

# Experimental Diabetic Neuropathy: A Newer Insight into Diet-Induced Models in Animals

Allampalli Sirisha\*, Pravati Pal, Gopal Krushna Pal

## ABSTRACT

Type 2 diabetes mellitus is the most prevalent form of diabetes and accounts for approximately 95% of diabetic cases. One of the most common and debilitating complications associated with diabetes is diabetic neuropathy (DN) which affects about 10% of newly diagnosed diabetes patients and more than 50% of patients with longstanding diabetes. Animal models are widely used in the research of diabetes and its complications, where rats and mice are most commonly used animals for these experimental models. The present review summarizes the current understanding of the metabolic profile and pathology involved in the development of diabetic neuropathy. Different models of diabetic neuropathy in an experimental setup are described and finally an insight of diet induced models of DN is highlighted. Recent studies have described that diet induced models are beneficial over chemical-mediated and genetically-mediated models in the development of type 2 diabetic neuropathy. The High Fat Diet (HFD) combined with low doses of streptozotocin is the most successful and well established model of diet induced neuropathy, which mimics natural progress of diabetes development as well as metabolic features in human type 2 diabetes. HFD causes obesity and insulin resistance in peripheral tissues due to lipotoxicity, while, low dose of streptozotocin induces mild defect in insulin secretion.

**Key words:** Diabetic neuropathy, Diet induced diabetes, Experimental neuropathy models, High fat diet.

## INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by persistent hyperglycemia and insufficiency of secretion or action of endogenous insulin.<sup>[1]</sup> The World Health Organization (WHO) projects that diabetes will be the seventh leading cause of death in 2030.<sup>[2]</sup> According to ICMR-INDIAB national study there are 62.4 million people with type 2 diabetes (T2DM) and 77.2 million people with pre-diabetes in India.<sup>[3]</sup> Diabetes is associated with several metabolic risk factors that contribute to micro and macrovascular complications. One of the most common and debilitating complications associated with diabetes is Diabetic Neuropathy (DN); it affects about 10% of newly diagnosed diabetes patients and more than 50% of patients with longstanding diabetes.<sup>[4]</sup> The diabetic neuropathies are heterogeneous, affecting different parts of the nervous system that present with diverse clinical manifestations. Most common among the neuropathies are chronic sensory-motor distal symmetric polyneuropathy and the autonomic neuropathies which are usually chronic and often progressive. The focal neuropathies are less common, usually acute in onset and often self-limited.<sup>[4,5]</sup>

## Diabetic Peripheral Neuropathy (DPN)

Diabetic Peripheral Neuropathy (DPN) is the most common type of DN, which is associated with impaired nerve conduction, abnormal thermal perception, axonal atrophy, demyelination, blunted regenerative potential and loss of nerve fibers.<sup>[5]</sup> In DPN the rate of peripheral nervous system deterioration is intimately correlated with the pathological interactions between neurons, Schwann cells and microvascular endothelium.<sup>[6]</sup> The presence of symptoms or signs of diabetic polyneuropathy may include decreased sensation, positive neuropathic sensory symptoms (e.g., "asleep numbness," pricking or stabbing, burning or aching pain) predominantly in the toes, feet, or legs; or signs of symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes. An abnormality of nerve conduction tests that is decreased Nerve Conduction Velocity (NCV), which is frequently subclinical, appears to be the first objective quantitative indication of polyneuropathy.<sup>[7]</sup>

## Pathogenesis of DN

Even though the exact pathogenic mechanism of DN is not clearly understood, recent studies state that hyperglycemia, activation of polyol, Advanced Glycation End Products (AGEs), hexosamine, diacylglycerol/

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## History

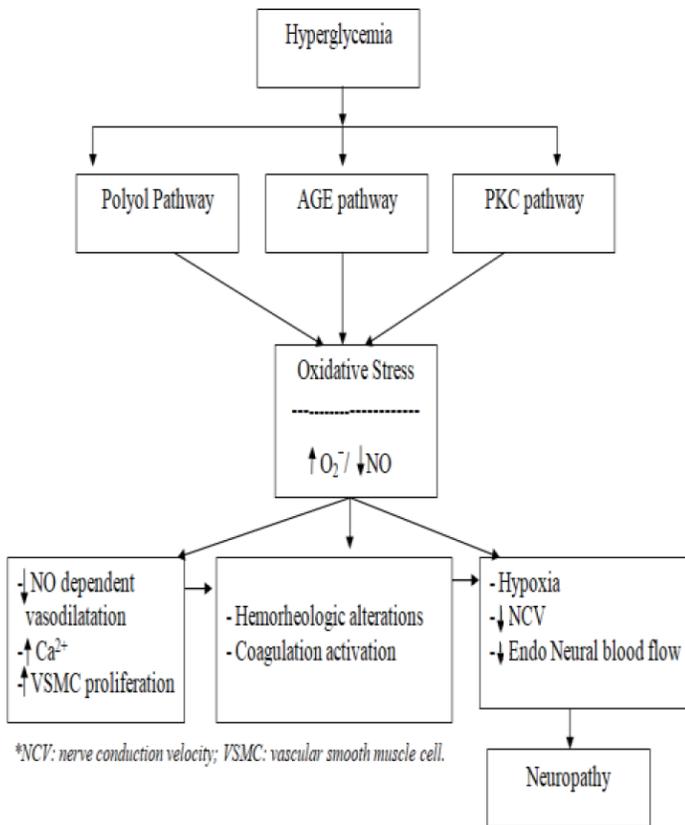
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**Figure 1:** Possible mechanisms of diabetic neuropathy.

Protein Kinase C (PKC), oxidative stress, nitric oxide and inflammation all play the major role in the pathogenesis of DN (Figure 1).

### Polyol Pathway

The metabolic mechanisms dependent on hyperglycemia are the contributing factors for diabetic complications. Hyperglycemia results in increased intracellular glucose levels in nerves, leading to saturation of the normal glycolytic pathway. This increased glucose level activates the polyol pathway producing sorbitol by aldose reductase. Increased polyol flux accumulates impermeable sorbitol causing intracellular hyperosmolarity and also there is compensatory efflux of other osmolytes such as myoinositol, taurine and adenosine. Decreased levels of myoinositol results in exhaustion of phosphatidylinositol and reduces formation of Adenosine Triphosphate (ATP). Together these all processes result in a reduced  $\text{Na}^+/\text{K}^+-\text{ATPase}$  activity and Protein Kinase C (PKC), impaired axonal transport and structural breakdown of nerves and finally presents abnormal action potential. Also, NADPH is consumed during aldose reductase-mediated reduction of glucose to sorbitol. As regeneration of reduced glutathione (GSH) requires NADPH, this directly contributes to oxidative stress.<sup>[8-10]</sup>

### Advanced Glycation End Products (AGEs)

Hyperglycemia accelerates generation of AGEs which affects cellular function. Also polyol pathway activation causes formation of fructose from sorbitol and increases AGEs. Extracellular AGEs bind to the Receptor of AGE (RAGE) which causes inflammatory flows, activates NADPH oxidases and causes oxidative stress. Long-term inflammatory responses up-regulate RAGE and stimulate Nuclear Factor Kappa B (NFκB). Finally AGEs results in diminished neurotrophic support, impaired nerve

blood flow, disrupted neuronal integrity and impaired repair mechanism.<sup>[10,11]</sup>

### Activation of Diacylglycerol Protein Kinase C

The PKC is an important element in function of nerves and pathogenesis of DN. Increased glucose causes formation of diacylglycerol, which activates the Diacylglycerol Protein Kinase C pathway. PKC activation initiates over expression of NFκB. The production of cytokines is increased which in turn enhances the contractility, permeability and proliferation of vascular endothelial cell and inhibits  $\text{Na}^+/\text{K}^+-\text{ATPase}$ .<sup>[9,12]</sup> Collectively reduced  $\text{Na}^+/\text{K}^+-\text{ATPase}$  and activation of PKC causes impaired axonal transport and structural breakdown of nerves and abnormal action potential. PKC activation triggers stress genes and alter the balance of gene expression resulting in oxidative stress.<sup>[13]</sup>

### Oxidative Stress

All the above-mentioned pathways increase the generation of free radicals. The high levels of free radicals inflict damage to cellular proteins, membrane lipids and nucleic acids and cause cell death. Free radicals also accelerate the formation of AGEs, which in turn increase free radicals formation by glycooxidation.<sup>[14]</sup> Increased production of superoxide anion by the mitochondrial electron transport chain in leads to binding of this ion to nitric oxide and forms the strong oxidant peroxynitrite, which is a powerful oxidizing agent and lethal to endothelial cells.<sup>[15]</sup>

### Dyslipidemia

In addition, some studies suggest that dyslipidemia may be an independent risk factor for development of DN. Glycation or oxidation of plasma lipoproteins, especially low-density lipoproteins (LDLs) and increase in RAGEs that activate NADPH oxidase result in oxidative stress.<sup>[11]</sup> Also, the increased cholesterol typically seen in T2DM gets oxidized to oxysterols to cause neuronal apoptosis. Together these mechanisms lead to dysfunction in neurons, decreased nerve conduction and reduced nerve blood flow causing neuropathy.<sup>[16]</sup>

### Experimental Models of DN

In order to identify the mechanisms and to devise new treatments of DN, it is necessary to select the precise animal model. To increase the translational research potential, researchers must select a model of DN that mimics the major physiologic and metabolic conditions found in humans. The selected animal model of DN should exhibit the features present in human pathology and diabetic rats should show many abnormalities that are seen in diabetic patients with neuropathy, including hyperalgesia, allodynia, slow NCV and progressive sensory and sensory-motor deficit.

### Chemically-Mediated DN

Alloxan and streptozotocin are cytotoxic glucose analogues. They are the prominent diabetogenic chemicals which develops an insulin-dependent type I like diabetes syndrome and all the morphological features of beta cell destruction. Although their cytotoxicity is achieved via different pathways, their mechanisms of beta cell selective action are similar.<sup>[17]</sup>

#### Alloxan Induced Models

This model was developed in earlier 1960s. A number of scientists reported diabetic neuropathy mostly in alloxan-induced diabetic models, which was first reported by Preston in 1967,<sup>[18]</sup> then by Lovelace in 1968.<sup>[19]</sup> Alloxan (2,4,5,6-tetraoxypyrimidine; 2,4,5,6-pyrimidinetetrone) was originally prepared by the oxidation of uric acid by nitric acid. Alloxan has been regarded as a strong oxidizing agent that forms a hemiacetal with its reduced reaction product.<sup>[20]</sup> The drug has been noted to exert its diabetogenic action when administered intravenously, intraperitoneally or subcutaneously. The dose of alloxan required for inducing diabetes

depends on the animal species, route of administration and nutritional status.<sup>[21]</sup> Alloxan has been used to induce experimental diabetes due to the selective destruction of the insulin-producing pancreatic beta-islets. Alloxan induces a multiphasic blood glucose response when injected into an experimental animal, which is accompanied by corresponding inverse changes in the plasma insulin concentration followed by sequential ultrastructural beta cell changes ultimately leading to necrotic cell death.<sup>[22]</sup>

#### Streptozotocin Induced Models

A complete animal (rat) model of DN was first reported with reduced sizes of nerve fiber, axon and myelin sheath, which contributed to impaired motor function in streptozotocin (STZ)-induced diabetic rats by Jakobsen and Lundbeck in 1976.<sup>[23]</sup> STZ is a broad-spectrum antibiotic that is toxic to the insulin producing  $\beta$  cells of pancreatic islets. The method of STZ action in  $\beta$  cell depletion has been studied extensively over the years. It is generally assumed that STZ is taken up via the cell membrane GLUT2 glucose transporter and causes DNA alkylation and eventual  $\beta$  cell death.<sup>[17,23]</sup> Multiple methods of STZ dosing exist in the literature depending on the type and severity of diabetes intended for the specific experimental protocol and the dose can vary greatly between gender and strain.<sup>[24]</sup> STZ is most commonly delivered by one of two routes, intraperitoneal (IP) for quick and easy administration or intravenous (IV); also other methods including subcutaneous, intracardiac and intramuscular delivery have been used in rodents.<sup>[23,24]</sup>

Injections of alloxan or streptozotocin principally induce the same blood glucose and plasma insulin responses and cause an insulin-dependent type 1-like diabetes syndrome. All of the described morphological features of beta cell destruction are characteristic of necrotic cell death.<sup>[25]</sup> This mechanism is clearly at variance with that which underlies autoimmune type 1 diabetes, both in humans and rodent models of the disease, where beta cell demise is the result of apoptotic cell death without leakage of insulin from ruptured secretory granules.<sup>[24,25]</sup>

#### Genetic Models of DN

In genetic models the animals are inbred in laboratories for many generations and are selected based on developing persistent hyperglycemia. As a result of this process, many genes and phenotypes are enriched, but all may not be relevant to the pathophysiology of diabetes. Inbred animals have benefits when studying other features of diabetes, as genetic heterogeneity need not be considered as a confounding factor.<sup>[26]</sup>

##### Genetic Models of Type 1 Diabetes Mellitus

The non-obese diabetic (NOD) mouse and bio breeding (BB) rat are the two most commonly used animals that spontaneously develop diseases similar to human Type 1 diabetes. NOD mice develop diabetes as a consequence of a heritable polygenic immunodeficiency that resembles T1DM in humans which is mediated by CD4- and CD8-positive T cell autoimmune responses against pancreatic  $\beta$  cells.<sup>[27]</sup> The diabetes prone BB rats lack T lymphocytes expressing the RT6 alloantigen, which precipitates auto-immune attack of the pancreas.<sup>[28,29]</sup> They have complete insulin/C-peptide deficiencies and require daily insulin supplementation. The BB rat develops nerve conduction changes after 2 weeks of diabetes. These animals are expensive and very labor intensive to maintain.<sup>[29]</sup>

##### Genetic Models of type 2 Diabetes Mellitus

Genetic mutations in leptin (ob/ob mice) or its receptor (db/db mice) result in compromised leptin signaling and a diabetic metabolic profile brought on by hyperphagia and consequent obesity, hyperglycemia and hyperinsulinemia.<sup>[30]</sup> Zucker (*fa/fa*) and Zucker Diabetic Fatty (ZDF) rats exhibit leptin receptor deficiency, promoting hyperphagia. They are the models of impaired glucose tolerance. The ZDF also causes impaired pancreatic beta cell function.<sup>[31]</sup> Obesity and the resultant insulin resistance

are the major indicators of Type 2 diabetes mellitus in humans. Hence, the animal models of obesity are used to mimic the human condition. Some strains like ob/ob mouse and fa/fa rats maintain euglycaemia by mounting a robust and persistent compensatory-cell response, matching the insulin resistance with hyperinsulinaemia. Others like db/db mouse rapidly develop hyperglycemia as their cells are unable to maintain the high levels of insulin secretion required throughout life.<sup>[29,31]</sup>

#### Diet-induced DN

The streptozotocin and the alloxan models of chemically-induced diabetes are commonly used to screen anti-diabetic formulations. However, these methods cause marked destruction of the pancreatic cell mass and mimic changes closer to type 1 diabetes rather than type 2 diabetes mellitus. Even though genetic models are available for T2DM, those models are not cost effective and difficult to maintain over a period of time. T2DM is the most prevalent form of diabetes and accounts for approximately 95% of diabetic cases.<sup>[32]</sup> T2DM is the result of a combination of several factors, like heredity, food habits, physical activity and sedentary lifestyle. These factors result in insulin resistance and often present as Impaired Glucose Tolerance (IGT) and prediabetes before the onset of overt hyperglycemia and diabetes. Furthermore, T2DM is a component of the metabolic syndrome; therefore, features of the metabolic syndrome including obesity, cholesterol, high blood pressure and triglycerides, also contribute to DPN pathogenesis in T2DM. However, achieving these features with chemical and genetically mediated models of DN is difficult as they mainly help in development type1 diabetes. Hence, the diet induced models for T2DM are being developed and used in these days which mimic the major metabolic complications of T2DM.

Recently, it has been reported that rats fed with High Fat Diet (HFD) in combination with streptozotocin develop type 2 diabetes, which resemble more closely to humans.<sup>[33]</sup> HFD causes insulin resistance in peripheral tissues due to lipotoxicity, while low dose of streptozotocin induces mild defect in insulin secretion.<sup>[34]</sup> Therefore, combination of HFD with low dose streptozotocin model has therefore successfully mimicked natural progress of diabetes development as well as metabolic features in human type 2 diabetes. The final event occurring in the development of type 2 diabetes is  $\beta$ -cell failure/death similar like T1DM. Hence, the usage of the  $\beta$ -cell toxin STZ in these animal models suggests the late T2DM. Reports suggest that the HFD/STZ rat model could mimic the case of early type 1 diabetes coexisting with obesity. However, obesity in T1DM is more often seen in patients after their diagnosis, whereas obesity in type 2 diabetes is often seen decades before the diagnosis. Thus, the order of these pathological events, obesity followed by  $\beta$ -cell failure, seen in HFD/STZ rats mimics type 2 diabetes rather than type 1 diabetes, despite the observed similarity between early type 1 diabetes and late type 2 diabetes. Furthermore, the loss of  $\beta$ -cell mass in the pathogenesis of type 1 diabetes occurs mainly as a result of an autoimmune reaction,<sup>[35]</sup> which is not the case in HFD/STZ rats. However to develop a diet model of type 2 diabetic neuropathy, the coexisting factors like lipotoxicity and/or glucolipotoxicity, insulin resistance, hyperinsulinemia, low-level inflammation should be developed in the animals. Even though hyperglycemia induces changes in different pathways causing oxidative stress and finally leads to neuropathy, dyslipidemia plays a major role in the development of oxidative stress and neuropathy. Studies report that dyslipidemia is associated with the onset and progression of neuropathy in both type 1 and type 2 diabetes.<sup>[36,37]</sup> Results from a cross-sectional study of type 2 diabetic subjects revealed that the prevalence of DN was two-fold higher in type 2 diabetic subjects with the metabolic syndrome, a condition characterized by dyslipidemia, obesity and hyperglycemia.<sup>[38]</sup> As the hyperglycemia or dyslipidemia alone cannot cause the changes that are leading to type 2 DN, these high fat diet induced models with low levels of streptozotocin may serve as

the best models to achieve this DN in animals as the lipotoxicity and glucotoxicity together develops type 2 DN. However, for the study of type 2 DN, several investigators have used high fat and high fructose diet along with streptozotocin and high sugar

diet with streptozotocin.<sup>[39,40]</sup> Combinations of carbohydrate and fat-rich dietary components have been used in rodents to mimic the signs and symptoms of human metabolic syndrome. Some of the diet

**Table 1: Criteria of some selective diet induced animal models of diabetic neuropathy.**

Animals Used	Diet Model	References	Diet and Dosage	Characterization of diabetic neuropathy
Sprague Dawley rats	High fat-high sugar diet with low levels of Streptozotocin	Jiang-Kun Dang <i>et al.</i> <sup>[39]</sup>	High fat-high sugar diet: 67% normal diet plus 10% lard, 20% sucrose, 2% cholesterol and 1% sodium Cholate for 8 weeks Streptozotocin dose: 35/kgBW	1. Decreased pain threshold 2. Decreased mechanical withdrawal threshold
Wistar rats	High-fat/highfructose diet and low-dose streptozotocin	David André <i>et al.</i> <sup>[40]</sup>	High fat-high fructose diet 46.5 wt% fructose and 25.7 wt% lard for 56 weeks Streptozotocin dose: 25/kgBW	1. Tactile allodynia 2. Decrease paw with-draw threshold 3. Glucose metabolic alteration within the limbic system as well as cingulate and frontal cortices 4. Glucose consumption decreases in the hippocampal formation
C57BL6/J mice	High fat diet	Irina G. Obrosova <i>et al.</i> <sup>[41]</sup>	High fat diet: D12330, 58 kcal% fat with corn starch; (Research diets, New Brunswick, NJ) for 16 weeks	1. large motor fiber neuropathy (manifested by MNCV), 2. large sensory fiber neuropathy (manifested by SNCV), 3. small sensory fiber neuropathy (thermal hypoalgesia and tactile allodynia), 4. some metabolic changes in the peripheral nerve (12/15-lipoxygenase overexpression)
C57Bl/6 mice	High fat diet and Streptozotocin	B. L. Guilford <i>et al.</i> <sup>[42]</sup>	High-fat diet:07011; Harlan Teklad; 54% kcals from fat comprised of lard and corn oil, 21% protein and 24% carbohydrate Streptozotocin dose: 180/kgBW in 10mM sodium citrate buffer	1. Painful neuropathy (mechanical allodynia) 2. modified DN phenotype and/or increase risk for developing DN
Wistar rats	Streptozotocin followed by high fat and high fructose diet	Jayshree Shriram Dawane <i>et al.</i> <sup>[43]</sup>	Streptozotocin dose: 35/kgBW in 10mM sodium citrate buffer High Fat-high fructose Diet: Vanaspati Ghee and Coconut oil inproportion of 2:3 and 10% fructose for drinking for 12 weeks	1. Hyperalgesia 2. The diameter of nerve fibres in cross-section was markedly reduced suggesting the shrinkage of nerve fibres 3. Marked axon atrophy and myelin vacuolization
C57Bl/6J mice	High fat diet followed by streptozotocin	Matthew S. Yorek <i>et al.</i> <sup>[44]</sup>	High fat for 8 weeks: 60% Kcal% high fat (D12492; Research Diets, New Brunswick, NJ) streptozotocin 75 mg/kg followed three days later with a second dose of streptozotocin (50 mg/kg).	1. Intraepidermal nerve fiber density was significantly decreased in skin from the hindpaw 2. Serum and dorsal root ganglion neuron nitrotyrosine levels were increased 3. Corneal nerve density decreased

induced models of type 2 DN along with the dosage and characterization of neuropathy are listed out below for better understanding (Table 1).

## CONCLUSION

In conclusion, diet induced models are beneficiary over chemical mediated and genetically mediated models, as the chemical mediation causes development of type 1 diabetes, whereas the genetically mediated models are not cost effective and difficult to breed and maintain over a period of time. The HFD combined with low doses of streptozotocin is the most accepted model of diet induced neuropathy, which successfully mimics natural progress of diabetes development as well as metabolic features in human type 2 diabetes as HFD causes obesity and insulin resistance in peripheral tissues due to lipotoxicity, while low dose of streptozotocin induces mild defect in insulin secretion.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

NCV: Nerve Conduction Velocity; AGEs: Advanced Glycation End Products; PKC: Protein Kinase C; HFD: High Fat Diet.

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