-0.78 to 0.28)	-0.58 (-1.16 to 0.01)
Dextromethorpan		-1.08 (-2.36 to 0.19)
Mexiletine		-1.07 (-1.81 to -0.33)*

CI, confidence interval; SMD, standardized mean difference. *Statistically significant values. †From direct and indirect comparison (refer to ref. [27, 28]).

The current treatment of diabetic autonomic neuropathy is largely aimed at alleviation of symptoms; it is not correcting the underlying autonomic nerve deficit. A number of novel potential candidates, including erythropoietin analogues, angiotensin II receptor type 2 antagonists, and sodium channel blockers are currently being evaluated in phase II clinical trials [30, 31].

Optimal glucose control presents the only broadly accepted therapeutic option though evidence of its benefit in type 2 diabetes is unclear. A number of symptomatic treatments are recommended in clinical guidelines for the management of painful diabetic peripheral neuropathy, including antidepressants such as amitriptyline and duloxetine, the γ- aminobutyric acid analogues gabapentin and pregabalin, opioids, and topical agents such as capsaicin. However, monotherapy is frequently ineffective in achieving complete resolution of pain in diabetic peripheral neuropathy.

There is level I evidence presented recently aiming to establish effective treatment for peripheral diabetic neuropathy. In a recent study in the US, capsaicin 8 % patch in patients with painful diabetic peripheral neuropathy significantly improved pain relief and sleep quality compared with placebo in a 12-week double-blind trial [32]. Another recent double blinded randomised trial has found comparable efficacy (P 0.703) of amitriptyline cream against capsaicin cream with fewer side effects (P 0.001) in treating diabetic peripheral neuropathy [30]. Nitroglycerin patches have been found to significantly reduce (P 0.048) pain of diabetic neuropathy when compared against placebo in a small study of 30 patients [31]. A recent non comparative study with 3 months follow-up, on treatment of diabetic neuropathic pain using 60 patients (where conventional treatments had been ineffective), evaluated the effectiveness of transcutaneous electrical nerve stimulation (TENS) and pulse radio frequency (PRF) sympathectomy and found out that both TENS and PRF lumbar sympathectomy are promising pain relief treatments for painful diabetic peripheral neuropathy. However, PRF lumbar sympathectomy seems to have a superior efficacy. However further studies with a larger sample size with longer follow-up period should be done to evaluate these treatments [33].

Future treatments for diabetic complications, including diabetic neuropathy

Because they block Polyol pathway (hence reducing diabetes complications), ARIs are of particular interest for ongoing and future research. ARIs developed so far vary structurally. Different structural classes of ARIs developed include:

- Carboxylic acid derivatives
  Epalrestat, Alrestatin, Zopalrestat, Zenarestat, Ponalrestat, Lidorestat, and Tolrestat.

- Spirohydantoins and related cyclic amides
  Sorbinil, Minalrestat, and Fidarestat

- Phenolic derivatives

Till now, Epalrestat is the only commercially available inhibitor. Some other ARIs such as Sorbinil and Ranirestat are into late stage of clinical trials and found to be safe for human beings. The potential benefits to adapting ARIs include in the prevention of sepsis complications, preventing angiogenesis, ameliorating mild or asymptomatic diabetic

cardiovascular autonomic neuropathy and appear to be a promising strategy for the treatment of diabetic complications including neuropathy [34].

CONCLUSION

Understanding cellular level mechanisms behind diabetic peripheral neuropathy and linking it with available and future pharmacological agents with regards to their mechanism of actions is an area for future research and can help to treat and possibly prevent the dreadful experiences of painful diabetic peripheral neuropathy. Future work needs to be done exploring cellular basis and mechanism of developing diabetic peripheral neuropathy.

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