Antioxidants: Futuristic Therapeutics in the Field of Diabetic Neuropathy

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Abstract

Diabetic neuropathy is one of the most widespread condition which leads to neurovascular disabilities. It is found in patients having advanced stage of diabetes with poor control on weight, unbalanced nutrition and sedentary lifestyle. It is more common when patients have high metabolic imbalance which is mainly due to oxidative stress. Reactive oxygen species produced by mitochondria leads to microvascular damage and hence can result in to post diabetic complication including diabetic neuropathy. Pathophysiological pathways involved in this are advanced glycation end product formation, protein kinase C, NF-κB activation and increased polyol flux etc. As diabetes cannot be singly controlled with changes in lifestyle and food, therapeutics are administered to control it. Available treatments majorly focus on maintaining the glycemic control in blood. Nowadays administration of antioxidants is also given importance as, they can combat the oxidative damage caused by reactive oxygen species by scavenging the same, thus reducing the oxidative stress. As oxidative stress is major factor leading to nerve dysfunction, many antioxidants are widely studied for their role in inhibiting the oxidative damage in case of diabetic neuropathy. Antioxidants have the possibility of upcoming as revolutionary therapeutics in the field of diabetic neuropathy. In this review, we are taking gamut of antioxidants- for example vitamin E, vitamin C, alpha lipoic acid, taurine etc. - and their role in controlling the hyperglycemic conditions which in turn helps in controlling the diabetic neuropathy.

Keywords: Diabetic neuropathy, pathogenetic pathways, therapeutics, antioxidants, nutraceuticals.
1. Introduction

The condition of hyperglycemia can lead to post diabetic complications like diabetic neuropathy. Oxidative stress that arises from hyperglycemia has been established as a link that forms a unifying mechanism for tissue damage. Various studies indicate the close relationship between regulation of hyperglycemia with respect to time and the subsequent effect of that control in development of complications. Hence, strict glycemic regulation can decrease the chances of initiation and progression of diabetic neuropathy. Although, no present therapies are able to reverse the damage caused by neuropathy or stop its progression, hence there is a need of new therapeutics which can negate this present predicament. Antioxidants hold a bright future as the oxidative stress is a major factor for the progression of this morbid disease. Here, we are trying to relate the use various antioxidants and their benefits in relation to controlling oxidative stress by scavenging Reactive Oxygen Species (ROS) in case of Diabetic Neuropathy (DN). Also, we are trying to advocate the use of nutraceuticals as a preventive measure in those people who are at high risk to develop diabetic neuropathy in future.

Diabetes and Diabetic Neuropathy: Diabetic neuropathy is a serious vascular disability that arises in 60% of the patients suffering from diabetes [Young et al., 1993]. When diabetes is not controlled, it can lead to the onset of various micro and macro vascular diseases including diabetic neuropathy which when activated, is irreversible. Also, DN is found to be more prevalent in patients with type 2 than with type 1 diabetes [Vincent et al., 2004]. It is estimated that 20-30 million people are suffering from DN worldwide, and the present growth rate of obesity and diabetes can make these figures double by 2030 [Said, 2007].

2. Pathogenesis of Diabetic Neuropathy

The development of DN is multi factorial and exact pathogenic mechanism is yet to be understood. A number of pathogenic pathways are suggested to be involved. The current belief is that the following pathways play a key role in DN:

2.1 Polyol pathway

The hyperglycemic condition of patients result in the increased glucose level in nerves and saturation of glycolytic pathway induces the activation of polyol pathway which produces sorbitol and then fructose by aldose reductase and sorbitol dehydrogenase respectively [Edwards et al., 2008]. This polyol flux increases the osmolarity in the cell by accumulation of impermeable sorbitol and to balance the osmolarity, efflux of myoinositol, taurine and adenosine takes place. Furthermore, deficiency of myoinositol leads to reduced activity of Na+/K+ - ATPase and PKC, which results in breakdown of nerves by increasing oxidative stress [Hossenini et al., 2013].
2.2 Advanced Glycation End Products (AGEs)
The generation of AGEs is increased by hyperglycaemia as glucose reacts with primary amino acids to form glycated residues known as “Amadori products”. They then get converted to AGE affecting cellular activities. AGE binds to its receptor RAGE, leading to inflammatory action and oxidative stress. Long term upregulation of RAGE leads to the activation of the NF-κB. [Toth et al., 2008] This leads to reduction in blood flow and impaired repair mechanisms [Callaghan et al., 2012].

2.3 Activation of Diacylglycerol Protein Kinase C
The main contributor in the formation of PKC is Diacylglycerol (DAG) [Cameron et al., 2002], activating the intracellular signaling cascade such as over-expression of NF-κB and TGF-β [Rajbhandari et al., 2005] resulting in production of ROS. Activation of NADPH oxidase of the mitochondria causes release of cytokines and inflammation occurs, leading to progression of diabetic neuropathy.

2.4 Hexosamine
Hyperglycemia shifts metabolic intermediate of glycolysis, fructose-6-phosphate, and converts it into glucosamine-6-phosphate by glutamine fructose-6-phosphate aminotransferase, resulting in the over-activation of transcriptional factor TGF-β1 and plasminogen activator inhibitor-1 (PAI-1). These factors have been implicated in insulin resistance and contributors to complications in diabetes; glucosamine elevates the level of H₂O₂ which is an oxidant and promotes oxidative stress.

2.5 PARP over-activation
Poly (ADP-Ribose) Polymerase catalyses the addition of ADP Ribose to DNA. Normally, PARP is under-expressed in cells and over-expression of PARP is closely linked with oxidative stress increasing DNA single-strand breakage.

As can be concluded from the discussion above, collectively Polyol, AGEs, Hexosamine, PKC and PARP, all contribute to oxidative stress and hence, neuronal damage [Evans et al, 2002].

3. Antioxidants
Studies of the pathways suggest that the diabetic state of patient and resistance to insulin are responsible for producing oxidative stress [Sharma et al., 2006]. The onset and progression of diabetic neuropathy is related to overproduction of ROS, like the superoxide (O₂⁻), by mitochondrial electron transport chain induced by hyperglycemia [Nishikawa et al., 2000]. Oxidative stress occurs when the rate of oxidant production is much faster than the rate of oxidant scavengers [Bedard et al., 2007]. As discussed above, oxidative stress is responsible for nerve dysfunction in diabetes, thus antioxidant therapy is emerging to be the futuristic approach for combating diabetic neuropathy. The various examples of antioxidants are:
3.1 Alpha lipoic acid (ALA)
Alpha-lipoic acid is a short chain fatty acid and is an important cofactor for many enzyme complexes which also include mitochondrial respiratory enzymes. Alpha-lipoic acid when given externally has shown to be an effective antioxidant [Sharon et al., 2013]. In animal studies, ALA has prevented or even reversed hyperglycemia-induced nerve dysfunction by reducing the oxidative stress mediated by free radicals [Bertolotto et al., 2012]. ALA improves blood flow in nerves, conduction in the peripheral nerve fibres, increases endoneurial glucose uptake and energy metabolism in experimental diabetic peripheral neuropathy [Low et al., 1997]. On the other hand, there is also a lack of any data relating to positive effects of ALA on the nerve condition velocity [Bertolotto et al., 2012].

3.2 Acetyl-L carnitine (LAC)
LAC is the acetylated ester of L-carnitine and has studied in improving neurophysiological factors and pain reduction. LAC upholds the potential, but it needs to be validated in future studies [Grandis et al., 2002].

3.3 Taurine
Taurine is an organic acid. It is also a major constituent of bile and can be found in the lower intestine and in small amounts in the tissues of many animals. The major benefits of taurine are because of its capability to mend mitochondrial function by steadying the electron transport chain and preventing the generation of ROS [Schaffer et al., 2009]. Additional studies reveal that diabetic complications are alleviated by supplementing taurine. Taurine supports nerve fibre integrity, and helps in slowing or reversing painful diabetic neuropathy [Askwith et al., 2012]. Taurine improves nerve blood flow and shows analgesic properties in patients with DN [Shakher et al., 2011].

3.4 Vitamin C
When Vitamin C was administered to patients with diabetes, the results showed decrease in microalbuminuria [Bursell et al., 1999]. It changes the intracellular erythrocyte sorbitol level and reduces neutropathic pain [Negi et al., 2011].

3.5 Vitamin E
Vitamin E, have a potential of playing an important role in the reduction of the neurological damage caused by diabetes .The studies in animal models have confirmed in reduction of glycaemia and its neuroprotective effect [Roldi et.al, 2009]. Hence, Vitamin E has bright promise in future as it has reached stage 3 of clinical trials [Sima et al., 2005].

3.6 Bardoxolone methyl
It is a synthetically derived extract and is available for oral administration. Bardoxolone methyl induces the Nrf2 pathway and is effective in curbing oxidative stress and inflammation. As it is a potential therapeutic, it is presently undergoing
clinical trials. Transcription factor Nrf2 (NFE2-related factor 2) regulates cellular detoxification. Up-regulation of Nrf2 and its downstream genes in response to hyperglycaemia was seen in renal cells [Li et al., 2011]. Bardoxolone methyl which reacts with cysteine residues on Keap1, allows Nrf2 translocation to the nucleus, which leads to better results in the patients with DN and reduces inflammatory effects [Pergola et al., 2011].

3.7 β-carotene
β-carotene is an antioxidant found mainly in plants and algae. It is a member of carotenoids and is considered as pro-vitamin since it gets converted into vitamin A. Treatment with β-carotene has been shown to decrease oxidants [Kowluru et al., 2005].

4. Herbal Extracts and their Active Constituents: Nutraceuticals
One of many causes for the morbid progression of diabetic neuropathy lies in lifestyle of the patient. Unhealthy eating habits, sedentary lifestyle and obesity is responsible for progression of diabetes. If this continues uninhibited, DN onset is sure and the neuronal damage is mostly irreversible when patient does not concentrate on improving the lifestyle. However, studies show positive results when patients leave these habits and adopt healthier eating habits and lifestyle. Regular exercise, proper control on blood sugar, and healthy diet plans are a must to control diabetes and hence, diabetic neuropathy.

Also, there is a need of those agents which can reduce the risk of onset of diabetes or can stop its progression, hence preventing the onset of neuropathy. Nutraceuticals are suggested as a good preventive source in this case. These substances are reported to have hypoglycemic, anti-inflammatory, anti-oxidative effects. Few examples which are reported to be effective are:

4.1 Allium sativum
It has shown good anti-oxidative effect in animal studies. Garlic contains a compound named Allicin, which has shown to have significant hypoglycemic effect [Modak et al., 2007].

4.2 Aloe vera
It has demonstrated anti-inflammatory activity and is reported to show improved diabetic wound healing in animal models. Due to its anti-oxidative effect it can prevent the onset of DN. Also, it was found to control the glucose level in animal models [Im et al., 2007]

4.3 Camellia sinensis
It upholds the beneficial properties for the prevention and treatment of human disease. Research is going on to find its role in DN too. Although, it has been reported that green tea has long-term beneficial effects on diabetic nephropathy in an animal model.
Green tea's catechins improve levels of serum glucose and glycosylated protein as well as the urine parameters [Modak et al., 2007].

4.4 Tinospora cordifolia
It is reported to control blood glucose activity in animal models. Tinospora cordifolia prevents the hyperalgesia in experimental diabetic neuropathy. It has an aldose reductase inhibitory activity in-vitro which may contribute to the beneficial effects [Nadiq et al., 2012].

4.5 Ocimum sanctum
This plant is famous for its wide range medicinal properties. The aqueous extract of leaves of Ocimum sanctum showed significant reduction in fasting blood glucose, uronic acid, total cholesterol, triglyceride and total lipid content indicated the hypoglycemic and hypolipidemic effects of this plant in diabetic rats. Even the oral administration of plant extract is useful in lowering plasma glucose level [Vats et al., 2002].

5. Conclusion
Generation of mitochondrial ROS is related to subsequent initiation and progression of diabetic neuropathy, and thus can be considered as a target for therapeutics. Antioxidants which target mitochondrial ROS have shown promise to curb the morbidity of this disease. The main factor to be understood is the relation between the level of oxidative stress in a system and the antioxidant dose provided to relieve the same. Better results are seen when the system has high level of antioxidant level. Also, the dosage needs to be optimized for different levels of ROS in system for satisfactory results. Good glycemic control is always the best measure to control diabetic neuropathy and attaining this is additionally helped by nutraceuticals. Administration of nutraceuticals helps in alleviation of the factors which are responsible for the production of oxidants in the body. Preventive therapeutics is always better that curative and many products are having the capability to provide security against diabetes. On the whole, nutraceuticals which display anti-inflammatory and anti-oxidative properties provide a potential approach for the prevention and treatment of diabetic complications.

References


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