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Mini Review

Type 2 diabetic neuropathy with special reference to mitochondrial role and its effective management

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Diabetic neuropathy denotes to a group of nerve disorders caused by diabetes. It may occur in both type 1 and type 2 diabetes patients. Mitochondria are essential for energy production as well as intermediary metabolism and equally important in the action of insulin on its targeted tissue. Recently, mitochondrial dysfunctions have been recognized as a cause of diabetes. Hyperglycemia enhances the activity of mitochondrial electron transport chain, leading to mitochondrial hyperpolarisation and elevates the reactive oxygen species (ROS) production. Increased electron availability causes partial reduction of oxygen to superoxide in the proximal electron transport chain which subsequently induces neurodegeneration in diabetes. Currently there is no satisfactory pharmacotherapy for painful diabetic neuropathy. This review summarizes mitochondrial role in type 2 diabetic neuropathy, diagnostic challenges, general treatments and benefits of alternative approach for effective management.

Keywords: Diabetic neuropathy, reactive oxygen species, mitochondrial dysfunctions, alternative management

INTRODUCTION

Diabetes is a chronic disease resulting in high blood sugar levels in the blood. Diabetic neuropathy is common complication in both type 1 and 2 diabetes. Its prevalence was estimated that 60-70% of people with diabetes have various form of neuropathy complication. Patients can develop nerve problem at any time but danger rises with age and longer duration of diabetes (Feldman *et al*., 2001; Polydefkis *et al*., 2003; Dyck *et al*., 1993). Defective pancreatic insulin secretion and defective insulin action represent the principal pathophysiological abnormalities leading to increase blood glucose levels (Kahn and Rossetti, 1998). The reduced synthesis of adenosine triphosphate (ATP) was found to be involved in the impaired defective secretion of insulin from pancreatic beta cells. The impairment of mitochondrial function reported to have basic relationship in the development of type 2 diabetes and its associated complication including neuropathy (Petersen et al., 2004). Recently, pathogenetic evidence suggests that diabetic neuropathy is marked by degeneration of dorsal root ganglion (DRG) neurons in peripheral nerves and that DRG mitochondrial are particularly affected

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(Beal, 2005). Wily and his co-workers demonstrated that isolated adult sensory neurons from streptozotocin (STZ) induced diabetes rats exhibit the depolarization of mitochondrial inner membrane (Russell *et al*., 2006). The disturbances in mitochondrial function have been linked to neurodegenerative disease in the central and peripheral nervous system (Zherebitskaya *et al*., 2009) and mitochondrial genes are also reasonable causative agents of type 2 diabetes and its associated complication (Lowell and Shulman, 2005; Ohkubo *et al*., 2001). But overall percentage of mitochondrial mutation in type 2 diabetes with neuropathy complication is currently unknown. Since developing better novel preventing strategies, diagnostic procedure and treatments for type 2 diabetic with neuropathy is matter of great urgent to provide patients in our society. So it is essential to understand the pathogenesis of type 2 diabetes and its neuropathy complication. At present conventional medicine can proffer several help to reduce the neuropathy pain but significant few side effects and do not address the underlying pathologies (Kathleen, 2006; Andrew and Boulton, 2005). There are certain alternative remedy, natural supplements, physical activity, relaxation technique that are all may play a role in reducing the risk and improvement in neurological function, stimulate the mitochondrial biogenesis and reducing severity of diabetic neuropathy (Kathleen, 2006; Ihara *et al*., 1989a; Bresolin *et al*., 1989b; Bendahan *et al*., 1992; Nishikawa *et al*., 1989b; Broedl and Goke, 2006; Lynda, 2005; Toledo *et al*., 2007; Trenell *et al*., 2008, Morrato *et al*., 2007). Hence this review article will highlight diabetic neuropathy causes, role of mitochondria in beta cell secretion, oxidative stress, mitochondrial DNA defect, diagnostic challenges, it will also briefly address certain aspects of diabetic neuropathy therapy and effective management practices.

CAUSES AND TYPES OF NEUROPATHY DIABETES

The high glucose levels are known to harm the nerves ability to transmit signals and damage the blood vessels that carry oxygen, nutrients to the nerves which result nerve damage (Said, 2007). Damaged nerve cannot carry messages between the brain and other parts of the body. Neuropathy complications may produce a wide range of symptoms and affect badly to the person, these tend to be gentle at first and get worse over time (Boulton *et al*., 2005). Several combination of factors contributes to cause the neuropathy diabetes. Inflammation in the nerves caused by an autoimmune response, genetic factors, alcohol abuse and smoking, which damage both nerves and blood vessels and significantly increase the risk of infections (Said, 2007). Another cause of nerve problem is due to continues use of drug for other major disease, for example drugs that lower the cholesterol may cause neuropathy (www.realfoodnutrients.com). Radiation treatment and chemotherapy drugs often cause neuropathy complication problem. However, mitochondrial dysfunctions have appeared as a common cause of many types of neuropathy diabetes. Additionally, a number of mutations that affect mitochondrial function are now thought to be accountable for several forms of inherited neuropathies (Suter and Scherer, 2003; Suzuki *et al*., 2002). The hypothesized with the intention of lipid peroxidation under hyperglycemic condition also causes mitochondrial mutation that increase oxygen radicals, causing further damage to the mitochondrial respiratory chain, ultimately resulting in sensory neuropathy (Suzuki *et al*., 2002).

Diabetic neuropathy types include

peripheral neuropathy, autonomic neuropathy, proximal neuropathy and focal neuropathy (Boulton *et al*., 2005). Peripheral neuropathy causes pain, numbness, tingling in the extremities and slow nerve conduction. Autonomic neuropathy may alter the digestion, bowel and bladder function, sexual response and perspiration, it can also affect the nerve that serve the heart and control blood pressure (Said, 2007). Proximal neuropathy causes pain in the hips or buttocks and leads to weakness in the legs. Focal neuropathy results in the sudden weakness in a group of nerves, causing muscle weakness or pain (http://diabetes.webmd.com/peripheral-neuropathy-risk-factors-symptoms).

MITOCHONDRIA FUNCTION AND β - CELL SECRETION

In pancreatic β-cells, the ATP/ADP ratio determines the opening probability of the K_{ATP} channel involved in insulin secretion. Changes in this ratio cause mitochondrial dysfunction and affect the setting of glucose stimulated insulin secreted (GSIS) in response (Lowell and Shulman, 2005). When the glucose transported across the cellular membrane by glucose transporters (GLUT-1), glycolysis transforms to pyruvate, of which more than 90% is shuttled into the mitochondria. The ratio of ATP/ADP increases as processing of the glucose through glycolysis, TCA cycle and increases in OXPHOS (Marmol *et al*., 2009; Paradies *et al*., 2009). This increase in ATP/ADP ratio causes the ATP-sensitive K^+ channels to close, causing depolarization of voltage-sensitive Ca^{2+} channel, triggering the exocytosis of insulin secretory vesicles (Paradies *et al*., 2009). The importance of OXPHOS in GSIS has been demonstrated by several *in vitro* studies. Specific inhibitors of the complexes of mitochondrial respiratory chain have found to be inhibiting the insulin release from pancreatic islet cells (Marmol *et al*., 2009). Cells lacking mitochondrial DNA also lose their ability to progressive enhancement of insulin secretion by glucose stimulation. These cells depleted of mitochondrial DNA have unequal changes in the nuclear to mitochondrial composition of electron transport complexes and a loss of respiratory efficiency, relying on glycolysis for ATP production. Repopulation of cells lacking mitochondrial DNA cells with foreign mitochondrial DNA restores the property of GSIS (Maechler *et al*., 2010). This confirms the mitochondrial DNA and the mitochondrial respiratory function are necessary for GSIS and plays an important role in insulin secretion.

MITOCHONDRIAL OXIDATIVE STRESS

Hyperglycemia resulting from uncontrolled glucose regulation is generally recognized as the fundamental relation between diabetes and its complication (Rolo and Palmeira, 2006). Four cellular pathway contributors to hyperglycemia induced cell damage: increased polyol pathway flux, increases advanced glycation end product, activation of protein kinase C and hexosamine pathways (Li *et al*., 2009; Li *et al*., 2008; Rola and Palmeira, 2006; Leinninger *et al*., 2006; Dimauro, 2007). Inhibition of any single pathway has not been shown to halt the progression of neuropathy diabetes. Recent evidence indicates that all of the pathways result from a common origin oxidative stress (increases cellular ROS). Oxidative stress is caused by an imbalance between the production of ROS and a biological system, ability to readily detoxify the reactive intermediates. Cell produces ROS during normal metabolic flux via the mitochondrial electron transport chain (Li *et al*., 2008). ROS are detoxified by cellular antioxidant. Hyperglycemia can lead to increase in a surplus of NADH, $FADH_2$ that then increases the flux trough the

mitochondrial electron transport chain. Subsequently, there is an increase of ATP/ADP ratio, hyperpolarization of the mitochondrial membrane potential. This high electrochemical likely difference trough generate by the proton gradient leads to partial inhibition of the electron transport in complex III, ensuing in an accumulation of electron to coenzyme Q. In turn, this drives partial reduction of O_2 to generate the free radical anion superoxide (Leinninger *et al*., 2006). High glucose stimulation increased ROS these induced the damage impairs nerve function and resulting in peripheral, autonomic nervous system injury and the symptoms of neuropathy diabetes. Recent evidence showed that the brain may also endure from the incorrect resistances anti-oxidative stress. Oxidative stress corresponds to an important leads to the damage of neuronal along with vascular cells in central nervous system (Feldman, 2003). DRG neurons are distinctively vulnerable to damage because they have long and mitochondria rich axons that straight access the nerve blood supply. As a result, axonal mitochondria are sensitively exposes to the hyperglycemic environment and as the sites of increased ROS production, are early targets of oxidative stress (Leinninger *et al*., 2006; Dimauro, 2007). Hyperglycemia induced oxidative stress in mitochondria, which leads to diabetes and its complication.

SIGNIFICANT OF MITOCHONDRIAL DNA

Mitochondrial DNA is the only constitutive extra chromosomal DNA within cells. It is very small genome consists of multicopy and circular double standard DNA molecules (16,569 bp in human), which encodes 37 genes, of the 37 gene, 22 tRNA genes and 2rRNA genes required for mitochondrial protein synthesis, 13 polypeptide genes, all of which encode essential compound of OXPHOS (Craven *et al*., 2011). Defects of the mitochondrial genome take the form of point mutations and deletions, these different mutations have been associated with many diseases. Mitochondrial DNA is highly vulnerable to oxidative damage by virtue of its close proximity to ROS production and lack of protective DNA binding protein such as histones, limited DNA repair mechanism (Leinninger *et al*., 2006). Oxidative damage to mitochondrial DNA by ROS was reported to lead DNA strand breaks and the occurrence of somatic mitochondrial DNA mutation. Accumulation of these mitochondrial DNA mutations may result in dysfunction of the respiratory chain, leading to ROS production in mitochondria and subsequent accumulation of more mitochondrial DNA mutation. This vicious cycle may account for an increase in oxidative damage during hyperglycemia. Consequently, mitochondrial DNA is more prone to oxidative damage and possibly contributed to neuropathy diabetes (Schapira, 1998). A few study is know about mitochondrial DNA integrity in the nerves of individual with diabetes (Rasmus *et al*., 2009; Knott *et al*., 2009; Ferrari *et al*., 2011; Cassidy Stone *et al*., 2008; Chen *et al*., 2009). Hence, it is necessary to understand the pathogenesis of mitochondrial defect in type 2 neuropathy diabetes.

DIAGNOSTIC CHALLENGES

Diagnosis of neuropathy diabetes can be difficult to determine. It highly under diagnosed both by endocrinologists as well as other physicians because its symptoms can be subclinical and not interfere with daily living. However, diagnosed based on the symptoms (numbness, tingling, or pain in feet, indigestion, nausea, or vomiting, diarrhea or constipation, problems with urination, dizziness) patient medical history and physical exam (Aristidis *et al*., 2008). Diagnostic procedure includes assessment of muscle strength, tone, tendon reflexes,

sensitivity to touch, temperature and vibration. Light touch perception have been evaluated by using a specifically calibrated devices (Semmes Weinstein (SWMF) 10- g in sizes ranging from 1.65 to 6.65). Vibration perception has been measured (Vibration by on/off (VO/O) with a 128-Hz tuning fork or less commonly range from 64 to 256 Hz tuning forks. Electrophysiologic studies/ Nerve conduction studies (NCS) measures shows how quickly the nerves in your arms and legs conduct electrical signals. Quantitative sensory testing is used to assess how the nerves respond to vibration and changes in temperature. Biothesiometry, Tip-therm temperature discriminator, superficial pain sensation (SPS) have been used for measuring the vibration perception threshold (VPT) (Rayaz, 2008; Broedl and Goke, 2006; Kinga *et al*., 2006). Molecular levels diagnoses are available only for testing the inherited neuropathy (Suter and Scherer, 2003; Broedl and Goke, 2006). Mitochondrial study can support to find out the accurate diagnostic route for neuropathy diabetes additionally it can provides prognostic information, near future which may be important for choice of the therapies (http://www.cmtausa.org/images/docs/AthenaTesting.pdf).

DIABETIC NEUROPATHY THERAPY

Treatment for neuropathy diabetes depends on symptoms and type of neuropathy complication. A large number of therapeutic agents have been proposed for the management of painful symptoms. However, diabetic neuropathy therapy can be classified into three types such as preventive, specific and symptomatic therapies (Geeta and Neera, 2007). The preventative therapy appears to be an association between polyneuropathy and predominantly painful polyneuropathy and abnormal glucose metabolism (Alberti and Zimmet, 1998). The valuable and premature treatment of hyperglycemia is an important factor in delaying the series of neuropathy (Maser *et al*., 1989). The specific therapy depends on the type of neuropathy the patient presents. But therapy options currently limited to symptomatic management while other specific therapy like drugs for nerve regeneration are still under experimental level. This specific therapy for diabetic neuropathy had proved to be disappointing (Elizabeth *et al*., 2009). A few specific therapies are aldose reductase inhibitors (ARI) are a class of medications that block the breakdown of glucose by specific metabolic pathway (polyol pathway) and potentially slow or reverse progression of neuropathy. ARI such as alrestatin, sorbinil, zenarestat, tolrestat, ponalrestat, zopolrestat and epalrestat are presently in use (Katrak, 2004; Mary and Nancy, 2008). Natural and semi-synthetic Gangliosides are used to enhance the axonal regeneration and maturation in the early stages of neuropathy diabetes (Maser *et al*., 1989). Gama linoleic acid is the best supplements, it gives beneficial effect to the diabetic neuropathy patient (Chalk *et al*., 2007). Nerve growth factors such as insulin-like growth factor-1, acetyl-L-carnitine (ALCAR), recombination human nerve growth factor (rhNGF) may helpful for treating the neuropathy diabetes. Various other nerve growth factors are also under evaluation (Stuart, 2002; Windebank and Feldman, 2001). The symptomatic therapy is mainly focused on pain control. Pain management is pivotal role in neuropathy diabetes. An appropriate pharmacologic approaches act at different levels of neuroaxis in the axis of central nerves system and obliging for the management of neuropathic pain (Windebank and Feldman, 2001).

Conventional remedies are highly significant and decrease the pain more effectively. Pharmacologic treatment therapy reduces the pain immediately but

does not eliminate it. There are several medications like duloxetine, pregabalin, tramadol, gabapentin are used for treating the neuropathy diabetes and also have been approved by the FDA. Initially, tricyclic antidepressants have been used for decreasing painful neuropathy symptoms but in recent times, these drugs are replaced in clinical use in most parts of the world by newer antidepressants such as the selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors to reduce the diabetic neuropathy pain and to increase the extracellular level of the neurotransmitter serotonin. However, these drugs typically have few side effects because these drugs are dosage dependent (Jeong *et al*., 2011; Llewelyn, 2003; Jin *et al*., 2008). Anticonvulsants drugs have been used for neurological surgery pain control and also used to treat trigeminal neuralgia (Llewelyn, 2003). Antiepileptic drugs are used as a first line treatment for painful neuropathy (Jin *et al*., 2008). Opioids drugs reduces the perception of pain, decreased reaction to pain as well as increased pain tolerance these drugs have been used for the treatment of neuropathy diabetes. N methyl D aspartate agonists (NMDA) drugs are the attractive target for treatment of chronic neuropathic pain (http://www.newyorkbuyersclub.org/resources/recommended-reading-files/24-NEUROPATHY.pdf). The American Diabetes Association recommends using tricyclic antidepressant as first line and followed by anticonvulsant and then use of opioids or tramadol. Tricyclic antidepressant should not be used in patient with cardiac disease and elderly peoples which give advisory effect to the patient. In general almost all the drugs have beneficial effective against the diabetic neuropathy and as well as side effects like sedation, constipation, drossiness, respiratory depression etc (Boulton *et al*., 2005; Llewelyn, 2003).

SIGNIFICANCE OF ALTERNATIVE THERAPIES

Use of alternative therapies is the safe and secure form of treatment. Hence scientists and medical practitioners are focused on the search of treatment for the several diseases including neuropathy diabetes in the field of ayurveda, homeopathy and siddha etc., as an alternative management. The number of alternative medication may also been recommended or prescribed for treating the neuropathy diabetes, these treatments maintain the sugar level and reduce the pain (Ertas *et al*., 1998; Bellavite *et al*., 2005; Kranthi and Vardhan, 2009; Lynda, 2005). Alternative therapies maintain the nerve restoring the sensation in feet and keep the sugar levels under control without causing any side effects. It can perform a beneficial function like scavenge the free radicals to eliminate oxidative stress in mitochondria, some of natural compound like antioxidant (Coenzyme Q, lipoic acid, α- tocopherol, glutathione), cofactors and their precursors (lipoic acid, B vitamins) which care for the mitochondria from oxidative damage and improve mitochondrial function. The Indian traditional herbs are auto regulatory, self healing medicine and supports to eliminate the disease from root causes (Bellavite *et al*., 2005). Proper diet management is a brilliant means of controlling or managing the neuropathy diabetes (www.ncdiabetes.org). The diet most often recommended are vegetables, (better gourd, string beans, carrot, radish, onion, garlic) high fiber content foods (cucumber, legumes, whole grain cereals, brewer's yeast, peanuts) non vegetarian foods includes eggs, fish and poultry meat, feed supplements like vitamins (B,C and E) and selected fruits supports the better neuropathy diabetes management (Lynda, 2005; Prabhu *et al*., 2012; Ezekiel, 2009). Apart from the siddha, Ayurveda,

homeopathy relaxation technique like yoga and exercise are also pivotal role for the proper management of blood glucose levels and may reduce neuropathic pain and even prevent the neuropathy diabetes. Yoga is a traditional Indian psychological spiritual exercise regimen that has been studied for several decades for management of several diseases including diabetes (Broedl and Goke, 2006). Yoga and meditation which connects our body and mind reduces stress level and help nerve signals travel properly. It has great effect on the pancreas and other glands such as adrenal, thyroid etc., Specific asanas like surya namaskar, bhujangasana, dhanurasana, shalabhasana trikonasana, tadasana, sukhasana, padmasana, bhastrika, pranayama, shavasana are a number of recommended asana for neuropathic diabetes patients (Lynda, 2005; Gupta *et al*., 2006; Prabhu *et al*., 2012; Health Administrator). Specifically, focused breathing (Pranayama) keeps our and mind to reduce the stress (Khattab *et al*., 2007). Hence yoga, meditation and exercise are very essential to manage neuropathy diabetes, these practices stimulates the mitochondrial biogenesis by increasing gene expression of PGC-1, NRF-1, TFAM (Toledo *et al*., 2007). Endurance exercise increase mitochondrial enzyme activity and manage the blood glucose level (Trenell *et al*., 2008; Morrato *et al*., 2007; Toledo *et al*., 2007). Acupuncture is another alternative medical practices for neuropathy diabetes it act on pancreas to enhance insulin synthesis and accelerate the utilization glucose and resulting in maintenance of blood sugar level. It is an alternative to conventional medical treatment of neuropathy diabetes (Irnich and Winnklmeier, 2002; Jiang *et al*., 2006). Transcutaneous electronic nerve stimulation (low voltage electrical frequency at 50Hz) is another alternative therapy used for neuropathy pain relief. Effective alternative management practices includes regular exercise, suitable yoga, meditation, planned diet and any one of medication which fits to the biological systems without having side effects to manage the neuropathy diabetes.

CONCLUSION

Uncontrolled glucose regulation is widely recognized as the causes like between diabetes and its associated disease, including neuropathy diabetes. Several combination of factors contributes to cause the neuropathy diabetes are autoimmune response, genetics factors, lifestyle changes, drugs, alcohol abuse, smoking etc. In genetically, mitochondrial dysfunction also plays a role in cause of neuropathy diabetes. Impairment of OXPHOS system, dysfunction and oxidative stress in mitochondria may cause diabetes and its neuropathy complication. Present, diagnostic protocol is depending on clinical symptom, medical history and physical examination. However, there is need to study the molecular level diagnosis for early detection of neuropathy diabetes. Mitochondrial research in this area is essential to support diagnostic procedure near future. Currently there is no effective disease modifying treatment available for neuropathy diabetes. Moreover, the development of better treatment and novel preventive strategies for type 2 neuropathy diabetes is the matter of great urgency to provide patients and their family with prognostic advice. Numbers of conventional therapies have been used to maintain the blood sugar and control of neuropathy pain, however these medicines have both control and side effects. Nowadays, alternative treatment is the one, mostly followed by the people to avoid the side effects. It can be used either first or after controlling disease with conventional medicine to eliminate the disease from the root cause or as a preventive medicine. Herbal medicine, natural antioxidant, nutritional supplement supports for

reduces ROS, stimulate the mitochondrial biogenesis, prevent the oxidative damage and improve mitochondrial function. The aim of the therapeutic strategies is to preserving the mitochondrial structure and function could be beneficial treatment for neuropathy diabetes. Yoga, meditation and exercise reduces stress level, help nerve signals to travel properly and also it stimulates the mitochondrial biogenesis, increase mitochondrial enzyme activity. Hence sufficient scientific evidence is not available in this area of mitochondrial potential therapy to apply such controlling measures in the cause of neuropathy diabetes. Researches, physician should to focus on mitochondria potential therapy in the field of alternative medicines, will be the helpful way to suggest safer treatment to neuropathy diabetes. In our understanding, along with appropriate medications, relaxation technique like exercise, yoga, meditation, proper diet regulation and right feed supplements confer better results to the neuropathy diabetes.

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