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ROLE OF ALPHA- LIPOIC ACID IN DIABETIC PERIPHERAL NEUROPATHY

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ABSTRACT

Diabetic peripheral neuropathy is becoming a major health problem due to its predominance in diabetic patients, that may lead to subsequent morbidity, mortality and impaired quality of life. The available medications which used to treat neuropathic pain in patients with diabetes are antidepressants, antiepileptics, and opioids. But, in the current scenario these medications are found to be having insufficient effectiveness with significant side effects. Oxidative stress is the most important factor contributing to the progression of neuropathy. So, as an alternative method alpha- lipoic acid, a very powerful antioxidative agent has been shown improved nerve blood flow, distal nerve conduction with reduced oxidative stress.

Neuropathy is assumed to be the result of oxidative stress which could be a outcome of either increased production of free radicals or altered antioxidant defenses. Combining with oxidative stress metabolic and vascular defects also contribute to the pathogenesis of diabetic neuropathy. Treatment approaches aims to prevent, slow or turn around DPN progression by reduction of oxidative stress and inhibition of the polyol, hexosamine, protein kinase, advanced glycosylation product, and poly(ADP-ribose) polymerase pathways. Several studies suggested that those who treated with 300–600 mg/day a-lipoic acid, intravenously (i.v.) for 2–4 weeks, was safe and showed significantly improved nerve conduction velocity and neuropathic symptoms, also treatment with 600mg/day a-lipoic acid, orally for 40 days was found to be helpful in reducing neuropathy symptoms and an overall improvement in patients' quality of life.

KEYWORDS :

INTRODUCTION

Diabetes mellitus (DM) is expected to affect 439 million adults all over the world by 2030 [1]. The Centers for Disease Control and Prevention (CDC) has reported the prevalence and incidence of diabetes and prediabetes in the Diabetes Statistics Report 2017, and they found that there are 30.3 million people with diabetes (9.4% of the US population) including 23.1 million people are diagnosed and 7.2 million people undiagnosed. They also found that 84.1 million adults (33.9% of the adult US population) have prediabetes, together with 23.1 million adults aged 65 years or older [2].

Complications of DM comprise of a variety of neuropathies, that can be classified as focal or diffuse. Cranial mononeuropathies, diabetic amyotrophy, and focal appendicular neuropathies are 'focal' neuropathies, but chronic inflammatory demyelinating polyneuropathy and diabetic sensorimotor polyneuropathy (DSPN) fall into the category of 'diffuse' neuropathy. [3].

The most common type of DPN is distal symmetrical sensorimotor polyneuropathy, it has a reported prevalence ranging from 28.5% to 45% in the diabetic population [4,5,6]. Distal symmetrical sensorimotor polyneuropathy represents a major cause of morbidity and the leading source of diabetes-related hospitalizations and non-traumatic amputations. It is also accountable for considerable physical disability, altered quality of life, and increased mortality [7,8].

The medications which used to treat neuropathic pain in patients with diabetes mainly consist of antidepressants, antiepileptics, and opioids. But the neuropathic pain associated with diabetes is difficult to treat because these medications do not have adequate effectiveness [9], they may cause significant side effects, and they do not have much role in the processes by which hyperglycaemia leads to cell damage [10].

The probable mechanism involved in the pathophysiology of DPN is the neural dysfunction caused due to the decreased blood flow to nerves as a result of hyperglycaemia, and increased oxidative stress, which induces local inflammatory reactions through reactive oxygen species (ROS). So, based on this mechanisms of DSPN, potential disease-modifying therapeutic approaches have been developed including antioxidants such as a-lipoic acid (ALA) [11,12] to diminish increased oxidative stress [13]. Several studies found that treatment with ALA either administered intravenously or orally for several weeks or months improves neuropathic symptoms and deficits [11,12]. However, as an antioxidant, ALA directly terminates free radicals, inhibits peroxidation, increases endoneurial blood flow and the reduced glutathione content of the peripheral nerve [14,15,16,17].

DIABETIC PERIPHERAL NEUROPATHY

Diabetic neuropathy can be explained as the signs and symptoms of peripheral nerve dysfunction in diabetic patients, in whom other causes of neuropathy have been excluded [18]. Diabetic peripheral neuropathy is the nerve damage caused by chronically high blood sugar that may leads to numbness, loss of sensation, and sometimes pain in your feet, legs, or hands [19]. The common complication of Diabetes patients was peripheral neuropathy with clinic based studies suggesting prevalence rates of 5.3–47.6% for peripheral sensorimotor neuropathy [20,21,22,23]. The main risk factors of diabetic peripheral neuropathy are older age, lengthy duration of diabetes mellitus, poor glycemic control, increased lipid levels and high blood pressure.

Diabetic peripheral neuropathy can be either focal or diffuse. Diffuse disease can affect the sensorimotor or the autonomic nervous systems or both. Sensorimotor disease can involve large or small nerve fibre, predominantly sensory, and may be painful [24]. Cranial mononeuropathies, diabetic amyotrophy, and focal appendicular neuropathies fall into the 'focal' category. 'Diffuse' neuropathies include chronic inflammatory demyelinating polyneuropathy and diabetic sensorimotor polyneuropathy (DSPN), the latter being a condition characterized by generalized, length-dependent, symmetric nerve dysfunction [25].

Pathogenetic mechanisms that may cause diabetic peripheral neuropathy are: The main cause of DPN is neural dysfunction caused by decreased blood flow to nerves as a result of hyperglycaemia, and increased oxidative stress, which induces local inflammatory reactions through reactive oxygen species [26].

1. Increased flux through polyol pathway, mediated by aldose reductase and sorbitol dehydrogenase, leading to accumulation of sorbitol and depletion of myo-inositol, due to decreased Na+-K+-ATPase activity [27]
2. Nitric oxide inactivation leading to endoneurial microvascular damage and hypoxia [28]
3. Activation of polyol and protein kinase pathways that leads to reduced nicotinamide adenine dinucleotide phosphate (NADPH) and subsequent depletion of glutathione and nitric oxide [29]
4. Basement membrane thickening and endothelial proliferation, which cause altered capillary permeability and local hypoxia [30]
5. Production of ROS and glycosylation end-products activates the NFkB pathway, that may increases oxidative stress and NADPH depletion [31]

All these mechanisms subsequently leads to mitochondrial dysfunction, followed by apoptosis, axonal degeneration, and axonal death. Local proinflammatory cytokines generated by oxidative stress promote macrophage recruitment that may cause glial failure, myelin breakdown, and impaired nerve regeneration [32]. Later this hyperglycaemia-induced inflammatory and oxidative state cause complications like axonal dystrophy, decreased nerve conduction velocity, diminished neurovascular flow and small- and large-fibre neuropathy [33].

Management of DPN

Management of DPN include the following goals:

1. target normoglycemia [27,34]
2. pathogenetically oriented therapy, 3. symptomatic therapy, and
4. avoidance of risk factors [27].

Management of DPN include medications that reduce symptoms and disease-modifying treatments. Symptomatic treatments aim to reduce pain; they include anticonvulsants, tricyclic antidepressants [35,36], serotonin and noradrenaline reuptake inhibitors [37], opioids and opioid-like drugs [38,39] systemic local anaesthetics [40], nonsteroidal anti-inflammatory agents [41,38,39] and non-drug therapies such as transcutaneous electrical nerve stimulation, pulsed radiofrequency sympathectomy and acupuncture [42]. The intention of disease-modifying treatment is to slow down, reverse or to prevent DPN progression by reduction of oxidative stress and inhibition of the polyol, hexosamine, protein kinase, advanced glycosylation product, and poly (ADP-ribose) polymerase pathways.

ALPHA LIPOIC ACID

Alpha lipoic acid (ALA) also known as thioctic acid (TA) and 1,2 dithiolane-3-pentanoic acid is a naturally occurring substance that is vital for the function of different enzymes of oxidative metabolism [43,44,45]. ALA is mostly found in vegetables (spinach, broccoli, tomato), meats mainly viscera and also in many dietary supplements. ALA can also be synthesized through enzymatic reactions in plants and animal's mitochondria from octanoic acid and cysteine [46,47]. Mammalian cells can produce ALA by the action of mitochondria lipoic acid synthase (LASY) [47].

ALA is absorbed by gastrointestinal tract and is transported to different organs such as brain because it has the potential to cross the blood brain barrier [45]. ALA is reduced to dihydrolipoic acid (DHLA) and metabolized in the liver into different metabolites like bisnorlipoate, tetranorlipoate and it is excreted through renal route [48].

A-lipoic acid is a crucial co-enzyme for energy production in mitochondria with significant antioxidant properties and an effect on whole-body physiology [49]. A-lipoic acid is found in very low quantities in almost all foods, and is used as a dietary supplement and a pharmaceutical agent [50]. It has been used in several oxidative-stress models such as diabetes, ischemia-reperfusion injury, cataract, and neurodegenerative disorders, as well as in mushroom and heavy metal poisoning. Adverse events of alpha-lipoic acid may include nausea, vomiting and mild skin reactions [51].

In vitro studies found that ALA and its reduced form, dihydrolipoic acid (DHLA) scavenge ROS including hydroxyl radicals, hypochlorous acid, and singlet oxygen [51]. In vivo studies also showed that ALA decreases oxidative stress [52], participates in restoring endogenous cellular antioxidant levels and reducing pro-inflammatory pathways [53], and may influence the regeneration of vitamins C and E [17].

ROLE OF ALPHA LIPOIC ACID IN DIABETIC PERIPHERAL NEUROPATHY

As we know peripheral neuropathy is the most common complication of diabetes which affects around 16% of diabetic patients [54]. It impairs quality of life and sleeping as it usually gets worse at night [18,27]. It is habitually the major complaint that encourage patients to seek health care [55]. So, several therapeutic approaches have been developed including antioxidants such as alpha -lipoic acid to reduce increased oxidative stress [7,56]. These drugs influence the underlying pathophysiology of the disorder, along with relieving pain, paresthesia and numbness [57].

Improvement in neuropathic pain with ALA is related with enhanced blood flow to nerves by antioxidant action and also due to nitric oxide mediated endothelium- dependent vasodilation in patients with diabetes [58,59,60,61,62]. Alpha lipoic acid had a role in reducing the levels of interleukin-6 and plasminogen activator-1 in plasma, signifying that the drug may recover endothelial dysfunction through anti-inflammatory and antithrombotic mechanisms [63]. The destruction of nitric oxide–mediated vasodilation in diabetes contributed to augmented vascular oxidative stress. Thus, acute infusion of ALA enhanced nitric oxide–mediated endothelium dependent vasodilation in patients with diabetes and peripheral neuropathy [64].

In a latest meta analysis it was found that those who treated with 300–600 mg/day ALA, intravenously for 2–4 weeks, was safe and showed significantly improved nerve conduction velocity and neuropathic symptoms, also treatment with 600mg/day ALA, orally for 40 days was found to be reducing neuropathy symptoms and an overall improvement in patients' quality of life [65]. Furthermore, another meta-analysis of 15 randomized controlled trials relating patients with diabetic peripheral neuropathy showed that treatment with 300–600mg/day ALA, i.v. for 2–4 weeks was statistically higher to the control group for increasing median and peroneal motor nerve conduction velocity and median and peroneal sensory nerve conduction velocity [65].

In the study of Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND), they administered 300mg of alpha- lipoic acid orally to patients with metabolic syndrome and they found a marked increase in endothelium-dependent brachial artery flow–mediated vasodilation and reductions in plasma levels of interleukin-6 and plasminogen activator-1 compared with placebo after 4 weeks [66].
It was proved that interaction of ALA with regulatory components of insulin signaling cascade is functionally complimentary to glucose uptake by skeletal muscle, whole-body glucose tolerance, supportive against insulin resistance [67,68], and improvements in glucose discarding in human patients with type 2 diabetes receiving LA either intravenously or orally [68,69,70]. ALA, and its reduced form, dihydrolipoic acid, act as antioxidants by destruction of reactive oxygen species, inhibition of reactive-oxygen generators, and by restoring the damage caused by other oxidants [66,50].

Alpha-lipoic acid treatment in diabetic peripheral neuropathy increases GSH both in vivo and in vitro [71,72]. Glutathione (GSH) is an essential endogenous antioxidant, when combine with lipoic acid, plays a major role in the redox-dependent mechanisms of various cellular targets [73,74]. It was found that ALA downregulate the expression of cell-adhesion molecules ICAM-1 and VCAM-1 in a dose-dependent manner [75]. This finding become a corner stone for the treatment and prevention of arteriosclerosis and other inflammatory disorders [76]. Clinical and postmarketing surveillance studies have uncovered highly approving safety profile of the drug [77].

CONCLUSION

Inspite of therapeutic advances, diabetic neuropathy is still associated with considerable morbidity, mortality and impaired quality of life. The main challenge is that DPN may cause foot ulceration leading to active or passive soft tissue infection, bone infection and subsequent lower extremity amputation. It was assumed that it was the oxidative stress that cause metabolic and vascular defects leading to nerve injury in diabetic patients.

Alpha lipoic acid is a very powerful antioxidative agent that increase blood flow to nerves, diminish oxidative stress and improves distal nerve conduction. It acts as a scavenger of reactive oxygen species (ROS), impair the production of free radicals, and restore the injury caused by ROS. So, alpha lipoic acid has a positive effect in diabetic peripheral neuropathy and thus it should be consider as a treatment approach in diabetes and peripheral neuropathy.

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