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Review Article

ANIMAL MODELS OF DIABETIC NEPHROPATHY

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ABSTRACT

Diabetic nephropathy (DN) is the most common complication of diabetes mellitus (DM). It is characterized by high blood glucose levels or hyperglycemia and is accompanied by changes in lipid, carbohydrate, and protein metabolism which can lead to an increased risk of complications due to vascular disease. DN is probably the most insidious among these complications, causing substantial morbidity and mortality. In this article, we will review the literature on animal models of diabetes. We will discuss several species as animal models for Type 1 and 2 diabetes, including zebrafish, rabbits, mice, rats, and rat models. This article also provides various methods used in research with model animals and presents the required result for studying diabetic DN.

Keywords: Animal model, Diabetes Mellitus, Nephropathy, Rat, Mice.

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INTRODUCTION

Diabetes is a disease metabolism marked chronic with enhancement rate of glucose blood and causes damage serious on the heart, blood vessels, eyes, kidneys, and nerves [1]. About 422 million adults lived with diabetes in 2014 compared with 108 million adults in 1980 [2]. The most common complication of diabetes mellitus (DM) is dyslipidemia, that is, enhancement of total cholesterol, the density of lipoprotein cholesterol low, and levels of triglycerides as well concentration of low-density lipoprotein cholesterol high-density lipoprotein in plasma. Compared to normal mice, streptozotocin (STZ) induction in animal tests will cause damage or atrophy and a decline in the size of big Langerhans Island [3].

DM incidence has steadily increased. As a major public health problem, its insulin ineffectiveness in DM patients causes metabolic disorders characterized by high blood glucose levels or hyperglycemia. It is accompanied by changes in lipid, carbohydrate, and protein metabolism which can lead to an increased risk of complications due to vascular disease. Global research reports state that DM is a non-communicable disease based on the number of cases and its prevalence has continued to increase over the last few decades [2,4].

The increasing incidence of DM worldwide is accompanied by a concomitant increase in diabetes complications, including retinopathy, neuropathy, and nephropathy [5].

Among these complications, diabetic nephropathy (DN) is probably the most insidious, causing substantial morbidity and mortality. DN is now a leading cause of end-stage renal disease (ESRD) in developed countries.

Despite decades of research and DN's huge public health burden, several unmet needs remain. The molecular pathogenesis is poorly understood, and no new drugs have been approved for the treatment of DN in almost 20 years. Only a subset of the diabetic population has DN, indicating a strong family contribution to this risk. Nonetheless, identifying the genetic variants controlling DN susceptibility in humans is difficult.

One important consideration that must be considered is how the disease is induced in the experimental model. The best model should reflect the pathophysiological pathways involved in developing and progressing DN in humans. Therefore, the main underlying processes leading to DN must be considered when evaluating the most suitable specific model, even though the mechanisms underlying the development of DN are not yet fully clear.

With this in mind, we will review the literature on animal models of DN. Naturally, a selection from the thousands of published studies must be made, and often we will limit ourselves to the most recent reviews. Per species animal, we will discuss the most important models for Type 1 and Type 2.

Researchers have recently used a similar technique of transcriptomics and peptidomics to determine which animal model best replicates the pathophysiology of man disease.

Implications from the-omics study, the researchers must consider several problems in choosing an animal model best for investigation. First, they must be clear about the stage of DN relevant to the human beings wanted they imitate, with animal models reflecting standards and the pathophysiology of DN early but not too late. Injury stimulus-relevant additions, for example, hypertension, may be needed for model progressive disease. Second, they can use transcriptomic data to choose the best model to recapitulate the therapeutic target pathway's activation status. More selection and rationale from the most appropriate animal model can make the study more efficient and improve the possibility that the result will translate into clinical practice [6].

This article will discuss several species as animal models for Type 1 and 2 diabetes, as shown in Fig. 1.

ANIMAL MODEL OF DN

Zebrafish

The zebrafish (*Danio rerio*) is the most studied fish species. The complete genome is known, and the structure of the kidney is simple, formed by a median line glomerulus fused with an ultrastructure indistinguishable from that of mammals, followed by a single nephron consisting of proximal and distal portions adjacent to each of the two cardinal veins while retains the biological complexity inherent in the kidneys of higher organisms.

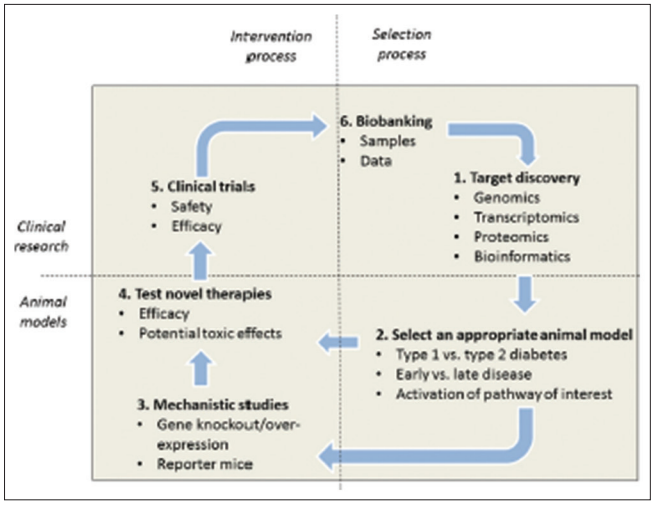

Fig. 1: Schematic of the discovery of new therapeutic agents. (1) A highly unbiased, highly "-omics" approach has identified hundreds of molecules associated with the development of human DN. (2) Whether these molecules can be targeted to slow the progression of nephropathy can be determined using the most appropriate animal model for a particular research question. (3) Genetically modified mice can offer mechanistic insights and suggest whether therapy development is warranted. (4) pharmaceutical agents can be tested for efficacy and potential side effects. (5) Therapies that work in robust animal studies can be taken to clinical trials. (6) Samples and data from these trials can be "biologically stored" to provide further mechanistic insight into distillation therapy [6]

In the diabetes field, zebrafish has been used to study glucose homeostasis and glucose regulation (hyperglycemia). Diabetes complications include diabetic retinopathy and fatty liver disease.

There is also a zebrafish model of DM and metabolic memory. These studies suggest that for a mechanistic understanding of the cellular and genetic events involved in DN, zebrafish may hold potential for future studies.

Fruit fly

Genetic ablation of insulin-producing cells located in the fruit fly (*Drosophila melanogaster*) brain can induce Type 1 diabetes (T1D) [7]. Increasing fruit fly larvae on a high-sugar diet induces obesity, insulin resistance in developing flies, and many aspects of Type 2 diabetes (T2D). Regarding DN, this model is very useful for the effect of Type 2 DM on podocytes, which reflects the typical loss of Nephrin ortholog Sns. Analogous changes in the pathways that regulate Sns expression are documented in ob/ob mice and patients with Type 2 DM. Indeed, saving Sns even prolongs flight life. Diabetic cardiomyopathy has been extensively studied in diabetic flies. However, other than the Sns (nephrin) pathway, DN remains to be explored in flies with DM. In fruit flies, models of Type 1 DM and Type 2 DM were recently reviewed.

Rodents

The rodent is the most common species used in study preclinical and, therefore most common animal used in diabetes studies [8]. Typically, rodents are used as animal models for diabetic kidney disease. Because strains' genetic makeup influences the susceptibility of strains to nephropathy, most models show varying degrees of resistance to the development of DN. Various rodent strains have been created to create a model that accurately mimics the properties of human DN.

DN is still the most common cause of ESRD. Developing new therapies is challenging because the underlying mechanisms are not fully understood. Rodent models can be used to gain insights into the sequential/temporal processes involved in disease onset, development, and progression, which can drive the development of targets and (pharmaceutical) interventions. However, this is hampered by the lack of reliable preclinical models. Using rodent models has the advantage of knowing the genetic blueprint, and driving genetic modifications such as knockout or overexpression is relatively easy.

In addition, rats reproduce quickly, and housing is relatively cheap. The usefulness of animal models in DN has been limited because most models fail to recapitulate important functional, structural, and pathological features of advanced human DN or only reach a mild stage of the disease. We will discuss some of the most commonly used T1D and T2D mouse models and evaluate their usefulness.

The nephropathy subcommittee of the Animal Model Diabetic Complications Consortium (AMDCC) has published the following validation criteria for a rat model of DN based on the clinical and pathological features of human DN: (1) >50% reduction in kidney function, (2) >10-fold increase in albuminuria, and (3) pathological features, including advanced mesangial matrix expansion (±nodules), thickening of the glomerular basement membrane (GBM), arteriolar hyalinosis, and tubulointerstitial fibrosis.

Diabetic kidney disease (also called "chronic kidney disease [CKD]" due to diabetes or DN) is defined in Type 1 and T2D as the presence of a severe increase in albuminuria >300 mg/24 h (or >200 µg/min), or albumin-to-creatinine ratio (ACR) >300 mg/g, confirmed in at least two of three samples. The broader term "kidney disease in diabetes" is used for patients with CKD (impaired kidney function: estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or proteinuria) regardless of background. Although impaired renal function with normal albuminuria (ACR <30 mg/g) is prevalent, especially in older adults, it is much less likely to develop without albuminuria.

The evolution of DN is one of many physiological and pathological processes influenced by a significant biological factor known as gender. Recent studies have shown that sex hormones and chromosomes can significantly change the biology of various organs in the body, including neurons and kidney cells. Acute or chronic renal ischemia, heart disease, hypertension, obesity, and other disorders are markedly marked by differences between the sexes in incidence, age of onset, manifestation, severity, and development. There have been reports of sex differences in renal structure or function and the prevalence and development of several renal disorders, including DN. Therefore, gender is an important aspect of research rigor and reproducibility, an issue emphasized by the National Institutes of Health recently.

In the mouse model certain of DN, gender variation in the onset of DM and its consequences accompanying kidney has been noted. For example, Gurley *et al*. disclose that mouse males show hyperglycemia and more kidney-critical damage than females in various mouse strains with streptozotocin-induced DN. Limited using a mouse model, this, since the description originally in 2006, may be caused by technique consuming breeding time used to produce many animal mutations. From various studies have been reported that possible to check DN using derived double-knockout mice from breeding on both types of sex without worrying about implication type sex on reproducibility investigation.

Screening

Frequent screening performed by people with diabetes is recommended to detect albuminuria levels and abnormal kidney function or change (i.e., EGFR), so treatment for renoprotective early can be started. Collection of morning urine day is enough for screening and monitoring and convenience for the patient. Two of three samples of spot urine in 3–6 months must be lifted to confirm the diagnosis. Collection of 24-h urine has been considered standard gold for albuminuria assessment. It can give important information addition about sodium and protein intake. However, collection complete often difficult for patients, so this method is usually limited to those who have diabetic kidney disease

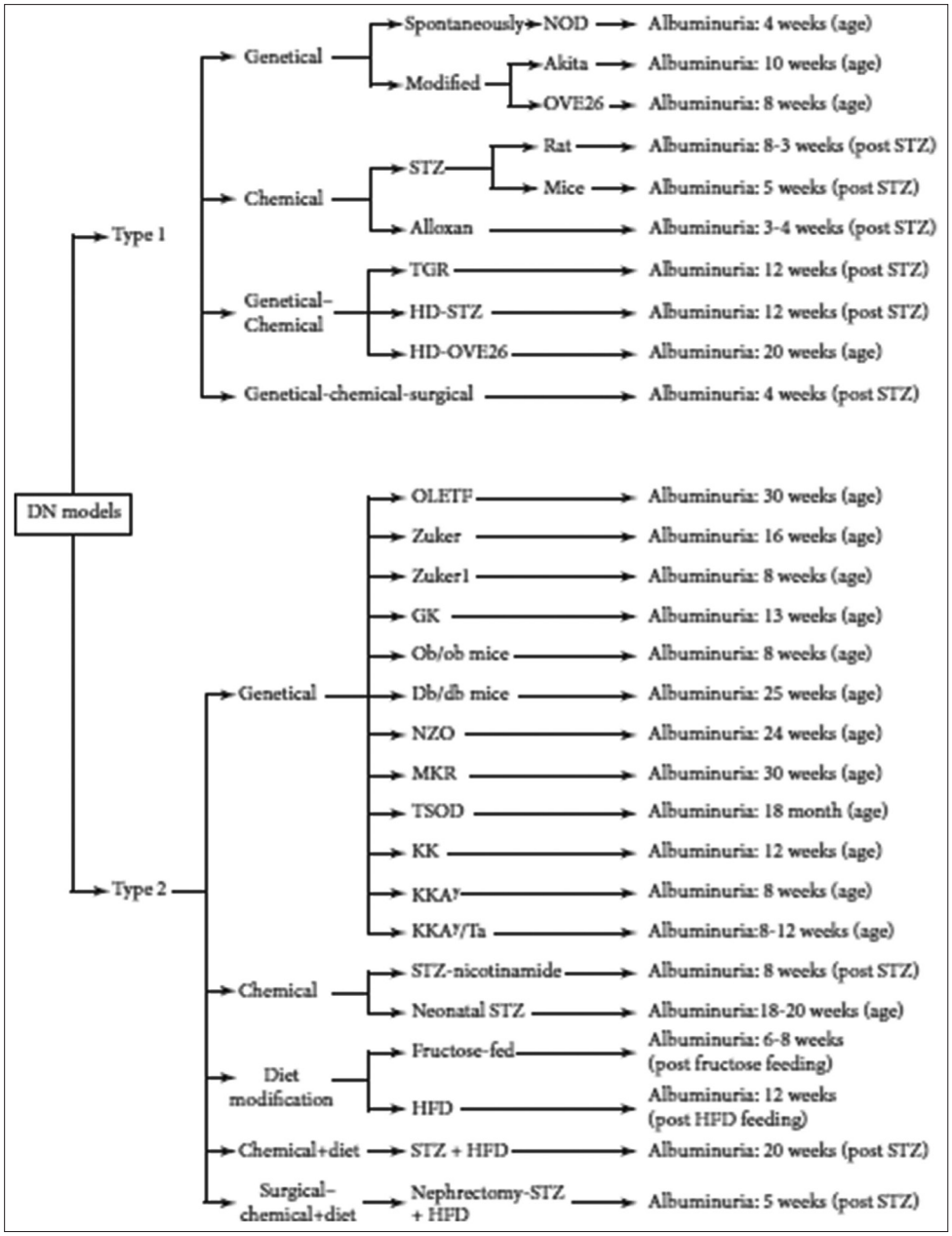

Fig. 2: Diabetic model nephropathy in albuminaria

already established. Need to be noted that urinary albumin excretion can increase regardless of the diseased kidney with factors like sports heavy within 24 h, infection channel urine severe, menstruation, heart failure, and marked hyperglycemia [9].

An ideal model of DN would display all DN features including reduced renal function (<50%) and albuminuria (>10-folds) as well as DN-induced histopatho- logical changes such as mesangial expansion, mesangiolysis, and nodular glomerulosclerosis, observed in humans (Fig. 2)

Variable clinical assessment in screening for kidney disease diabetic is eGFR, using a formula-based creatinine-like equality Collaboration Disease Kidney Chronic (CKD-EPI). Otherwise treated, road nephropathy "natural" diabetes shows a continuation decline annual in eGFR between 2 and 20 mL/min/1.73 m^2 (mean 12 mL/min/1.73 m^2), but effective treatment target glycemia, control pressure blood, blocking renin-angiotensin system, reduction rate cholesterol blood, and increase factor style life can limit development to 2–5 mL/min/1.73 m^2/year, showed importance screening and intervention.

A full rat model develops all features of nephropathy diabetic man moment that is unavailable. However, diabetic rat models are available and can be useful in studies of nephropathy diabetics with an increased understanding of the features of each diabetes.

Phenotype histological addition for nephropathy models diabetic with disease carry-on must include [8]:

1. Quantification expression mesangial matrix, ideally with analysis morphometric and detectable mesangiolysis and microaneurysms with the stain-appropriate network.
2. Exception disease complex immune with Immunohistochemistry on section frozen for IgG, IgM, and IgA.
3. Demonstration of GBM thickening by electron microscopy.
4. Demonstration of podocyte loss by a plausible morphometric system.

MICE

T1D

T1D is an autoimmune disease in which system immunity destroys beta cells in the pancreas. In rats, this can be induced with poison that

destroys pancreatic beta cells. Many compounds have been tested for inducing T1D in mice and rats; However, the material the most prominent and routine chemistry used is STZ, which is analog glucose causing cytotoxicity ablation later pancreatic β cells that produce absolute insulin deficiency, hyperglycemia, and decreased weight. STZ is taken up by pancreatic β cells via the GLUT2 glucose transporter. The intracellular action of STZ results in DNA changes that lead to fragmentation. DNA alkylation is the main reason for STZ-induced β-cell death, as shown in Table 1.

Since the early 1980s, STZ has been frequently used to cause T1D in rats and mice because STZ is highly damaging to pancreatic cells. However, a fundamental problem with this model of diabetes is that STZ also confers toxicity to renal tubular cells; consequently, renal lesions may be directly related to STZ toxicity in the kidney. STZ-induced DNA damage activates poly-ADP ribosylation. This process leads to depletion of NAD+, further reduction of ATP content, and subsequent inhibition of insulin synthesis and secretion, thereby leading to insulin resistance. High doses of STZ can be toxic and directly cause organ injury, including the kidneys. Repeated injection of a lower dose is therefore preferred. Besides insulin resistance, term STZ treatment induces decreased body weight and osmotic diuresis.

T2D

Typical T2D models use animal obesity hereditary can leptin deficiency (ob/ob mice) or own mutations that do not act on leptin receptors (db/db mice). Animals: This shows hyperphagia, obesity, and insulin resistance and develops relative insulin resistance in 8 weeks of first life. Dietary intervention or pharmacy above background behind genetics can be used for more carry-on induced features of DN. This can be used for more carry-on induced features of DN. The degree of hyperglycemia depends on the nature of the genetic modification and the type and sex of the mice, as shown in Table 2.

Ob/ob BTBR

Mouse brachyuric black and brown experience resistance to insulin, and when mutation ob/ob is placed on this strain, mice show hyperglycemia sustainable from 6 weeks to front. Mouse models resemble feature classic DN man including change pathological such as arteriolar hyalinosis, mesangial expansion, mesangiolysis, focal nodular glomerulosclerosis, and reduced amount of porosity. The profit of these models is that DN developed faster than type others. This presents an interesting model for learning features of classic DN moderate in humans. Rats that hypotension and difficult development reproduce and have a high mortality level around 24 weeks of age.

Leptin deficiency is present in Ob/ob mice, though track leptin signaling is unaffected. The C57BL/6, C57BLKS/J, FVB/N, and DBA2 strains are all mutate. The Ob/ob mutation in C57BLKS/J causes severe hyperglycemia and cellular atrophy. Ob/ob C57BL/6 mice gain weight and develop mild hyperglycemia but do not develop the kidney lesions associated with diabetes in humans. At 6–10 weeks of age, Ob/ob BTBR mice exhibit persistent hyperglycemia. Ob/ob BTBR mice exhibit some pathological traits of human DN, in contrast to ob/ob C57BL/6J mice. In contrast to most DN patients, ob/ob BTBR mice were not only not hypertensive but only mildly hypotensive. However, proteinuria and death podocytes can be seen since 8 weeks old.

Db/db on C57BL/Ks Background

Mutation db/db, in the background behind C57BL/Ks, is a mutation first described for influencing the onset of diabetes in mice. Distinctive features resembling early-onset DN man including albuminuria from 8 weeks to ahead, though this No too progressive. Cohen *et al*. describe journey time mesangial expansion. Nodular lesions were observed from 22 weeks to the front. Development disease more carry on can UNX induced. This model is a good model for learning change early in human DNA.

In the mouse model db/db, mutation-induced leptin receptor gene in a manner experience or with manipulation genetics produces phenotype obesity consequence track faulty leptin signaling in the hypothalamus. Besides sterile and deficient hormone growth, mice db/db also shows hyperphagia, obesity premature onset, hyperglycemia, dyslipidemia, insulin resistance, hypertension, and nephropathy, such as the ZDF mouse. C57BLKS/J strain and C57BL/6, C57BLKS, DBA, FVB, and CBA were all found to bring mutation db original. In rats db/db and ob/ ob with the background behind C57BL/6J, hyperglycemia result was not too bad. However, animals with the background behind C57BLKS had fulminant diabetes after 24 weeks of age. Db/db mice are resistant to leptin compared to ob/ob mice, but they are also obese and diabetic and insulin resistant like ob/ob mice.

The leptin levels of the db/db mice increased because they had defective leptin receptors, but they remained severely obese. Compared with ob/ob mice, db/db mice significantly developed DN. Given that leptin has been shown to increase matrix formation directly, this may be due to their different genetic backgrounds or the absence of circulating leptin in ob/ob mice. At 25 weeks of age, DN in this model appears as the growth of the mesangial matrix and increases in extracellular matrix proteins such as fibronectin, Type IV collagen, and laminin. Approximately 6 months after diabetes induction, tubular atrophy, dilatation, apoptosis, and early interstitial fibrosis are seen. An increase in interstitial volume reflects this.

In general, nodular mesangial sclerosis or progressive renal failure does not occur in db/db mice. Consequently, these mice serve as excellent models for diabetes and early-stage DN in humans but do not exhibit symptoms of advanced DN. In addition, this model takes longer to generate DNs and does not exhibit advanced DN characteristics.

KUO KONDO (KK) MICE

The large body size of the KK rat (KK) is a breeding objective. This strain gradually gains weight at maturity and exhibits compensatory

Table 1: Summary of mice model for Type II diabetes mellitus

Animal	Strains	Total	M/F	Drugs	Average weight	Average age	References
Mice	ICR mice	56	M	metformin (200 mg/kg)	-	5 weeks	[10]
	C57BL/6 mice	30	M	DMBG (dimethyl biguanide) 300 mg/kg	20±2 g	5–9 weeks	[11]
	C57BL/6 mice	70	M	Oral metformin (100 mg/kg) once daily	18–22 g	6–8 weeks	[12]
	C57BL/6 mice	50	M	10 mg/kg losartan	-	-	[13]

Table 2: Mice model for Type II diabetes mellitus

Animal	Strains	Total	M/F	study length	Average weight	Average age	References
Mice	db/db mice C57BL/KsJ	30	M		-	6 weeks	[14]
	BTBR ob/ob	27	F	12	-	12 weeks	[15]
	BTBR ob/ob		M		-	8 weeks	[16]
	BTBR ob/ob		F		-	8 weeks	[17]

hyperinsulinemia and insulin resistance due to islet cell hyperplasia. Mild peripheral glomerular basal membrane thickening, mesangial expansion, and hypercellularity are the pathogenic characteristics of DN in these mice. In KK mice, proteinuria and microalbuminuria were also found. Although the KK mice produced a transgenic version, this model did not acquire advanced DN, and it took a long time to develop diabetes. According to a report, these rats will develop overt diabetes if their diet or environment changes.

Introducing the yellow obesity Ay gene into the KK mouse strain, Nishimura created KK mice with a genetic predisposition to obesity. KKAy mice have heterozygous mutations of the agouti gene and are the offspring of yellow fat male Ay mice and black female KK mice. At approximately 8–12 weeks of age, this strain exhibits significant obesity, hyperlipidemia, insulin resistance, and insulin insufficiency. Diabetes in mice manifests as diffuse glomerulosclerosis, nodular changes, and albuminuria, which increases significantly from 4 weeks of age and progressively worsens with time.

KKAy/Ta mice, also known as obese and diabetic rats with hyperinsulinemia, hyperglycemia, and dyslipidemia. The yellow obesity gene (Ay), the model for Type 2 DN, was transfected into KK/Ta mice to produce KKAy/Ta animals. Because kidney damage in KKAy/Ta mice is very similar to DN in humans, these mice are an excellent model for studying Type 2 DN. Between weeks 8 and 12, the rat urine ACR doubled. At approximately 16 weeks, KKAy/Ta mice exhibit extracellular mesangial matrix and proliferative glomerular nephritis with enlarged glomeruli.

RATS

The vast knowledge of rat physiology makes it the species of choice for modeling aspects of DN and carrying out therapeutic strategies *in vivo* [18]. Body size facilitates blood sampling and monitoring of renal and cardiovascular function. In addition, mice are more susceptible than mice to many cardiovascular diseases, including hypertension, and for many traits, genetics and pathophysiology in mice have proven to be more relevant to human diseases [6,19].

T1D

Predictable symptom onset and relatively low cost compared to spontaneously breeding diabetic mice, alloxan, and STZ have been used for many years. Many compounds have been tested to induce T1D in rats and mice; however, the most prominent and routinely used chemicals are alloxan and STZ and cytotoxic glucose analogs. Although their cytotoxic effects are achieved through different downstream pathways, both ultimately lead to pancreatic β-cell ablation, resulting in absolute insulin deficiency, hyperglycemia, and weight loss. All models are summarized in Table 3.

The toxic effect of alloxan on pancreatic β- cells is the sum of several processes, such as oxidation of essential thiol groups, inhibition of glucokinase, formation of free radicals, and disturbances in intracellular calcium homeostasis. Alloxan exerts its diabetogenic action when administered parenterally: Intravenously, intraperitoneally, or subcutaneously. The dose required to induce diabetes depends on the animal species, route of administration, and nutritional status. The range of diabetogenic alloxan doses is narrow, and even a slight overdose may be highly toxic.

This STZ-induced diabetes rat model has been used extensively to study therapeutic interventions to ameliorate DN. Naturally, many of these studies focus on lowering blood glucose levels in these animals. Although glucose-lowering agents do not affect glucose levels in Wistar rats, it appears to increase the hyperfiltration in this model. In addition, antihypertensive therapy leads to the normalization of hyperfiltration and a large increase in GS.

In animal models, T1D rats, based on the table on Lots, used mouse strain Sprague-Dawley rats.

T2D

For the T2D mouse model, further distinctions can be made between non-obese and obese mouse strains. As shown in Table 4, the obesity model consists of strains with leptin-deficient or inactivating mutations in the leptin receptor.

In animal models, T2D rats based on the table on Lots used mouse strain of Zucker Diabetic Fatty (ZDF) Rats.

ZDF RATS

Zucker fatty rats carry a homozygous missense mutation (fa) in the fa gene that encodes for the leptin receptor. This strain exhibits hyperphagia, obesity, and hyperlipidemia with only mild elevations in blood glucose levels. By crossbreeding ZF mice with Kyoto Wistar rats, an insulin-resistant and less glucose-tolerant strain, the ZDF rat was derived [34]. These mice exhibit obesity with diabetes and are widely

Table 3: Rat model of Type II diabetes mellitus

Animal	Strains	Total	M/F	Drugs	Average weight	Average age	References
Rats	Sprague-Dawley rats	50	M	Nrf2 tert-butyl hydroquinone (tBHQ, 25 mg/kg)	200–220 g	-	[20]
	Sprague Dawley rats	50	M	IRB (15 mg/kg),	200–220 g	-	[21]
	Sprague Dawley rats	48	M	metformin hydrochloride at a dose of 80 mg/kg/day	-	-	[22]
	Sprague Dawley rats	24	M	Acarbose 10mg/kg BM	160-200 g	-	[23]
	Adult Wistar rats	60	M	10 mg/kg losartan	180–200 g	-	[24]
	Wistar rats, SPF	70	M	Metformin (0.33 g/kg)	200–220 g	-	[14]
	Wistar rats	25	M	metformin (250 mg/kg)	100–150 g	-	[25]

Table 4: Rat model of Type II diabetes mellitus

Animal	Strains	Total	M/F	Study length	Average weight	Average age	References
Rats	SDT Fatty	16	F	24	-	6 weeks	[26]
	Goto-Kakizaki (NO)	12	M	20	-	16 weeks	[27]
	ZSF1	10	M	16	-	9 weeks	[28]
	OLETF	19	M	12	-	5–6 weeks	[29]
	OLETF	30	M	12		14 weeks	[30]
	ZDF	30	M	8	-	12 weeks	[31]
	ZDF	10	M	8	110–130 g	6 weeks	[32]
	ZDF	40	M	15		5–6 weeks	[33]

Table 5: Chemical-induced diabetes mellitus on animal model

Inducer	Animal	m/f	Study length (weeks)	dose	References
Streptozotocin					
	Rat	M	12	ip; 60mg/kg	[24]
	Rat	M	4	ip; 135 mg/kg single dose	[21]
	Rat	M	9	ip; 60 mg/kg single dose	[20]
	Mice	M	16	ip; 50 mg/kg single dose	[10]
	Mice	M	6	ip; 100mg/kg for 2 successive days.	[11]
	Mice	-	8	iP 60 mg/kg for 5 consecutive days.	[77]
	Mice	M	8	ip 50 mg/kg for 5 days	[13]
Alloxan	Rabbit	M	12	IV 100 mg/kg. Diabetic rabbits are given high-fat feed (4% lard+1% cholesterol+95% standard diet) for 2 weeks consecutive For developing a DN after a successful DM model.	[78]
	Rabbit	M	26	IV 65 mg/kg single dose	[79]
	Mice	M	8	ip ; 200mg/kg; single dose	[80]
	Rat	M	4	i.p. 150 mg/kg; single dose	[23]
Combination	Rat	M	9	The diabetic rat model was fed a high-fat-high-glucose diet. Four Sundays Then, model mice were injected with 40 mg/kg of STZ intraperitoneally.	[81]
	Rat	M	4	High in fat and high in sugar (sucrose: lard: powdered milk: eggs: feed general=30:20:4:2:63) for 4 weeks. After fast for 12 h, 112 rats were injected with STZ 25 mg/kg (reconstituted in acid buffer citrate) in the sublingual vein.	[14]
	Rat	M	10	high- fat diet consists of 70% laboratory chow standard, 15% sucrose, 10% lard, and 5% powdered yellow egg for 4 weeks. Animal group normal control receive food standard laboratory. Streptozotocin (STZ) was administered intraperitoneally with a low dose (35 mg/kg)	[25]
	Rat	M	12	High-fat diet, for period early 6 weeks. After 6 weeks of diet manipulation, animals fed HFD received streptozotocin dose low (ip) single (STZ, 35 mg/kg bw).	[82]
	Rat	M	4	low- fat diet (6% fat, 22% protein, and 70% carbohydrates) was administered ad libitum to the group of healthy controls, whereas a high- fat diet (32% fat, 18% protein, and 48% carbohydrates) was administered to the diabetic group for 5 weeks. Therefore, diabetes is induced in fasting animals overnight with a reconstituted intraperitoneal injection of streptozotocin (STZ). In citrate buffer 0.1M (pH 4.5) with a dose of 30 mg/kg body weight	[83]
	Rat	M	8	prepared high-fat diet by mixing cane sugar (20%), lard (10%), cholesterol (2.5%), and bile salt (1%) with food animal rodent standard, After 4 weeks, the rats were fasted overnight and injected intraperitoneally with fresh streptozotocin (30 mg/kg).	[84]
	Mice	M	4	high- fat diet (contains 10% sucrose, 10% yolk eggs, 10% aksungia, 1.5% cholesterol, 0.5% bile salts, and 68% forage basic). Four Sundays then, DN mice were induced with repeated intraperitoneal injections of STZ (40 mg/kg-d) for 5 days	[85]
	Mice	-	20	injected intraperitoneally (ip) at 40 mg/kg body weight. streptozotocin, given eating a high - fat, high- fat Western diet cholesterol (WD, TD88137) from Harlan-Teklad (Madison, WI) after the onset of diabetes	[86]
	Mice	M	8	ip; 80mg/kg; given Eat on a high diet glucose and high fat (HFD, Research Diets, Inc., New Brunswick, United States of America) during four Sunday	[12]
	Mice			Mouse undergoes unilateral nephrectomy (Unx) with intrarenal administration with shTim-3-lv or ctrl-lv (2 106 IU/kidney) to still kidney whole. After recovery One Sunday from unilateral nephrectomy, rats made diabetes induced by intraperitoneal (IP) injection of STZ (S0130, Sigma, St. Louis, MO, USA) with a 50 mg per kg body weight.	[86]

used in studies of T2D and its complications. Excessive diabetes was found early in this model, despite compensatory insulin hypersecretion, indicating insulin resistance [34]. Due to exhaustion of insulin secretion with impaired glucose tolerance, these mice become diabetic between 8 and 10 weeks. ZDF mice spontaneously develop DN characterized by heavy proteinuria.

Wistar Kyoto mice, which have leptin receptor mutations and insulin resistance, were crossed with obese fa/fa Zucker mice to produce ZDF mice. ZDF has leptin receptor mutations that cause nephropathy, hypertension, hyperglycemia, insulin resistance, obesity, hyperglycemia, and dyslipidemia. The reduction in cell mass causes these mice to develop diabetes. The possible cause of beta cell mass expansion failure is glucotoxicity/lipotoxicity. In this model, albuminuria levels in male ZDF mice increased slightly at 6 weeks of age, indicating reduced insulin production and glucose tolerance, and overt diabetes developed at 8 weeks of age. At 16 weeks of age and after 10 weeks, ZDF mice developed the onset of DN, characterized by proteinuria and severe glomerulosclerosis.

SPONTANEOUSLY DIABETIC TORII (SDT) FATTY RATS

SDT fatty rats are reduced with enter fa allele of Zucker mice to in genome SDT normal mice. SDT normal (non-fat) mice are a useful model of T2D non-obese who spontaneously develop hyperglycemia and intolerance glucose from about 20 weeks produced by decline accompanying insulin secretion degeneration β cells [35]. Mouse fatty SDT already have diabetes ever since 5 weeks old. Mouse fatty SDT from the second type sex shows significant hyperphagia and obesity. Serum glucose level increases from 6 weeks of age and lipid parameters from 4 weeks of age [35].

ZSF 1 RATS

Obese diabetic Zucker fatty/spontaneously hypertensive heart failure F1 hybrid (ZSF1) mice were derived from cross-strain mice with two

mutations and different leptin receptors (fa and facp): Rat fatty female diabetic Zucker (ZDF, fa) and male slender spontaneous mouse fail heart hypertension (SHHF, facp). Lean and obese ZSF1 mice show pressure blood tall when they inherit the hypertension gene of the spontaneously hypertensive rats (SHR) strain. Only ZSF1 mice are homozygous with two mutations affected receptors dyslipidemia, hyperglycemia, sclerosis kidney, and fibrosis [36]. Recently, this showed the development of kidney disease in the ZSF1 mouse model in part big No depending on hypertension. Therefore, ZSF1 rat separates renal pathophysiology due to obesity, hyperglycaemia, and dyslipidaemia from changes caused by hypertension [37]. Obese ZSF1 mice developed metabolic syndrome and diabetes as early as 8 weeks. Metabolic changes are associated with early signs of kidney disease, such as increased proteinuria and glomerular and peritubular capillary density regression.

Obese ZSF1 mice are animal-created hybrids with a married skinny mouse man with failed heart hypertension spontaneous (SHHF) with female mouse ZDF (ZDF-/fa). At 8 weeks of age, ZSF1 mice show symptom syndrome metabolic, which includes hyperlipidemia, hypertension, and diabetes, and at 32 weeks, they experience nephropathy, which is characterized by extreme proteinuria, severe tubulointerstitial and vascular damage, glomerulosclerosis, and decreased GFR. Compared to ZDF parental diabetic mice, they experienced ZSF1 mice hypertension and disease more kidney badly; however, no experience of hydronephrosis, which possibly makes it more difficult to evaluate the function and structure kidney.

GOTO - KAKIZAKI RATS

Mouse Goto Kakizaki (GK) is a non-obese, non-hypertensive model of spontaneous T2D (Kitada *et al*., 2016). GK strains were developed from Wistar rats through breeding selectively from Lots generation mice with a rate of glucose blood high. GK mice show glucose intolerance at 2 weeks of age and experience mild hyperglycemia and hyperinsulinemia between 3 and 4 weeks. At 12 weeks, GK mice developed marked T2D with enhanced rate glucose prolonged fasting and insulin.

Type II non-insulin dependent diabetes mellitus (NIDDM) models that do not obese, normotensive, spontaneous, and mild are mouse GK. Goto and colleagues at Tohoku University in Sendai created GK mice with chosen partner breeding from stock Wistar rats during a generation that has rated glucose blood highest based on the OGTT (test tolerance glucose). Insulin resistance, poor insulin production, and disorders in glucose metabolism are all present in GK mice. At 3–4 weeks of age, GK mice started to show hyperglycemia and hyperinsulinemia medium. Temporary GK mice experienced increased proteinuria, glomerulosclerosis, and interstitial fibrosis. They are resistant to DN developments and only develop glomerular hypertrophy and glomerular and tubular basement membrane thickness. Recently, a crossbreed GK mouse substrain was developed.

OTSUKA LONG-EVANS TOKUSHIMA FATTY (OLETF) RATS

OLETF is a T2D model already established. This model is derived from the development of spontaneous obesity in a colony of Long-Evans mice. OLETF and Long-Evans Tokushima Otsuka controls were then developed by selective breeding. OLETF mice were originally studied as a model of late-onset T2D, as older OLETF mice are not only obese but also hyperglycemic and insulin-resistant [38]. In male OLETF mice, impaired glucose tolerance was observed from 8 weeks, and plasma glucose levels increased from 18 weeks of age. Hyperglycemia and hyperinsulinemia are indicated in the beginning phase of the disease as a consequence of hyperplasia cell islets and peripheral insulin resistance.

OLETF mice are an animal model of Type 2 DM or NIDDM with deficiency CCK-A receptors, hyperphagia, increased size eating, obesity light on age around 6 weeks, insulin resistance that occurs with age around 12 weeks, NIDDM on age around 30 weeks, and induced DN after 30 weeks [39].

SIMULATION SPONTANEOUS ANIMAL FOR DN

Animals that spontaneously develop DN due to disabled genetics are bred to provide animal models of DN. Due to abnormalities in kidneys shown in animals; this copy abnormality seen in patients with DN, the spontaneous DN model can be trusted. These models are difficult. Requirements gift eating and breeding challenging, and owning cost height and long cycle modeling. However, various applications for this model keep going growing. The most common spontaneous model of T1D used in the study is LEW.1AR1/Ztm-iddm mice, mice bio breeding (BB), and diabetic non-obese mice (NOD) [40].

Mice

NOD mice are known as a model of hypoinsulinemic T1D. Because, in a manner, they spontaneously develop autoimmune diabetes with features resembling T1D in humans. In NOD mice, the onset of diabetes occurs between ages 3 and 4 weeks; a majority of the woman show disease at week 40, but the confirmed incidence of diabetes in men in a manner significantly lowers. NOD mice were used for more DN investigations seldom than induced animal models in a manner chemical because diabetes requires time to grow. Development abnormality only kidney a little as well as disease kidney spontaneous which is not is known the cause has observed in NOD mice. In this model, lymphocytes infiltrate the kidney; however, tissue injury kidney new seen. Increased urinary albumin excretion has been reported in these animals 4 weeks after diabetes onset.

BB mice

BB mice demonstrate naturally diabetic rats' insulin insufficiency due to death cell autoimmune. Diabetes affects men and women with equal frequency and is more severe. Diabetes strikes suddenly between the ages of 8 and 16 weeks. The GBM and GFR in BB mice thicken several days after the onset of diabetes, although there are no substantial albuminuria or mesangial changes [40-42].

GENETICALLY MODIFIED DIABETIC RATS

Akita mouse

Akita mice are a genetically engineered species susceptible to T1D. This genetic engineering results in mutations in the insulin gene, accumulating misfolded insulin proteins in pancreatic beta cells and resulting in Type I diabetes. Albuminuria tends to increase in this period and becomes much more height after 10 weeks of age. Glucose levels increased significantly in infants aged 4 weeks. The severity of kidney damage is affected by the development of DN in Akita mice, which has a significant genetic component. In strains C57BL/6, DBA/2, and 129/SvEv, DN was seen after inducing the Akita mutation; however, strains 129/SvEv and DBA/2 are more susceptible to nephritis.

The degree of hyperglycemia experienced by these rats varied, as well as the symptoms of nephropathy. For example, only C57BL/6 and 129/SvEv mice exhibit mesangial matrix enlargement. Compared to other mice, DBA/2 animals had a higher level of albuminuria. No investigation, regardless of type, demonstrated structural changes such as mesangial matrix enlargement, mesangiolysis, and nodular glomerulosclerosis seen in advanced human DN. In contrast to male Akita rats, female Akita rats experience milder hyperglycemia. It has been demonstrated that Akita rats experience more significant and prolonged hyperglycemia than STZ-induced diabetic rats.

OVE26 mice

OVE26 transgenic mice develop Type I diabetes, deficits in insulin production, and overexpression of calmodulin in pancreatic beta cells. OVE26 mice develop diabetes within the 1st week of life and can survive more than a year without receiving insulin. At 8 weeks of age, OVE26 mice developed marked albuminuria.

At the moment animals reach the age of 6 months, expression excess of calmodulin in the background behind FVB generates expansion mesangial matrix, worldwide glomerulosclerosis, decline amount

podocytes, renal fibrosis, and >10-fold increase in albuminuria [43]. Regardless of the sensitivity of DBA/2 mice against the development of DN, all visible DN characteristics will be greatly reduced if the calmodulin gene is mutated in DBA/2 or C57BL/6 strains [44,45]. As a result, weakness is fundamental in the mouse model. This is a condition that involves mutation. This is expressed in strain FVB mice to get desired DN characteristics.

MARMOT AND RABBIT

T1D in guinea pigs can be induced with STZ [46]. The kidney is enlarged, but changes in kidney function have not been described. T1D in rabbits was mostly induced with alloxan. Without exception, only male rabbits were studied.

T2D in rabbits is mostly due to diet. These rabbits tend to be obese, hyperglycemia, hypertension, hyperlipidemia, and hyperinsulinemia. Information regarding the kidneys is scarce. The kidney becomes larger, promotes lipid deposition, and attacks the medullary hyaluronan accumulations with thickened uroepithelium. Renal perfusion increases. Interestingly, T2D has generally been studied in female rabbits. Whether converting rabbits back to normal chow can reverse, these striking morphological changes are unknown.

CHEMICAL INDUCER

Streptozotocin

STZ is a permanent diabetogenic compound produced by the Gram-positive bacterium streptomyces achromogenes, exhibiting broad-spectrum antibacterial properties. STZ induces DM in laboratory animals by killing insulin-producing pancreatic β cells. STZ is a toxic glucose analyzer that preferentially accumulates in pancreatic beta cells through the low-affinity glucose transporter GLUT2. The toxic effector mechanism of STZ begins with its decomposed products and the resulting free radicals, which destroy pancreatic β cells using DNA alkylation, damage the mitochondrial system, and inhibit O-GlcNAcase.

STZ is degraded to glucose and methyl nitrosourea in β *cells*. STZ alters DNA fragments due to alkylation characteristics. STZ also causes greater damage to the liver, intestines, and kidneys, which have lower GLUT2 levels than the pancreas. STZ impacts DNA due to its alkylation characteristics. The consequent DNA damage leads to ROS production and rapid necrosis of pancreatic cells. Genetic background and STZ dose affect the severity of nephropathy in STZ-treated animals [47,48].

Sprague-Dawley rats, Wistar Kyoto, SHR, and mice commonly induce DN using STZ [49]. Because their pancreatic cells are more sensitive to the cytotoxic effects of STZ than rabbits, mice and rats are currently frequently used to produce diabetes [50]. STZ and glucose fight their way into the beta cells. Animals must be fasted as a result. Since rats and mice only feed at night, fasting should begin before blood sampling. Overnight fasting lasts longer (approximately 24 h), triggering many physiological processes that can cause disturbances and erroneous blood glucose readings (AMDCC; http://www.amdcc.org). To reduce the toxic effects of STZ on other organs, such as the kidney, administering smaller doses for five consecutive days is suggested in rats [40,50].

Morphologically, diabetic rats showed increased mesangial matrix protein, mesangial matrix fraction, and Type 4 collagen accumulation compared to control mice. However, no severe mesangial matrix accumulation, nodular lesions in the glomeruli, severe tubular cell destruction, or tubulointerstitial fibrosis were observed. In addition, oxidative stress and inflammation were observed in the kidneys of diabetic rats.

Possible STZ-induced diabetic rats are useful as a model for change beginning nephropathy diabetic. However, change-induced morphology hyperglycemia in the kidney from the mouse model is not significant enough compared to that observed in STZ-induced diabetic mice [40]. Usually given in a manner intravenously or intraperitoneal, STZ has also been injected in a manner intramuscularly, subcutaneously, or even intracardiac in several cases. Maintenance intravenously, however, resulted in more reliable diabetes models. Damage tissue on dose height and injection systemic limits weakness STZ uses to induce DN. In the kidney, STZ has a cytotoxic effect in general. This owns a detrimental impact on tubular cells, in particular, resulting in acute kidney injury in mice and rats. Since STZ contains cancer-causing characteristics, care must be taken when preparing it.

Alloxan

Alloxan is one of the most common diabetogenic agents used to assess the antidiabetic potential of pure compounds or plant extracts in studies involving diabetes. Alloxan-induced diabetes is a form of insulin-dependent DM due to alloxan administration or animal injection. Alloxan causes diabetes by a mechanism that involves the partial degradation of pancreatic beta (b) cells and allows for the subsequent compromise in the quality and quantity of insulin produced by these cells.

Redox, alloxan, and acids dilaurate (product side reduced from alloxan) produces radical superoxide during the reaction cycle. In the end, Fenton's reaction was the destructive network of pancreas animals, including rats, mice, rabbits, and dogs [51]. Hydrogen peroxides and radical's hydroxyl are produced as a result. Alloxan can be given in a manner subcutaneously, intravenously, or intraperitoneally.

The method of how to gift influences the dose of alloxan. For example, the dose of alloxan most common intravenous for diabetes production in rats is 65 mg/kg. The dosage is 2–3 times taller than a dose of intravenous alloxan (i.e., >150 mg/kg bw) and should be calculated if given intraperitoneally or subcutaneously [52]. The fasting animal is more prone to alloxan because similarity structural between alloxan and glucose, as has been proven. Its efficiency is low than STZ and alloxan is seldom used to induce diabetes [53]. In 3–4 weeks after getting an injection of alloxan, nephropathy diabetes grows [54].

INDUCTION OF TYPE 2 DN (T2DN) WITH DIET MODIFICATION

Eating a high-fat diet (HFD) is known to cause a variety of systemic metabolic changes in mice, including obesity, insulin resistance, hyperglycemia, and abnormal lipid profiles. These changes are similar to those observed in patients with metabolic syndrome; T2D is closely associated with metabolic syndrome. One study has shown that there was an increase in body weight and blood glucose levels of C57BL/6 mice on HFD compared to mice on a low-fat diet at 4, 8, and 12 weeks after initiation of the dietary intervention [40].

Mice fed fructose consumption

These mice serve as models of insulin resistance and hypertension, exhibiting features of the metabolic syndrome. Aldose reductase reduces intracellular glucose in the polyol pathway to sorbitol, which is then oxidized to fructose by sorbitol dehydrogenase. Activation of the polyol pathway increases fructose levels in the kidney and other organs of STZ-induced diabetic rats. Fructose buildup can lead to diabetic problems, although this effect can be reduced by inhibiting sorbitol dehydrogenase and preventing fructose synthesis. There are two ways to administer fructose: In a 60% fructose diet or drinking water (10% or 20% W/V) [55-57].

High sugar intake directly contributes to hypertension, possibly by causing inflammation. Studies reveal that rats on a high-fructose diet have higher levels of insulin and hydrogen peroxide (free radicals) in plasma. When treated for 6–8 weeks, fructose-induced metabolic syndrome is associated with renal disease characterized by arteriolopathy, renal hypertrophy, and glomerular hypertension. This relationship holds whether fructose is given orally or through food [40,58].

TYPE 2 DIABETIC RATS PRODUCED BY A HFD

According to several findings, people with metabolic disease syndrome own a relative risk of getting kidney disease chronic. Mice fed a

high- fat diet showed damage to kidneys and systemic disorders similar to syndrome metabolism in humans. Induce syndrome metabolic (60% Fat), which is characterized by obesity, hyperinsulinemia, hyperglycemia, and hypertension, in C57BL/6 mice for 12 weeks, has been associated with damaged kidney, including albuminuria, increased wide glomerular bundle, increased accumulation collagen Type IV glomerulus, mesangial expansion, and disruption sodium.

The genetic background can determine the tendency to develop metabolic syndrome after HFD administration. For example, some strains such as C3H/He, A/J, and 129Sv mice are resistant to obesity and the development of diabetes, whereas C57BL/6 mice are thought to be prone to obesity and insulin resistance. Besides, the source and composition of fat also affect the development of injured kidneys. Therefore, these factors must be considered before using the HFD as a DN model. This chemical and combination inducer will shown as in the Table 5.

SURGERY

Unilateral nephrectomy (UNx), deep diabetes context, first described by Steffes *et al*. STZ-induced Sprague-Dawley diabetic rats exposed show more kidney injury. Several years later, this model was applied to CD-1 mice as well. In both studies, UNx accelerated the development of glomerular lesions and decreased renal function in STZ-induced diabetic mice. At the same time, UNx alone induced only a low number of glomerular lesions and minimal reduction in renal function, suggesting a synergistic effect of STZ + UNx. Comparative studies of the STZ and STZ + UNx models for Type 1 DN (T1D) are lacking, particularly in B6 mice, results from studies using the DN model have indicated that UNx accelerates the development of DN Type 1 DN (T1DN) Surgical Model [59].

Complete or partial pancreatectomy in animals can also lead to Type 1 or 2 diabetes. This approach is now hardly used in diabetes research. Only a few scientists have used this technique to induce diabetes in mice, pigs, dogs, and primates. The pancreas must be removed completely to induce T1D [60]. The application of this method is limited by difficulties such as the high risk of infection, the need for appropriate post-operative antibiotic and analgesic treatment, technical knowledge and appropriate surgical settings, malabsorption, and loss of pancreatic sensitivity to hypoglycemia [40,61,62].

DIETARY OR SURGICAL INTERVENTION FOR T1DN INDUCTION

Given that it has been demonstrated that hypertension promotes the development of DN, researchers have tried increasing hypertension in animal models. Hemodynamic stress can also be delivered through uninephrectomy, which is easy to use in most animal models of DN. In diabetic rodents, UN causes albuminuria, mononuclear inflammatory cell infiltration, fibrosis, and accelerating DN development. However, the findings of this investigation suggest that the hemodynamic anomalies induced by nephrectomy may not be a perfect mimic of the pathophysiology of human DN. At week 4, after the onset of diabetes, there was a marked increase in the nephron and urinary podocin expression and GBM thickness. In research conducted in the 1980s, a high-protein diet was used to increase glomerular pressure and causes damage in diabetic rats, but no again was practiced.

COMBINATION

High fat diet with low dosage of STZ

Because animals rarely develop overt hyperglycemia due to compensatory hyperinsulinemia, HFDs are usually not used to induce DN; however, this procedure is useful for examining the processes underlying insulin resistance. According to Buettner *et al*., the best way to fatten animals is to feed them a semi-refined, HFD with more than 40% of their energy from animal fats, supplemented with small amounts of n-3 fatty acids and even less vegetable oil rich in n-6 and n-9 fatty acids.

The HFD contains 72% of total calories as fat, or 49.5% (g/100 g of total dry food). To create insulin resistance and reduce plasma insulin concentrations and diabetes in humans, a modest STZ dose (35 mg/kg) that first causes cell dysfunction is administered [63-65]. After a 2–4-week feeding intervention, the mice received small doses of STZ by injection. Four weeks after STZ injection, renal damage, including increased albuminuria, renal indices, and pathological changes, was noted [40,66].

INDUCTION (T2DN) WITH ADMINISTRATION OF CHEMICALS, SURGICAL INTERVENTION, AND DIET MODIFICATION

Low Dose STZ + High Fat Diet + Nephrectomy

According to Sugano *et al*., performing nephrectomy after receiving low-dose STZ injections caused mild glucose intolerance in rats. In addition, when these mice were fed a HFD, they developed a mouse model of DN comparable to that observed in people with T2D. After receiving the STZ injection, microalbuminuria appeared 15 weeks later, and at 20 weeks after eating HFD, proteinuria opens, mesangial matrix proliferation, and interstitial edema appears. The amount of STZ (25–40 mg/kg), dietary fat (40–58% of calories), and nephrectomy rates vary [67].

Monogenic manipulation of eNOS deficiency

Vascular eNOS activity is altered in diabetes. It has been reported that in the early diabetic state, NO production is increased; however, with prolonged diabetes, renal eNOS production decreases. eNOS knockout (eNOS-/-) mice were used to determine whether eNOS deficiency results in a nephrodiabetic mouse model.

Different types of diabetes models lacking eNOS activity were generated. Type 1 DN models included STZ-induced diabetic B6-eNOS-/- mice (low dose and high dose), B6-eNOS-/-Ins2Akita/+ mice [68,69]. Compared with eNOS-/- mice, diabetic eNOS-/- mice had a 10-fold increase in diabetic albuminuria after administering low doses of STZ and a 40-fold increase after administering high doses of STZ. Development of DN in eNOS-/-Ins2Akita/+ diabetic rats depends on the strain. B6-eNOS -/-Ins2Akita/+ mice died soon after weaning and did not live long enough to develop DN. However, the first generation (F1) between B6 and 129SvEv survives as long as B6-eNOS+/-Ins2Akita/+ diabetic mice and develops DN [70]. However, the first generation (F1) between B6 and 129SvEv survives during B6-eNOS+/+Ins2Akita/+ diabetic mice and develops DN [40,70].

C57BLKS (BKS)-db/db mice (eNOS/eNOS mice with BKS background) are a Type 2 DN model. At 6–8 weeks of age, hyperglycemia can be detected, and at 16–20 weeks of age, abnormalities of nephropathy are seen. A decrease in GFR is one from change, together with hypertension, substantial albuminuria, GBM thickening, mesangial expansion, nodular glomerulosclerosis, and tubulointerstitial damage [40,71].

Lack receptors bradykinin B2

A number study finds a connection between RASS and early and developmental DN. Inhibitor enzyme angiotensin converter (ACE) and inhibitors angiotensin receptors also have proven their effect on the protection of kidneys in DN [40,72,73].

Angiotensin II levels are very low, affected by a 50% of increase in ACE gene expression in mice. However, the rate of bradykinin decreases drastically. This show that bradykinin is more important for the response kidney in diabetes than angiotensin II. Consequently, the researchers focus on deletion receptor bradykinin 2 (B2R) in Ins2Akita/+ mice with the background behind B6 to learn the evolving role of bradykinin in DN [74]. At present, 6 months old, B2R- deficient Ins2Akita/+ mice showed a 4-a fold increase in albuminuria, strong mesangial enlargement, and glomerulosclerosis. According to researchers, almost all benefit profitable of ACE inhibitors on renal function and albuminuria are reversed by the antagonist receptor B2R non-peptide in diabetic and BKS-db/db mice. Both in 129S6/SvEvTac mice and mice background behind B6 dose-induced STZ diabetes low, B2R activation protects the kidney from DN. At the end period of 6 months, STZ diabetic mice without B2R secreted more albumin than STZ diabetic rats with intact B2R receptors [40,75,76].

Table 6: Laboratory analysis of animal model

Animal	Strains	Method	References
Mice	ICR	Histological study (H&E stain), Western blot analysis, fasting blood glucose, serum creatinine, blood urea nitrogen, and 24-h urine protein levels	[10]
	Mus musculus	creatinine (Scr), blood urea nitrogen (BUN), and urine albumin, Histopathological Analysis by Masson stain, Western blotting analysis, 20-HETE level, Cell culture, and treatment, Cell prefoliation test by MTT	[85]
	Swiss albinos	Inspection of glucose, blood urea nitrogen, creatinine, and total protein, Examination histological with coloring hematoxylin and eosin; Immunohistochemistry, discharge cytokines, stress oxidative, protein content, lipid peroxidation, superoxide dismutase (SOD), glutathione reduced (GSH), catalase.	[80]
Mice	C57BL/6 mice	biochemistry, histology hematoxylin-eosin (H&E), acid -Schiff periodic (PAS), acids silver-periodic methenamine (PASM) and staining Masson's trichrome, chemistry urine and blood, reactions chain polymerase time real, Western blotting procedure, measurement of intracellular ROS, and malondialdehyde (MDA)	[86]
Mice		extraction and time PCR analysis real, Western blot analysis, staining test Immunohistochemistry, staining Immunofluorescence, podocyte co-culture with macrophages, culture, and treatment cell	[90]
Mice	C57BL/6 mice	Western blot, staining hematoxylin-eosin (H&E) and Periodic Acid-Schiff (PAS) staining, time PCR manifest, serum creatinine, and urea nitrogen, Immunofluorescence	[12]
Mice	C57BL/6 mice	Western blot, hematoxylin, and eosin (H&E). The kidney sections are also stained with Periodic acid-Schiff (PAS) and Masson, (TNF-α) and (IL-6)	[11]
Mice	C57BL/6 mice	Western blot, Transcription reverse and quantitative PCR time real, Immunofluorescence and Immunohistochemistry, determination ROS production (DHE staining), serum BUN and albumin, H and E histology, staining Sirius red, and trichrome Masson	[77]
Mice	C57BL6-Ins2Akita/J	Immunostaining, Western blot analysis, Determination dimerization eNOS, histology with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), methenamine silver or trichrome, Quantification morphology kidney, and Measurement superoxide.	[91]
Mice		extraction and time PCR analysis real, Western blot analysis, staining test Immunohistochemistry, staining Immunofluorescence, podocyte coculture with macrophages, culture, and treatment cell	[90]
Mice	C57BL/6J	Biochemical parameters blood and urine, histology hematoxylin and eosin or sour periodic -Schiff, or with antibody for 4-hydroxynonenal (4-HNE), Cell culture, ROS measurement, Transfection, Western blot, Reaction chain transcriptase-quantitative polymerase backward	[13]
	BTBR ob/ob	Renal Function: Renal weight and the ratio of BUN, Creatinine, and histology to hematoxylin and eosin (H&E). Sour Schiff periodic (PAS), Western Blot Analysis, and RT-PCR	[16]
	db/db mice C57BL/KsJ	Coloring immunofluorescence, analysis Immunohistochemistry, staining histology Coloring Periodic acid -Schiff (PAS), cell culture and intervention, lentiviral infection and plasmid transfection, Western blot analysis, real-time RT-PCR, Luciferase reporter assay, immunoprecipitation, Biotin-MCL- bound protein pull-down	[14]
	BTBR ob/ob	GFR Determination, Test tolerance glucose, Analysis of blood and urine, Periodic acid-Schiff histology or Picro Sirius Red, Immunoblotting, and RT-qPCR	[15]
rat	Wistar	Histology H and E, GSP, IA, TG, TC, LDL, HDL, MDA, insulin, SOD, GSH, BUN, and Cr in serum.	[92]
rat	Sprague-Dawley	Measurement serum biochemistry, enzyme assays lipid peroxidation and antioxidants, histology hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) and Masson's trichrome (MT), Western blot analysis, and detection species oxygen reactive intracellular (ROS)	[20]
Rat	Wistar	Protein isolation and microarray analysis, Stress parameters oxidative and nitrosative, Analysis histology network kidney H and E, and Analysis biochemistry,	[83]
Rat	Sprague-Dawley rats	Biochemical test, H and E histology, Immunohistochemistry, and Western blotting test	[84]
Rat	Sprague-Dawley rats	Biochemical test, FBG and OGTT, analysis histopathology kidney (HE, Masson's trichrome, and Periodic Acid-Schiff (PAS)), RNA extraction and RT-PCR analysis, western blot, Immunohistochemistry, and Analysis immunofluorescence	[81]
rats	Sprague-Dawley rats	Analysis biochemistry, acids tendon blood, creatinine, triglycerides (TG) and total cholesterol (TC), body weight and weight kidney, Staining histopathology. Coloring hematoxylin-eosin and Schiff, staining sour shift periodically, cytokines inflammation including IL-6, IL-1β, and TNF-α, Western blot analysis	[21]
	Sprague Dawley	Urinary protein excretion, blood urea nitrogen (BUN) levels, serum creatinine levels, and uric acid levels in serum and urine. β and TNF- α levels, Western blotting, Real-time qPCR, AGEs levels in the kidney, Glo-1 activity in the kidney, fibronectin, and collagen IV levels	[20]
Rat	Wistar	Biochemical Parameters, Hematological Parameters, Lipid Peroxidation/Activity antioxidant in vivo, δ-aminolevulinate dehydratase (δ-ALA-D) activity	[25]
Rat	Wistar	Biochemical Parameters, Hematological Parameters, Lipid Peroxidation/Activity antioxidant in vivo, δ-aminolevulinate dehydratase (δ-ALA-D) activity	[25]
Rat	Sprague Dawley	Biochemical test, Examination histological hematoxylin-eosin.	[23]
Rabbit	Japanese white rabbit	Western blot analysis, Serum creatinine (SCr), and urea nitrogen (BUN) concentrations. Determination, Enzyme-linked immunosorbent assay (ELISA), Immunohistochemical staining with MCP-1 and ICAM-1 expression, Real-time RT-PCR determination, 24-h urine protein determination.	[78]
Rabbit	New Zealand White (NZW)	Weight Animals, Urea, Creatinine, Electrolytes, and Serum Glucose, Binding Sites Autoradiography [3H] - L-NOARG, Histochemistry of NADPH Diaphorase containing 0.2% Triton X-100.	[79]
Rabbit	Japanese white rabbit	Western blot analysis, Serum creatinine (SCr), and urea nitrogen (BUN) concentrations. Determination, Enzyme-linked immunosorbent assay (ELISA), Immunohistochemical staining with MCP-1 and ICAM-1 expression, Real-time RT-PCR determination, 24-h urine protein determination	[78]
Rabbit	New Zealand White (NZW)	Weight Animals, Urea, Creatinine, Electrolytes, and Serum Glucose, Binding Sites Autoradiography [3H] - L-NOARG, Histochemistry of NADPH Diaphorase containing 0.2% Triton X-100.	[79]

METHOD ANALYSIS

All methods are shown in Table 6 of analysis biochemistry.

Urinary albumin creatinine ratio (RKAU) or UACR

UACR is used to assess the permeability of GFB to albumin. Albumin in the urine indicates increased permeability in GFB, normalized to creatinine to control for variations in urine flow rate. Albuminuria is a marker of general for disease kidney chronic [87].

PLASMA CREATININE

Plasma creatinine is increased in the diseased kidney, showing a decline in glomerular filtration capacity. Blood urea nitrogen level can also be rated [87].

STUDIES HISTOLOGICAL

Acid schiff stains periodic or periodic acid schiff (PAS) stain

PAS stain will highlight the basement membrane of glomerular capillary loops and tubular epithelium. This possible visualization of glomerular cells, mesangial matrix, potentials expansion, and potential GBM changes (e.g., thickening and aberrations) is detailed [87].

Trichrome stains

Evaluation of the historical use of various stains in histology shows that part big pathologists are attracted by the stain, which results in the colors on the specimen network. With this, stains trichomes developed from need this [88].

Various stains, such as blue-eosin and Masson's trichomes, have become popular in modern histology. Trichrome stain shows how complicated the method of coloring is in looking for efficient and consistent coloring that will show network refined and differentiated [89].

Hematoxylin and eosin (H&E)

H&E is one method of coloring most histologically used and is the method of contrast main in medical diagnosis specimen biopsy. Properly managed, H&E stains can yield a surprising amount of useful information.

The H&E staining method involves the application of hematoxylin, a basic dye, to produce a blue-purple contrast in basophilic structures. Acidic eosin shows a bright pink eosinophilic structure. Various colors may also be present in the sample, including yellow and brown, due to intrinsic pigments such as melanin. The hydrophobic structure, including adipocytes, the myelin around neuron axons, and the Golgi membrane, remains clear.

Immunofluorescence and immunohistochemistry

Immunostaining allows visualization of protein expression patterns, such as endothelial capillary loops, which can collapse in glomerular disease [87].

PROTEIN ANALYSIS

Western blot analysis

Western blotting allowed us to assess the expression of dysregulated proteins in kidney disease. For example, reduced podocin and nephrin expression indicates podocyte loss [87].

Real-time PCR analysis

Analysis of mRNA expression allows us to determine how genes are regulated in the diseased kidney, for example, change alternative gene expression and splicing.

RULE NEPHRODIABETIC ANIMAL MODEL

One obstacle in developing a new therapy for DN is the lack of available preclinical models reliable. Targeted knockout or overexpression of genes can, in a manner, determine the role of molecule certain in the disease and what agent represents candidate therapy new. However, the utility of animal models in DN research has been limited because most models fail [93,94] This possibly explains that lots of therapy that has been found beneficial in preclinical models is not yet proven effective in clinical trials.

CONCLUSION

Many animal models of current diabetes available explain diabetes pathophysiology and test therapy new for complications, including nephropathy diabetes.

However, animal models' utility is limited for understanding the pathogenesis of nephropathy diabetics further, in part because there is an ideal model that shows all feature histological keys from nephropathy diabetic humans, like glomerular nodular lesions and with tubulointerstitial fibrosis insufficiency kidney progressive.

The article also provides various methods used in DN research with model animals and presentation the required result for studying DN.

AUTHORS CONTRIBUTION

DUA writing the manuscript and browsed all papers which included in this paper; AB writing the manuscript and translate to English version.

CONFLICTS OF INTERESTS

We declare that all authors have no conflicts of interest.

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