ALPHA LIPOIC ACID: AN ANTIOXIDANT FOR THE TREATMENT OF DIABETIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS PATIENT

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ABSTRACT
Diabetes is a chronic and multi-faceted metabolic disorder where there is increased oxidative stress that contributes to the pathogenesis of the deliberating complication of diabetes such as diabetic neuropathy. Diabetic neuropathy is a common complication of diabetes and it represents major health problem worldwide that affects about 40-45% people of diabetes mellitus. It usually progresses gradually and involves small and large sensory fibres. The primary cause of diabetic neuropathy may be persistent hyperglycaemia condition with symptoms including loss of ability to sense pain, loss of temperature sensation. The aim of this review to focuses on the efficacious effect of alpha lipoic acid (an antioxidant) in the treatment of diabetic neuropathy in type 2 diabetes mellitus patient. The antioxidant property of alpha lipoic acid quenches the reactive oxidative stress that mainly leads to diabetic neuropathy. Alpha lipoic acid, considered as primary choice, is most potent agent for treatment of neuropathy. Alpha lipoic acid, naturally occurring compound that is also known as 1, 2-dithiolane-3-pentanoic acid or thioctic acid. Rather than antioxidant property of alpha lipoic acid, it has many other biological functions that are summarised in this review and discussed the oxidative mechanism of alpha lipoic acid for the treatment of diabetic neuropathy. The results of other studies also showed that 600 mg day dose of alpha lipoic acid effective for patient those who are suffering from neuropathic pain. This review emphasises on benefits of antioxidant property of alpha lipoic acid in treatment of diabetic neuropathy.
1. INTRODUCTION:

1.1. Diabetes- A metabolic Disorder
Diabetes is a chronic metabolic disorder that continues to represent a major worldwide health problem. It is characterized by absolute or relative deficiencies in insulin secretion or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism that is responsible for substantial morbidity, increased mortality, and impaired quality of life. As a consequence of the metabolic derangements in diabetes, various complications develop including both macro and micro-vascular dysfunctions. [1]

1.2. Oxidative stress
Oxidative stress, mediated mainly by hyperglycemia-induced generation of free radicals, contributes to the development and progression of diabetes and related complications. [2] Oxidative stress leads to an altered cellular redox status and tissue damage due to persistent imbalance in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). [3] That persistent imbalance leads to change in the antioxidant balance and causes the biological damage. Mechanisms leading to neuronal degeneration in hyperglycemia involve reactive oxygen species (ROS) formation. [4] Due to these events, the balance normally present in cells between radical formation and protection against them is disturbed. This leads to oxidative damage of cell components such as proteins, lipids, and nucleic acids. Dominant among all factors is glucose autoxidation leading to the production of free radicals. Other factors include cellular oxidation/reduction imbalances and reduction in antioxidant defenses (including decreased cellular antioxidant levels and a reduction in the activity of enzymes that dispose of free radicals). In addition, levels of some prooxidants such as ferritin and homocysteine are elevated in diabetes. Another important factor is the interaction of advanced glycation end products (AGEs) with specific cellular receptors called AGE receptors (RAGE). Elevated levels of AGE are formed under hyperglycemic conditions. Their formation is initiated when glucose interacts with specific amino acids on proteins forming a compound that then undergoes further chemical reactions. Glycation of protein alters protein and cellular function, and binding of AGEs to their receptors can lead to modification in cell signalling and further production of free radicals.[5]

1.3. Diabetic Neuropathy: Micro vascular Complication
Diabetic neuropathy is defined by the signs and symptoms of peripheral nerve dysfunction in diabetic patients. Over 50% of diabetic patients have clinical manifestations of diabetic neuropathy. [6] Diabetic neuropathy manifest with painful and painless symptoms and many patients experience both. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs. The highest rates of neuropathy are among people who have diabetes for at least 25 years.
Diabetic neuropathies also appear to be more common in people who have problems controlling their blood glucose, also called blood sugar, as well as those with high levels of blood fat and blood pressure and those who are overweight. Diabetic neuropathy includes a number of different syndromes, depending on the classes of nerve fibers involved. [7] Many types of nerves can be affected, including large-fiber sensory, small-fiber sensory, autonomic, and motor, and findings may or may not be symmetric. Distal nerves as well as large nerve trunks, nerve roots, and cranial nerves can be damaged. [8] The most common of these syndromes is the diabetic sensorimotor polyneuropathy, which can produce mild distal sensory abnormalities as well as distal weakness. Distal symmetric polyneuropathy is a major contributing factor for diabetic foot ulcer, osteoarthropathy, osteomyelitis, and lower limb amputation. Neuropathic pain affects approximately 16% of diabetic patients. [9] This subjective symptom impairs quality of life and sleeping as it usually gets worse at night. [10] It is often the major complaint that motivates patients to seek health care. [11] However, treatment of painful diabetic symmetric polyneuropathy is still a challenge for the physician. [12]

1.3.1 Classification of Diabetic Neuropathies [13]

1. Distal symmetrical sensory polyneuropathy
   • Small fiber type
   • Large fiber type
   • Mixed type

2. Autonomic neuropathy

3. Focal and multifocal diabetic neuropathy
   • Cranial neuropathy
   • Thoracoabdominal neuropathy
   • Proximal neuropathy

4. Non diabetic neuropathy
   • Chronic inflammatory demyelinating neuropathy
   • Entrapment neuropathies
   • Neuropathy due to renal failure

1.4. Treatment approach

Treatment of diabetic neuropathy is based on: 1. aiming at near-normoglycaemia, 2. pathogenetically oriented therapy, 3. symptomatic therapy, and 4. avoidance of risk factors. [10] To control the hyperglycemic level is generally the first approach towards preventing diabetic neuropathy. [14] As normoglycaemia is difficult to achieve, additional treatment of painful symptoms is frequently required. Pathogenetically oriented therapy may delay, stop, or reverse the progression of
neuropathy and may alleviate pain. Whilst symptomatic therapy does not influence the course leading to neuropathy, it may alleviate painful symptoms. [15]

Antidepressants (SSRIs and tricyclic), opioids (e.g. controlled-release oxycodone), and older anticonvulsants (e.g. carbamazepine) all seem to alleviate pain, but have several adverse side effects. Newer anticonvulsants such as gabapentin and pregabalin have a high affinity binding to \( \alpha_2-\delta \) subunit of voltage-activated calcium channels. They combat painful diabetic neuropathy, partly via calcium channel modulation in the pathogenesis of diabetic neuropathy.[16]

This review focuses on the therapeutic efficacy and safety of alpha lipoic acid. It discusses the impact of alpha lipoic acid on hyperglycemia induced oxidative stress and examines the role of alpha lipoic acid in preventing the diabetic neuropathy.

2. Pathogenesis of Diabetic Neuropathy

The exact etiologic factor of diabetic neuropathy is unknown and believed to be multifactorial. [17, 18] The following mechanism seems to be involved:

a. Increased flux through the polyol pathway, mediated by aldose reductase and sorbitol dehydrogenase, leading to accumulation of sorbitol and depletion of myo-inositol. The latter reduction is associated with reduced Na\(^+\)-K\(^+\)-ATPase activity\(^{10}\). (figure 1)

b. Endoneurial micro vascular damage and hypoxia due to nitric oxide inactivation. [19]

c. Accumulation of advanced glycation end products (AGEs) that exert their damaging effects by binding to specific receptors on the surface of neurons. Binding of AGEs to their receptors causes oxidative stress and activates nuclear factor-\( \kappa \)B (NF-\( \kappa \)B). There is increasing evidence that the diverse agents able to activate NF-\( \kappa \)B elevate levels of reactive oxygen species (ROS). Also, chemically distinct antioxidants and over expression of antioxidant enzymes can inhibit NF-\( \kappa \)B activation. [10, 19]

d. Increased nerve lipid per oxidation in vivo. The most reliable index of increased oxidative stress is reduction in GSH. [19]

e. Activation of protein kinase C (PKC) by increased release of intracellular diacylglycerol (DAG) due to glycolysis. Hyperglycemia activates PKC, increased vascular permeability that impaired nitric oxide synthesis and changes in the blood flow. It play a critical role in the perception of pain. [18]

Hyperglycemia causes neural degeneration via increased oxidative stress that accompanies diabetes. The chronic hyperglycemic condition leads to increased production of reactive oxygen species that disturbed the antioxidant capacity in the body. High reactivity of ROS determines chemical changes in virtually all cellular components, leading to lipid per oxidation. ROS-induced per oxidation of membrane lipids alters the structure and the fluidity of biological membranes, which ultimately
affects function. All these pathological modifications contribute to the pathogenesis of vascular dysfunction that ultimately leads to diabetes complication such as diabetic neuropathy.

Figure 1. Increased oxidative stress in diabetes appears to be mainly due to hyperglycemia, which leads to AGE formation and polyol pathway activation, resulting in subsequent formation of reactive oxygen species. AGE: advanced glycation end product. [17]

Hyperglycemic induced ischemia and auto oxidative lipid per oxidation suggested causing diabetic neuropathy. The increased oxidative stress and decreased activity of Na\(^+\)K\(^+\)-ATPase also elucidates that these factors leads to the complications of diabetes mellitus, in which diabetic neuropathy is major.

Endoneurial hypoxia is secondary to a reduction in nerve blood flow and increased endoneurial vascular resistance. Hyperglycemia acts via a reduction in nitric oxide resulting in impaired microvascular tone, reduced nerve blood flow, and endoneurial hypoxia.

The effectiveness and tolerability of aldose reductase inhibitors and protein kinase C inhibitors are currently being investigated. [20] Besides, acetyl-L-carnitine is deficient in diabetes. Substitution with acetyl-L-carnitine corrects perturbations of neural Na\(^+\)K\(^+\)-ATPase, myo-inositol, and nitric oxide. It also improves nerve fiber regeneration and alleviates symptoms, particularly pain in patients with established diabetic neuropathy. [21] Alpha-lipoic acid seems to normalize endoneurial Na\(^+\)-K\(^+\)-ATPase activity in experimental diabetic nerves. Alpha-lipoic acid has an effect on glucose uptake, thereby increasing polyl pathway activity. The effects of alpha-lipoic acid on glucose uptake and polyl metabolites, as well as the ability of alpha-lipoic acid to increase pyruvate dehydrogenase and \(\alpha\)-ketoglutarate activity in a number of non-neural tissues, suggest that the
effects of alpha-lipoic acid on the polyol pathway and the Krebs cycle are worth further exploration. [22].

Other study also showed that chronic hyperglycemia leads to impaired glucose tolerance leads to the development of both small and large nerve fiber damage and thus neuropathic pain causes genesis of nerve damage. The study also elucidates that association with increased formation of free radicals and decreased antioxidant potential, leading to oxidative damage of cell components and direct increase of reactive oxygen species (ROS) generation since glucose undergoes anti oxidation to generate hydroxide radicals. [18]

3. Alpha lipoic acid: An Antioxidant

3.1. History of alpha lipoic acid:
Lipoic acid (LA) or α-lipoic acid (ALA) is a naturally occurring compound that is also known as 1, 2-dithiolane-3-pentanoic acid or thioctic acid. [23] It is synthesized enzymatically in plant and animal mitochondria from octanoic acid and cysteine (as a sulfur source) and marketed as the dietary supplement. ALA acts as a cofactor for pyruvate dehydrogenase and α-keto-glutarate dehydrogenase activity, [24] and is also required for the oxidative decarboxylation of pyruvate to acetyl-CoA, a critical step bridging glycolysis and the citric acid cycle. [25] The other study by Snell et al also determines that R-alpha-lipoic acid (1, 2-dithiolane-3-pentanoic acid) was discovered in 1937, who found that certain bacteria needed a compound from potato extract for growth. [26] In 1951, the so-called potato-growth factor was isolated by Reed and colleagues, and lipoic acid was discovered as a molecule that assists in acyl-group transfer and as a co-enzyme in the tricarboxylic acid cycle (Krebs cycle). [27, 28] In the 1980s, alpha-lipoic acid was recognized as a powerful antioxidant. It is the only fat- and water-soluble antioxidant. It is produced by animals and humans. [29]

3.2. Biological function of lipoic acid:

a. Quenching reactive oxygen species: Based on the definition of an antioxidant provided by Halliwell and Gutteridge as being “any substance that when present at low concentrations compared to those of an oxidizable substrate significantly delays or prevents oxidation of that substrate,” LA has several unique characteristics among other natural antioxidants to fulfill this criterion. [30] Common antioxidants are either water-soluble or lipid soluble agents. In contrast, LA has both hydrophilic and hydrophobic properties. Being both water and fat-soluble means that ALA is widely distributed in plants and animals in both cellular membranes and in the cytosol. [31] Therefore, it can elicit its antioxidant action in both the cytosol and plasma membrane in contrast to vitamin C (which is lipophobic) and vitamin E (which is lipophilic). Both LA and DHLA scavenge hydroxyl radicals and hypochlorous acid and prevent protein carbonyl formation. In addition DHLA may also be able to regenerate other endogenous antioxidants such
as vitamins C and E, and has the beneficial property of neutralizing free radicals without itself becoming one in the process. [32,33]

b. **Regeneration of other antioxidants:** When an antioxidant molecule reacts with an unstable free radical molecule, the antioxidant molecule itself becomes oxidized and loses its benefits until it is reduced again. DHLA has the ability of reducing the oxidized forms of other antioxidants such as vitamin C and E, and GSH. Lipoic acid regenerates vitamin E either as a result of the direct reaction with tocopheroxyl radical or indirectly by reducing dehydroascorbate, which in turn reduces alpha tocopherol. DHLA is also able to reduce ubiquinone (CoQ10) to ubiquinol, which is an important component of the mitochondrial electron transport chain. [33]

c. **Chelation of metal ions:** Because of the presence of two thiol groups, LA and DHLA both have metal chelating properties. In fact, ALA is a potent chelator of divalent metal ions in vitro and forms stable complexes with Mn$^{2+}$, Cu$^{2+}$, Fe$^{2+}$, Pb$^{2+}$, and Zn$^{2+}$. [34] Decreased iron uptake and its diminished cytosolic reactive pool have been shown in cultured lens epithelial cells following LA administration. These changes were associated with increased cell resistance to a H2O2 challenge, thus allowing LA to reduce the risk of iron induced oxidative stress. [35]

d. **Regulation of gene transcription:** Lipoic acid shown to modulate peroxisome proliferator activated receptors (PPARs)-regulated genes. The PPARs are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes. Lipooic acid activates both PPAR-$\alpha$ and –$\gamma$. PPAR-$\alpha$ regulates the expression of carnitine palmitoyltransferase 1A and acetyl-CoA synthase and PPAR-$\gamma$ increases the expression of fatty acid translocase/CD36, adipocyte fatty acid binding protein, and lipoprotein lipase. [36]

e. **Inhibition of the activation of NF-kB:** Nuclear factor kappa B is a protein complex that controls the transcription of DNA and plays a key role in regulating the immune response to infection. It is been shown that LA inhibits IκB degradation and NF-κB-dependent gene expression by inhibition of IKK2, suggesting that LA inhibits NF-κB activation independent of its antioxidant function. [37] This system is a signaling pathway of intracellular protein kinases that can transduce signals from the cell surface to changes in gene expression.

Alpha lipoic acid has key role in regulating the micro vascular complication including where ROS has been implicated associated with the Diabetes mellitus. The functions regarding alpha lipoic acid provides safety in patients with end stage renal failure as well as hepatic diseases.

3.3. **A therapeutic adjuvant: Alpha lipoic acid**

Alpha lipoic acid has effective and potential therapeutic application for the pathology of the diabetes mellitus and its complications. One important action of LA is on the expression of AMPK in the hypothalamus and peripheral tissues. The AMPK complex is evolutionally a well-conserved...
serine/threonine kinase that functions as a fuel sensor in the cell and is activated when cellular energy is depleted and AMP/ADP ratio rises. [38] The result of AMPK activation is the inhibition of energy-consuming biosynthetic pathways and the activation of ATP producing catabolic pathways. AMPK can also affect transcription of specific genes involved in energy metabolism, thereby exerting long-term metabolic control. [39] After the discovery of the effect of insulin-sensitizing anti-diabetic drugs such as metformin and thiazolidinediones on the activation of AMPK, much interest was generated toward targeting this pathway for the treatment of diabetes. Targeting towards the pathway of activation of AMPK became more interesting for research work after the discovery of effect of insulin-sensitizing anti diabetic drugs on AMPK activation. AMPK also stimulates GLUT4 translocation to the plasma membrane in an insulin independent manner and increases the expression of the GLUT4 gene through enhanced binding of the transcription factor MEF-2 (myocyte enhancer factor-2) to promoters in the GLUT4 gene. [40]

Insulin sensitivity is also improved through reduced triglyceride accumulation by skeletal muscles. [41] This occurs as a result of AMPK phosphorylating, and thus inactivation, of acetyl-CoA carboxylase (ACC), resulting in decreases in malonyl-coenzyme A. [42, 43] ACC is an important rate-limiting enzyme for the synthesis of malonyl-CoA, which in turn is a critical precursor of fatty acids biosynthesis and a potent inhibitor of mitochondrial fatty acid oxidation. Decrease in malonyl-CoA content results in reduction of fatty acid synthesis and increases in fatty acid oxidation. Triglyceride accumulation in skeletal muscle contributes to insulin resistance in obesity associated insulin resistance and type 2 diabetes. [44] In a study by Lee et al, 2005, muscular AMPK is decreased in Obese Long Evans Tokushima Fatty rats, which are prone to diabetes. [45] When these rats are administered ALA, there is increased insulin stimulated whole body glucose disposal and also in skeletal muscle. ALA also increased fatty acid oxidation and stimulated AMPK in skeletal muscle.

Based on the pathophysiological state and concentration of alpha lipoic acid, it can have both detrimental and cytoprotective effects on pancreatic beta cells. In type 2 diabetes, oxidative stress is an important contributor in lowering of beta cell numbers by a significant increase in beta cell apoptosis. [36] The prolonged AMPK activation by ALA leads to enhanced production of mitochondria-derived oxygen radicals and onset of an intrinsic mitochondrial apoptosis pathway. [46] A review of the literature indicates that ALA effects are concentration dependent. [47]

ROS-induced vascular dysfunction is one of the main features of diabetic mellitus; this state of ROS accumulation is strongly associated with impaired endothelium dependent NO-mediated vasodilation. Activated PKC has a variety of effects on gene expression, such as decreased expression of eNOS and increases in the expression of endothelin, vascular endothelial growth
factor, plasminogen activator inhibitor-1, transforming growth factor-β, NAD(P)H oxidases, and NFκB. [48] LA improves the redox state of the plasma and endothelium dependent vasodilation. It is known that insulin receptor tyrosine kinase, phosphatidylinositol 3-kinase (PI 3-kinase), and Akt are essential components of insulin signaling pathways related to production of NO in vascular endothelium. Phosphorylation of endothelial nitric oxide synthase (eNOS) by Akt is also necessary for its activation by insulin. In aged endothelial cells, administration of LA partially restores the reductions in eNOS phosphorylation through Akt. ALA also induces Akt phosphorylation in human umbilical vascular endothelial cells. [36] In diabetic neuropathy the pathogenesis of alpha lipoic acid contributes vital role in treatment. In a small study on a group of diabetic patients with neuropathy, ALA increased low pre-treatment level of plasma nitrates and nitrites, which are commonly, used markers of NO production. Increased NO production theoretically increases circulation to the neurons. [49] A single daily dose of 600 mg LA for 70 days reduced serum lipid per oxidation. [50]

4. Conclusion:

The unique properties of alpha lipoic acid provide a fertile field for the further researches. A number of experimental and clinical studies have shown the beneficial antioxidant effect of ALA as a therapeutic agent for a diverse spectrum of diseases that is diabetes, and its various complications. Alpha lipoic acid affects the biological process including the regulation of gene transcription and the activity of enzymes and receptors. The antioxidant effect of alpha lipoic acid prevents the production of oxidative stress leads in the management of diabetes and its complication; diabetic neuropathy. ALA also prevents beta cell destruction, enhances glucose uptake and regulates the sugar level that is beneficial in the prevention of diabetic micro vascular complications. Some studies result shown that alpha lipoic acid improves motor nerve conduction velocity in diabetic neuropathy. It is believed that better designed experiments with appropriate doses, duration, and the selection of populations based on a specific pathophysiology may provide evidence for some of the hidden therapeutic potential of ALA.

5. Abbreviations:


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