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# REVIEW ON ANIMAL MODELS OF DIABETIC NEPHROPATHY

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## ABSTRACT

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD), which is associated with increased morbidity and death. Moreover, in affluent countries, the prevalence of DN is steadily rising. Many rodent models of type 1 and type 2 diabetes have been developed in order to better understand the pathophysiology of diabetes and test new treatments for DN. Chemical, surgical, genetic, pharmacological, and diet/nutrition interventions, as well as a combination of two or more methods, are used to create these models. An animal model of DN should show the basic hallmarks of DN, such as a loss in renal function, albuminuria and mesangiolysis, mesangial enlargement, and nodular glomerulosclerosis. However, a rodent model of human DN with all of the aforementioned characteristics has yet to be developed. Furthermore, in terms of albuminuria and the development of glomerular and tubulointerstitial lesions, mice of various genetic backgrounds and strains demonstrate varying levels of vulnerability to DN. As a result, the type of diabetes, the progression of nephropathy, the length of the study, the expense of maintaining and breeding, and the death rate of the animals are all key elements that could be influenced by the DN model. The advantages and disadvantages of various diabetes rodent models used to research DN are discussed in this review.

**Keywords: Diabetes, Nephropathy, rodent model, albuminuria, mesangial matrix expansion, tubulointerstitial fibrosis**

## INTRODUCTION

Diabetes mellitus has become more common in recent years all across the world. Diabetes produces vascular alterations and malfunction, and diabetes complications are the leading cause of morbidity and mortality in diabetic patients **[1]**. Diabetic nephropathy is the most common vascular consequence of diabetes, affecting 40% of patients and still the primary cause of end-stage renal disease (ESRD) globally. Diabetic nephropathy requires multifactorial management, which includes nutrition therapy and glycemic, blood pressure (BP), and lipid control. Despite receiving sufficient multimodal treatment, some individuals with severe diabetic nephropathy rapidly proceed to ESRD. As a result, a new and more effective treatment for diabetic nephropathy must be created **[2, 3]**.

Diabetic nephropathy is a clinical condition in humans that includes albuminuria, a progressive deterioration in renal function, and a higher risk of cardiovascular disease. Albuminuria is the most common biomarker for the diagnosis of diabetic nephropathy, and it's also used to stage the disease **[4]**. Glomerular hypertrophy, a thickening of the glomerular basement membrane, and mesangial matrix enlargement, including the formation of glomerular nodular lesions known as Kimmelstiel-Wilson nodules, are histological hallmarks of diabetic nephropathy in humans. Tubulointerstitial lesions, in addition to glomerular lesions, play a substantial role in the loss in renal function in human diabetic nephropathy. Both glomerulosclerosis and tubulointerstitial fibrosis are associated to decline in renal function. The severity of tubulointerstitial fibrosis, rather than the number of glomerular lesions, is thought to be the most important predictor of progressive renal failure **[4, 5]**. As a result, an animal model of diabetic nephropathy should show this renal histology characteristic in the glomeruli and tubulointerstitial area, which is related to increased albuminuria and a reduction in renal function.

There is apparently no rodent model that develops all of the symptoms of human diabetic nephropathy. The existing diabetic rodent models can be beneficial in the research of diabetic nephropathy if we deepen our understanding of the peculiarities of each diabetic rodent model. This review discusses Type 1 and Type 2 diabetic rodent models for the investigation of diabetic nephropathy.

## ANIMAL MODELS

### RODENT MODELS OF TYPE 1 DIABETES

#### Chemical Models of Type 1 Diabetic Nephropathy (T1DN)

T1DM and, as a result, DN are routinely induced with alloxan and streptozotocin (STZ). The GLUT 2 transporter transports these molecules, which are structurally identical to glucose, into pancreatic -cells, but they are not accepted by other glucose transporters. Because -cells express very large levels of GLUT2, this explains why alloxan and STZ are relatively toxic to them. Alloxan and STZ's diabetogenic effects are mediated by the formation of reactive oxygen species (ROS), which leads to pancreatic -cell necrosis. Hyperglycemia leads to diabetic kidney impairment as time goes on **[6]**.

**STZ-induced diabetic rats**

Diabetic nephropathy has also been studied using STZ-induced diabetic rats. A single intravenous dose of STZ (50–55 mg/kg body weight) causes diabetes in male Sprague-Dawley (S-D) or other rats weighing 170–200 g **[7, 8]**. Urinary albumin excretion in STZ-induced diabetic S-D rats (12 ± 1.3 mg/day) was higher than in control rats (1.0 ± 0.5 mg/day) 24 weeks after diabetes induction, according to Mima *et al* **[9]**. In diabetic rats, creatinine clearance (Ccr) increased from 8.3 ± 0.2 mL/day/100 g body wt to 26.9 mL/day/100 g body wt, compared to 8.3 ± 0.2 mL/day/100 g body wt in control rats. The STZ-induced diabetic rat's blood pressures were not significantly different from the control rats, and the STZ-induced diabetic rats did not develop hypertension. In comparison to the control rats, diabetic rats had higher levels of mesangial matrix proteins, mesangial matrix fraction, and type 4 collagen accumulation. There was no evidence of severe mesangial matrix accumulation, glomerular nodular lesions, severe tubular cell destruction, or tubulointerstitial fibrosis. Additionally, diabetic rats' kidneys showed signs of oxidative stress and inflammation **[8]**. As a consequence, STZ-induced diabetic rats could be advantageous as a model for early diabetic nephropathy alterations. The morphological changes in this rat model's kidneys caused by hyperglycemia were less significant than those reported in STZ-induced diabetic mice.

**Alloxan-Induced DN**

During redox cycle processes, dialuric acid and alloxan (alloxan's reduced product) produce superoxide radicals. The Fenton reaction is responsible for the generation of free radicals like hydrogen peroxide and hydroxyl radicals and which results in the injury of pancreatic tissues seen in rodents **[9]**. Intravenously, intraperitoneally, or subcutaneously is how alloxan is given **[10]**. The induction of diabetes in rats, are generally with an initial dose of 65 mg/kg which is the most often recommended dose. When compared to the intravenous dose, 2-3 times higher doses (>150 mg/kg b.w.) ought to be considered

if alloxan is given intraperitoneally or subcutaneously **[11]**. Because alloxan has a structure that is comparable to glucose, fasting animals are more vulnerable to alloxan. STZ is more widely used for diabetes induction than Alloxan because of its lesser efficacy **[12]**. Diabetic nephropathy develops 3-4 weeks after alloxan administration **[13]**.

## GENETIC MODELS OF TYPE 1 DIABETIC NEPHROPATHY (T1DN)

### Akita mice

Akita mice are a transgenic species that is prone to type 1 diabetes due to abnormalities in the insulin genes, which result in the build-up of misfolded insulin protein in pancreatic -cells, resulting in decreased insulin secretion capability and type 1 diabetes **[14, 15]**. Albuminuria tends to grow at this period and is greatly increased after 10 weeks of age, with glucose levels significantly higher at 4 weeks of age. The intensity of nephrotoxicity in Akita mice is regulated by their genetic history, which is an important feature of DN progression. In C57BL/6, DBA/2, and 129/SvEv strains, DN was detected after the Akita mutation was induced. The strains 129/SvEv and DBA/2 are more prone to nephropathy **[16, 17, 18]**. When compared to mice with diabetes caused by STZ, the Akita mice exhibit more significant and sustained hyperglycemia **[19]**.

### OVE26 Mice

OVE26 mice are mutant mice that have calmodulin overabundance in pancreatic cells, insulin inadequacy, and type 1 diabetes. The OVE26 mice acquire diabetes within a week of life and can go without insulin for over a year. OVE26 mice had acquired significant albuminuria by the eighth week of life **[20]**. On the FVB background, calmodulin overexpression produces mesangial matrix growth, global glomerulonephritis, diminished podocyte number, renal fibrosis, and a >ten - fold elevation in albuminuria by 6 months of age **[20, 21, 22]**. As a consequence, the necessity for such alterations to be replicated in the FVB mouse breed in order to establish the required DN features is a basic limitation of these mouse models.

### Nonobese Diabetic Mouse

The nonobese diabetic (NOD) mouse has been the most extensively studied genetic model of type 1 diabetes in mice **[23]**. At around 5 months of age, these animals suffer spontaneous autoimmune cell damage, albeit the exact age of development of diabetes is slightly varied. Furthermore, insulin is required to keep NOD species alive for every length of time after hyperglycemia develops, indicating a more acute insulin deficit than in STZ mice. Furthermore, unlike male mice with increased vulnerability to STZ diabetes, the NOD line has a female predominance with

a male:female ratio of roughly 1:4. The hallmarks of autoimmune disease that results in cell death in NOD mice were widely explored, and the animal resembles human type 1 diabetes in many ways **[13, 24, 25]**.

**TYPE 2 MODELS OF DIABETIC NEPHROPATHY (T2DN)**

Insulin levels in T2D could be elevated, average, or low, unlike T1D. High blood pressure, dyslipidemia, adiposity, insulin resistance, and hyperglycaemia, are all risk factors for heart disease (CVD1).The metabolic syndrome, commonly known as syndrome X, is made up of these diseases **[26]**.

**GENETIC MODELS OF TYPE 2 DIABETIC NEPHROPATHY**

**Otsuka Long-Evans Tokushima Fatty Rats (OLETF)**

OLETF rats are a type 2 or non-insulin dependent diabetes mellitus (NIDDM) animal model characterized by CCK-A receptor dysfunction, hyperphagia, increased meal size, modest obesity, late-onset insulin resistance, NIDDM, and DN at roughly 30 weeks of age **[27]**.

**The Zucker diabetic fatty rats (ZDF)**

The Zucker diabetic fatty rats (ZDF) were created by crossing obese Zucker fa/fa rats with Wistar Kyoto rats, both of which have leptin-receptor mutations and insulin resistance. Obesity, insulin resistance, hyperglycemia, dyslipidemia, hypertension, and nephropathy are all linked to leptin receptor mutations in ZDF. Because of the reduction of -cell mass, these rats develop diabetes. Gluco/lipotoxicity may be to blame for the failure of -cell mass expansion **[28]**. Male ZDF rats had mildly higher albuminuria at 6 weeks of age, indicating that this animal model, which has impaired glucose tolerance and insulin production, develops overt diabetes as early as 8 weeks of age. ZDF rats acquire DN at 16 weeks of age, with considerable glomerulosclerosis and proteinuria, and major albuminuria at 10 weeks of age **[29]**.

**The Goto Kakizaki (GK) rats**

The nonobese, normotensive, spontaneous, and moderate NIDDM type II Goto Kakizaki (GK) rats are used as a model **[29]**. Goto and colleagues at Tohoku University in Sendai developed the GK rats by selecting breeding couples with the highest blood glucose levels from a population of Wistar rats over many decades using a glucose tolerance test (OGTT) **[30]**. In GK rats, glucose metabolism, insulin secretion, and insulin resistance are all compromised. At 3-4 weeks of age, GK rats exhibit moderate hyperglycemia and hyperinsulinemia **[31]**. GK rats show capillary enlargement and thickening of the renal tubular basement membranes, but they are less prone to DN and do not develop increasing proteinuria, glomerulosclerosis, or interstitial fibrosis.

By the age of 12-13 weeks, a substrain of GK rats has been established by crossing GK and Fawn Hooded-hypertensive (FHH) rats, which develops overt diabetes and progressive proteinuria **[29]**.

**Ob/ob mice**

Ob/ob mice are leptin deficient, although their leptin signalling pathways are unaffected. C57BL/6, C57BLKS/J, FVB/N, and DBA2 strains have mutations **[32, 33]**. In C57BLKS/J, the Ob/ob mutation induces cell atrophy and severe hyperglycemia. Obesity and mild hyperglycemia develop in Ob/ob C57BL/6 mice, but not the kidney abnormalities associated with human diabetes **[34]**. By 6-10 weeks of age, Ob/ob BTBR mice had chronic hyperglycemia **[35]**. In contrast to ob/ob C57BL/6J mice, ob/ob BTBR animals have several human DN pathogenic features **[36]**. BTBR ob/ob mice, unlike the majority of people with DN, do not develop hypertension and are somewhat hypotensive. However, by 8 weeks of age, podocyte disintegration and the onset of proteinuria can be seen **[36]**. Renal disease in the ob/ob mice is characterised by widespread and nodular lipohyaline alterations in the glomerulus Using BTBR ob/ob mice as a DN model has several benefits, including the rapid development of DN and the emergence of some pathological hallmarks of human DN. This model's shortcomings include difficult breeding and significant mortality rates after 24 weeks of age, which limit its use in the evaluation of advanced nephropathy **[37]**.

**db/db mice model**

Obesity is developed in the db/db mice model due to spontaneous or genetically induced mutations in the leptin receptor gene that result in a faulty leptin-signaling pathway in the hypothalamus. db/db mice develop hyperphagia, early-onset obesity, hyperglycemia, dyslipidemia, insulin resistance, hypertension, and nephropathy, as well as being infertile and lacking in growth hormone, similar to ZDF rats. The C57BLKS/J strain, as well as C57BL/6, C57BLKS, DBA, FVB, and CBA strains, were found to have the first-ever db mutation. db/db and ob/ob mice with a C57BL/6J background had less severe hyperglycemia, whereas C57BLKS animals acquire fulminant diabetes after 24 weeks **[38, 39]**. db/db mice, like ob/ob mice, are insulin-resistant and develop fat and diabetes, but unlike ob/ob mice, they are leptin-resistant. Despite the fact that the db/db mice have a defective leptin receptor, their leptin levels are significantly high, these mice are morbidly obese. In comparison to ob/ob mice, the db/db mouse develops considerable DN **[40]**. This could be owing to their distinct backgrounds or the ob/ob mice's absence of circulating leptin, which has been shown to directly drive matrix synthesis. By 25 weeks of age,

DN in these mice is reflected by mesangial matrix growth, which includes increases in extracellular matrix proteins such fibronectin, type IV collagen, and laminin **[41]**.

At around 6 months after diabetes induction, tubular atrophy, dilatation, apoptosis, and early interstitial fibrosis reflected by an increase in interstitial volume are visible **[41, 42, 43]**. In general, nodular mesangial sclerosis or progressive renal failure does not develop in db/db mice. As a result, these mice are a decent model of diabetes and the early stages of DN in humans, but they lack advanced DN traits. Furthermore, this model fails to display advanced DN characteristics and necessitates lengthier DN creation times.

**The New Zealand obese (NZO) mouse**

Diabetes is inherited polygenetically in the New Zealand obese (NZO) mouse strain. Obesity, hyperinsulinemia, hyperglycemia, glucose intolerance, and insulin resistance are all present in NZO mice, making them a good model for researching insulin-resistant diabetes **[44]**. At 24 weeks of age, GBM thickness and diffuse and nodular growth of the mesangial matrix in NZO mice show increasing renal pathological characteristics **[45]**.

## CHEMICAL MODELS OF TYPE 2 DIABETIC NEPHROPATHY (T2DN)

**Induction of DN Using STZ and Nicotinamide**

This model combines STZ with nicotinamide (NA), a niacin (B3) derivative that protects -cells from the toxic effects of STZ by scavenging free oxygen radicals, restoring NAD+, inducing NO production, inhibiting PARP and cytokine-induced MHC class II expression, regeneration of -cells, and inhibiting islet cell apoptosis. This model causes nonfasting hyperglycemia with a 40-60% reduction in -cells and insulin production, but neither insulin resistance or glucose intolerance **[46]**. This model was created using various doses of STZ (45 to 65 mg/kg) and NA (60 to 290 mg/kg). Importantly, 15 minutes before STZ, NA must be administered **[57]**. Given that STZ causes direct renal damage, it's difficult to tell if renal impairment is caused by STZ or by a diabetes-related consequence. The former idea is reinforced by studies demonstrating that NA can prevent renal failure, casting doubt on the model's usefulness for researching DN **[48]**. As early as 8 weeks of life, proteinuria can be identified **[40, 50]**.

**STZ Diabetic Rat**

Adult rats were given a single high dose of STZ, which resulted in the development of type 1 diabetes, whereas neonatal rats (2-5 days old) were given a single low dose of STZ, which resulted in the development of type 2 diabetes in adult rats. Between the ages of 12 and 20 weeks, albuminuria was observed in rats **[51, 52]**.

**INDUCTION OF TYPE 2 DIABETIC NEPHROPATHY (T2DN) BY MODIFICATION OF THE DIET**

**Fructose-Fed Rats**

As an insulin-resistant and hypertensive model, these rats display the characteristics of metabolic syndrome. Intracellular glucose is converted to sorbitol by aldose reductase, and afterwards sorbitol is oxidised to produce fructose by sorbitol dehydrogenase through the polyol pathway. Fructose levels in the kidney and other organs of STZ-induced diabetic rats rise whenever the polyol pathway is triggered. The accumulation of fructose may be a trigger for diabetes problems, and these consequences may be mitigated by inhibiting sorbitol dehydrogenase and blocking fructose synthesis. Fructose is given in two forms: as a 10% or 20% W/V solution in drinking water, or as a 60% fructose diet **[53, 54]**. High-fructose diets cause hypertension through generating inflammation, which is thought to be the cause. Experiments revealed that rats fed high fructose had higher hydrogen peroxide (a free radical) and insulin levels in their blood. Fructose-induced metabolic syndrome is related with renal abnormalities such as arteriolopathy, renal hypertrophy, and glomerular hypertension after 6-8 weeks of therapy **[55]**.

**High-Fat Diet-Induced Type 2 Diabetic Mice**

People with metabolic syndrome have a greater risk of having chronic renal damage, according to several studies **[56, 57]**. When the animals have been served a high-fat diet, they exhibited systemic alterations akin to the human metabolic syndrome, as well as kidney impairment in various kinds **[58]**. These have been noted that feeding C57BL/6 mice a 60% fat diet for 12 weeks causes metabolic syndrome (obesity, hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and hypertension), as well as kidney injuries such as albuminuria, increased glomerular tuft area, increased type IV collagen accumulation in glomeruli, mesangial expansion, and impaired sodium handling **[59]**. Overall, genetic background can influence the likelihood of developing metabolic syndrome after an HFD diet. For example, some strains of mice, such as C3H/He, A/J, and 129Sv mice, are resistant to obesity and diabetes, whereas C57BL/6 mice are susceptible to obesity and insulin resistance. Furthermore, the source and composition of fat have an impact on the progression of renal damage **[59]**. As a result, before using the HFD as a DN model, the following considerations must be considered.

**INDUCTION OF (T2DN) BY ADMINISTRATION OF CHEMICALS +MODIFICATION OF THE DIET**

**High-Fat Diet+Low Dose of STZ**

A high-fat diet is not commonly used for DN induction since the animals seldom develop overt hyperglycemia due to compensatory hyperinsulinemia; nonetheless, this strategy is useful for studying the underlying mechanisms of insulin resistance **[60]**. According to Buettner *et al* ., the best way to get animals to gain weight is to offer them semi-purified high-fat diets with more than 40% of calories coming from animal fats, supplemented with a low quantity of n-3 fatty acids and a low amount of plant oils rich in n-6 and n-9 fatty acids **[64]**.

A high-fat diet seems to have a fat composition of 49.5 percent (g/100 g total dry diet), providing for 72 percent of total energy. To create insulin resistance and decrease insulin plasma concentrations, as well as human diabetes, a modest dosage of STZ (35 mg/kg) that causes early -cell dysfunction is administered **[61, 62, 63]**. After a 2-4 week dietary intervention, rats are injected with a low dosage of STZ. 4 weeks after STZ injection, renal damage can be evident, notably elevated albuminuria, kidney index, and histological changes **[64]**.

**INDUCTION OF (T2DN) BY ADMINISTRATION OF CHEMICALS, SURGICAL INTERVENTIONS, AND MODIFICATION OF THE DIET**

**Low Dose STZ+High-Fat Diet+Nephrectomy**

Conducting a nephrectomy following a low-dose STZ injection produces modest glucose intolerance in rats, according to Sugano *et al*. Furthermore, when these rats are fed a high-fat diet, they produce a rat model that is similar to the DN seen in people with type 2 diabetes. Microalbuminuria appears 15 weeks after STZ injection, followed by HFD feeding and mesangial matrix growth, overt proteinuria, , and interstitial edoema by 20 weeks **[65]**. The proportion of nephrectomy, the STZ dosage (25-40 mg/kg), and the quantity of fat in the diet (40-58%), are all variables **[66, 67, 68]**.

**Monogenic Manipulations of eNOS Deficiency**

The activity of eNOS in the blood arteries is affected by diabetes. NO production increases in early diabetic stages, while renal eNOS production decreases as diabetes advances, according to research. Researchers used eNOS knockout (eNOS/) mice to examine if an eNOS deficiency led in a mouse model of DN. Different types of diabetic models with low eNOS activity were created. Type 1 DN models include STZ-induced diabetic B6-eNOS-/- mice (low dose and high dose) and B6-eNOS/Ins2Akita/+ mice **[69, 70]**. In comparison to eNOS/ mice, diabetic eNOS/ mice had a 10-fold increase in diabetic albuminuria following low-dose STZ treatment and a 40-fold increase after high-

dose STZ administration. In eNOS/Ins2Akita/+ diabetic mice, the strain has an effect on DN development. Because B6-eNOS/Ins2Akita/+ mice die soon after weaning, they are unable to develop DN. B6- eNOS+/+Ins2Akita/+ mice of the first generation (F1), on the other hand, live as long as diabetic B6- eNOS+/+Ins2Akita/+ mice and develop DN **[71]**.

**CONCLUSION**

In summary, animal models have certain limitations in terms of contributing to our understanding of the pathogenesis of DN because no model encompasses all of the characteristic features of human DN. OVE26 mice, ob/ob mice, OLETF rats and eNOS/db/db mice appear to be the most resilient models for developing structurally advanced DN. In terms of albuminuria and the development of different genetic backgrounds, morphological abnormalities, and strains demonstrate varying levels of vulnerability to DN. As a conclusion, the kind of diabetes, nephropathy development technique, cost of maintaining and breeding, study period, and animal death rate are all critical factors that might be influenced by the type of DN model. Moreover, evaluating if renal function deteriorates in any of these DN models will be extremely beneficial.

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