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## Diabetic Neuropathy And The Mitochondria, Can Coenzyme Q Be Of Help

**Author(s):** Mr. Sandeep Khare, Dr. Sanjay Kalra, Dr. Bharti Klara, Ms. Priyanka Arora

**Corresponding Author:**

Mr. Sandeep Khare,  
Clinical Researcher, Bharti Research Institute of Diabetes and Endocrinology, BRIDE Bharti Hospital Karnal,  
132001 - India

**Submitting Author:**

Mr. Sandeep Khare,  
Clinical Researcher, Bharti Research Institute of Diabetes and Endocrinology, BRIDE Bharti Hospital Karnal,  
132001 - India

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# Diabetic Neuropathy And The Mitochondria, Can Coenzyme Q Be Of Help

## Abstract

### Abstract

The pathogenesis of neuropathy is multifaceted and complicated. Various researchers implicate oxidative stress, and point towards the central role of the mitochondria in development of this complication. Coenzyme Q is an important contributor to mitochondrial bioenergetics. This article reviews the hypothesis that Coenzyme Q can be used to manage diabetic neuropathy.

**Key words:** Diabetes, Neuropathy, Mitochondria, Coenzyme Q, Oxidative Stress

## Introduction

Diabetic neuropathy encompasses a wide spectrum of clinical conditions, including sensory, motor and autonomic dysfunction.

Sensory neuropathy, the most common manifestation, is characterized by functional changes such as slowing of nerve conduction velocity, and structural changes such as microangiopathy, abnormal Schwann cells, axonal degeneration, paranodal demyelization, and loss of both myelinated and demyelinated fibres.<sup>[1]</sup>

The neurodegeneration noted in diabetic neuropathy is most visible in long axons, and there is no pathognomic feature of this disease on histopathology.<sup>[2,3]</sup> The major features of distal dying-back of axons, and axonal dystrophy are also seen in other pathologies of the nervous system.<sup>[4]</sup>

### Oxidative stress and diabetic neuropathy

Multiple mechanisms have been put forward to explain the occurrence of neuropathy in diabetes.

The major mechanism, however, is thought to be oxidative stress, caused by microangiopathy. This has been studied in animals models of both diabetes.<sup>[5,6]</sup>

Increased levels of reactive oxygen species (ROS),<sup>[7]</sup> lipid peroxidation<sup>[7,8]</sup> and protein nitrosylation have been observed, as are lower levels of ascorbates and reduced glutathione<sup>[7]</sup>.

The importance of oxidative stress is underscored by the fact that antioxidants such as  $\alpha$ -lipoic acid and  $\gamma$ -linolenic acid are useful in the management of neuropathy in diabetes<sup>[9,10]</sup>.

### The mitochondria and neuropathy

Mitochondrial dysfunction has been implicated in the pathophysiology of diabetic complications through various pathways. The nerves, heart, muscle and kidney all demonstrate abnormalities of mitochondrial structure and function in both clinical as well as animal models of diabetes<sup>[11]</sup>.

Hyperglycemia has been suggested to enhance activity of the mitochondrial electron transport chain [ETC], leading to mitochondrial hyperpolarization, and elevated ROS production<sup>[12]</sup>. The increased electron availability causes partial reduction of oxygen to super oxide in the proximal ETC<sup>[13]</sup>, which subsequently induces neurodegeneration.

Hyperglycemia may also cause apoptosis through a mitochondrial pathway in cultured embryonic sensory neurons<sup>[9]</sup>, though such a phenomenon has not been noted in either animal or human models of diabetes<sup>[14,15]</sup>.

The mitochondria of sensory neurons respond differently to hyperglycemia from the endothelial cells in diabetic animal models<sup>[16,17]</sup>. While endothelial cells exposed to hyperglycemia exhibit hyperpolarization, the mitochondrial inner membrane is depolarized.

This depolarization can be prevented by low-dose insulin, and by neurotrophin-3, a neurotrophic growth factor, through a PI3K- dependent pathway<sup>[18]</sup>, rather than a glucose- dependent mechanism.

This and other studies, reveal that hyperglycemia is not able to cause apoptosis or oxidative stress directly in adult sensory neurons, unlike in embryonic neurons and endothelial cells<sup>[10]</sup>.

This leads us to search for other mechanisms, or pathways, by which neural damage occurs in diabetes.

Diabetes is associated with impaired calcium homeostasis<sup>[19]</sup>. Reports of increased steady state intracellular  $Ca^{2+}$  concentration, increased frequency of high threshold  $Ca^{2+}$  currents and decreased depolarization-include  $Ca^{2+}$  signals in diabetes are

available <sup>[20]</sup>.

Impaired  $\text{Ca}^{2+}$  homeostasis is shown to be more severe in neurons with long axons <sup>[21]</sup>, i.e.; lumbar dorsal root ganglion neurons, which are targeted early in human diabetic neuropathy. Mitochondrial buffering of  $\text{Ca}^{2+}$  is deranged in diabetes, and high intra-mitochondrial  $\text{Ca}^{2+}$  levels, which cause inner membrane depolarization <sup>[22]</sup>, are seen.

Increased  $\text{Ca}^{2+}$  levels also promote oxidative stress by stimulating ROS production <sup>[23,24,25]</sup>. This occurs through the Krebs cycle.  $\text{Ca}^{2+}$  promotes action of pyruvate dehydrogenase, isocitrate dehydrogenase and  $\alpha$ -Ketoglutarate dehydrogenase <sup>[26]</sup> which lead to NADH production.  $\text{Ca}^{2+}$  also activates adenine nucleotide translocase <sup>[27]</sup> and enhance ATP production.

$\text{Ca}^{2+}$  stimulates the mitochondria to work faster, consume oxygen, and enhance ROS output, which is associated with a higher metabolic rate <sup>[28, 29]</sup>.

The central position of the mitochondria in the pathogenesis of diabetic neuropathy is reflected in studies demonstrating the altered function and structure of these organelles. These abnormalities have been reviewed in detail earlier <sup>[10]</sup>.

The mechanism of development of neuropathy is thought to be through the Crabtree effect <sup>[30]</sup> and through the AMP-activated protein Kinase and PPAR- $\alpha$  activator 1 pathways. While antioxidant pathways are impaired, ROS generation is increased, probably due to altered mitochondrial bioenergetics, aldose reductase activity, and NADPH oxidase. Hyperglycemia in the intracellular compartment inhibits oxidative phosphorylation, shifting glucose metabolism to anaerobic glycolysis (Crabtree effect), <sup>[30]</sup>. This reduces the need for an effective mitochondrial proteome, but also allows mitochondrial damage to go on unchecked, and permits change in mitochondrial trafficking.

Elevated ROS leads to a vicious cycle in the mitochondria, by increasing lipid peroxidation, changing mitochondrial trafficking, and causing mitochondrial fragmentation.

Mitochondria may undergo fission or fragmentation in response to increased nitric oxide levels (nitrosative stress), and this may further lead to fall in ATP, increase of ROS, over expression of Drp 1 and neuronal damage <sup>[31]</sup>.

#### Coenzyme Q10

Coenzyme Q10 is a quinone with the structure of 2,3-diamethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, which was first isolated from bovine heart

mitochondria, [32]. It is also known as ubiquinone, because it is found in virtually all human cells.

The reduced form of Coenzyme Q acts as an antioxidant, combats free radicals, prevents lipid peroxidation, and protects mitochondrial DNA.

The antioxidant activity of Co Q 10 is directly related to its energy carrier function. The Q cycle regulates ROS production through the reduced ubiquinone or coenzyme Q (QH-) entity. ROS is increased when the effective concentration of QH-is reduced. Coenzyme Q stimulates the production of ATP from NADH, and ensure optimal mitochondrial bioenergetics.

Supplementing Coenzyme Q has been suggested as a means of increasing antioxidant activity and ensuring mitochondrial protection in the body. As dietary sources of Coenzyme Q are limited, supplementation is usually done by pharmacological means.

Coenzyme Q supplementation may help ensure more efficient mitochondrial bioenergetics, and prevent development of neuropathy in patient with diabetes.

No clinical studies have been done this aspect of diabetic neuropathy, but the logic is tempting.

Coenzyme Q levels, if enhanced, will have an antioxidant effect, and improve mitochondrial efficiency. This will suppress ROS production, and thereby improve neuronal health.

## Conclusion(s)

The hypothesis that Coenzyme Q can be need to manage diabetic neuropathy is strong, and has scientific rationale.

Large studies are needed to prove the effect of Coenzyme Q in the prevention and management of diabetic neuropathy. The lack of patent protection for this molecule may prevent major sponsors from funding such studies

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