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REVIEW ARTICLE

Review on in-vitro Techniques and in-vivo Animals Models for Screening Diabetes and Diabetic Complications

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Abstract: Diabetes mellitus is type of metabolic disorder. Various pharmaceutical interventions and animal models have been used to investigate the genetic, environmental, and etiological aspects of diabetes and its effects. In recent years for the development of ant-diabetic remedies, numerous novel genetically modified animals, pharmaceutical substances, medical techniques, vi-ruses, and hormones have been developed to screen diabetic complications. A unique disease- treating drug with new properties is still being sought after. The current review tried to include all published models and cutting-edge techniques. Experimental induction of diabetes mellitus in animal models and in vitro methods are essential for advancing our knowledge, a thorough grasp of pathophysiology, and the creation of novel therapeutics. Animal models and in vitro techniques are necessary to develop innovative diabetic medications. New approaches and additional animal models are required for diabetes research to advance. This is particularly true for models produced via dietary modifications, which have various macronutrient compositions. In this article, we review the rodent models of diet-induced diabetic peripheral neuropathy, diabetic retinopathy, and diabetic nephropathy and critically compare the key characteristics of these micro-vascular complications in humans and the diagnostic criteria with the parameters used in preclinical research using rodent models, taking into consideration the potential need for factors that can accelerate or aggravate the- se conditions.

Keywords: Diabetes mellitus, Microvascular, complications, *In-vivo*, Animal models, *In vitro*, techniques.

1. INTRODUCTION

Up to 183 million people may not be aware they have di-abetes, according to the IDF. The three countries with the most enormous anticipated numbers of diabetic patients by 2030 are India, China, and the United States [1]. The two types of diabetes are type-1 diabetes mellitus and type-2 diabetes mellitus. Although there is a great deal of interest in creating new drugs to lessen the effects of the condition, the scientific community has concentrated on analyzing unpro-cessed or isolated natural substances in experimental re-search; very few have been investigated therapeutically in humans [2]. To better understand the pathophysiology and etiology of the disease and to develop new treatments, exper-imental diabetes research must use contemporary in vitro methods and animal models. As a result, since they provide novel insights into human diabetes, animal models of diabe-tes are crucial for scientific research. Rats are utilized in dia-betes mellitus has included genetic, chemical, and surgical interventions [3]. For screening novel chemical entities most modern models since they are inexpensive, small, and have quick production cycles. Experimental study on (NCEs) and other therapeutic modalities for treating diabe-tes, it is also critical to choose a suitable animal model [4]. The major goal of this study is to bring all of the different in vivo animal models and in vitro approaches for diabetes re-search together in one place.

2. MODELS FOR SCREENING THE DIABETES

2.1. Chemical Induced Diabetes Models

2.1.1. Alloxan Induced Diabetes

Alloxan is the chemical used most frequently in studies on factors that cause diabetes. In trials, it has been used to cause Type 1 diabetes. Alloxan, a urea product, preferential-ly kills pancreatic islet cells [5]. By adjusting the amount of alloxan utilized, it has frequently been used to cause experi-mental diabetes in animals like rabbits, rats, mice, and dogs with varied degrees of disease severity [6].

2.1.2. Streptozotocin (STZ) Induced Diabetes

Ion also contributes to supraphysiological insulin release, which, in combination with ROS, leads to beta cell destruc-

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tion in pancreatic islets [7]. When administered in tiny doses, the naturally occurring chemical streptozotocin can result in Type 1 diabetes in animals and Type 2 diabetes in people. In medicine, it is additionally employed to treat islets of Langerhans metastatic cancer [8].

2.1.3. Dithizone Induced Diabetes

Diabetes-related symptoms and signs seen in mice, cats, rabbits, golden hamsters, and rabbits treated with dithizone. Copper and magnesium levels were unchanged, while serum levels of zinc, iron, and potassium were found to be above average in dithizonized diabetic mice. Except for the blood potassium and magnesium levels, the bulk of these serum readings were usual following insulin therapy [9].

2.1.4. Gold thioglucose Induced Diabetes

Gold thioglucose is a diabetogenic substance that causes hyperphagia and Type 2 diabetes in those who are severely obese.

2.2. Hormone Induced Diabetes

2.2.1. Growth hormone-induced diabetes

Growth hormone has a long history in diabetes, and it may have a role in developing kidney problems [10]. Adult cats and dogs who receive growth hormone therapy regularly acquire diabetes and all its symptoms, including severe ketonuria and ketonemia. Long-term growth hormone administration resulted in the beta cell and islet death, permanent diabetes, and the pancreas's limited ability to store insulin [11].

2.2.2. Corticosteroid induced diabetes

Corticosteroids, which are administered to treat inflammation, can cause steroid diabetes. Prednisolone and dexamethasone are the two glucocorticoids that frequently cause steroid diabetes. Insulin resistance, hyperglycemia, and hyperlipidemia are all caused by the effects of glucocorticoids, which impede insulin action and increase gluconeogenesis, particularly in the liver [12].

2.3. Spontaneous Diabetic Obese Rodent Models

2.3.1. Obese mouse (Ob/ob mouse)

Because of a mutation in the leptin gene that causes severe insulin resistance, the ob/ob mouse strain has leptin insufficiency [13]. The ob/ob mice rapidly put on weight, develop insulin resistance, and produce excessive amounts of insulin. The ob/ob model exhibits hyperinsulinemia, hyperphagia, and insulin resistance between 3 and 4 weeks of birth. As evidenced by a consistent decline in plasma insulin levels in the second year of life and glucose tolerance and insulin resistance, the symptom of Type 2 DM in ob/ob mice diminishes with age [14].

2.3.2. Diabetes induced by db/db mouse model

Extreme obesity and several metabolic abnormalities, including hyperphagia, hyperglycemia, hyperinsulinemia, and infertility, are seen in db/db mice. In C57BL/KsJ mice lacking leptin receptors, the db gene mutation results from a spontaneous chromosome 4 mutation [15]. The db/db mouse develops obesity, insulin resistance, hyperphagia, and hyperinsulinemia within 2 weeks of birth. The onset of hyperglycemia occurs between 4 and 8 weeks of age. The mouse enters ketosis and starts to lose weight at this age. The effects of diabetes on the kidneys and the microcirculation were examined using db/db mice [16].

2.3.3. Diabetes induced by Kuo Kondo mouse (KK mouse)

The Kuo Kondo (KK) mouse was used to model Type 2 Diabetes and obesity. It has crossed with the C57BL/6J Bar Harbor mouse. The KK mouse develops obesity, hyperglycemia, and hyperinsulinemia on its own. The KK mouse developed obesity at two months of age due to hyperphagia, insulin resistance, and compensatory hyperinsulinemia. At five months, insulin resistance and hyperinsulinemia peaked [17].

2.3.4. Zucker Diabetic Fatty (ZDF) rat model

Insufficient insulin production causes the Zucker diabetic fatty (ZDF) rats to be less obese, more insulin resistant, and to develop diabetes more quickly. At 12 weeks, full-blown diabetes manifests in the male ZDF rat. When male ZDF rats are between 7 and 10 weeks old, their blood insulin levels peak, but because they cannot respond to glucose stimulation, their insulin levels fall [18].

2.3.5. New Zealand Obese (NZO) mouse

This model is used for autoimmune diabetes. Obese New Zealand mice begin gaining weight at the age of 10 weeks due to hyperphagia, hyperglycemia, and hyperinsulinemia. The NZO mouse develops insulin resistance at an early age. Blood glucose levels in NZO mice reach 300-400 mg/dL at ages 20 to 24 weeks as hyperglycemia and glucose tolerance increase with growth. It is a suitable model for research on diabetes and obesity [19].

2.3.6. Otsuka Long-Evans Tokushima Fatty (OLETF) rat

When the OLETF rat is 18 to 25 weeks old, hyperglycemia occurs. Obesity, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, hypercholesterolemia, and the beginning of diabetes in OLETF rats are the same as in Type 2 diabetic people. In OLETF rats, the onset of diabetes is mediated by numerous recessive genes, including those on the X chromosome [20].

2.3.7. Diabetes-induced Nagoya-Shibata-Yasuda (NSY) mouse model

By displaying modest obesity, decreased insulin sensitivity, and insulin resistance-all of which contribute to the development of diabetes and age-dependent-the NSY mouse resembles Type 2 diabetes in humans. All male NSY mice develop diabetes, but only about 30% of females do. Particularly helpful for evaluating the phenotypes of Type 2 DM and age-related impairments is the NSY mouse [21].

2.3.8. Tsumura Suzuki Obese Diabetes (TSOD) Mouse Model

The TSOD animal begins to exhibit fat and insulin resistance at two months of age, which helps to cause hyperinsulinemia and hyperglycemia. In TSOD mice, pancreatic islets are hypertrophic. The TSOD animals have reduced insulin sensitivity and insulin resistance due to impaired GLUT4 translocation in skeletal muscle and adipocytes [22].

2.3.9. Diabetes Induced by M16 Mouse Model

Hyperphagia causes obesity in M16 mice of all ages. All M16 mice had hyperglycemia, hyperinsulinemia, and hypercholesterolemia at 8 weeks of age [24].

2.4. Spontaneous Diabetic Non-Obese Rodent Models

2.4.1. Goto Kakizaki (GK) Rat Model

The GK rat is a non-obese T2DM model that exhibits insulin resistance, hyperinsulinemia, and hyperglycemia. After the first two weeks, GK rats developed persistent fasting hyperglycemia. After eight weeks, hyperglycemia disappears, and glucose controls the production of islet insulin. Diabetic problems,including retinopathy and peripheral neuropathy, appear in GK rats [24].

2.4.2. Cohen Diabetic Rat Model

The Cohen diabetic rat is a genetic model for human Type 2 DM that developed from a diet-induced Type 2 DM paradigm in which the rat was fed a diet deficient in copper and sucrose by 72 percent for two months. Some signs include non-obesity, hyperinsulinemia, and insulin resistance [25].

2.4.3. Spontaneously Diabetic Torii (SDT) Rat Model

A new strain of diabetic rats that is not naturally obese is the SDT rat. Symptoms include glucose intolerance, hyperglycemia, hyperinsulinemia, and hypertriglyceridemia [26]. SDT rats develop diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy as a result of extreme hyperglycemia. This model is appropriate for researching human T2DM problems [27].

2.5. Surgical Procedures for Diabetes Mellitus

The pancreas is completely removed during surgery to cause diabetes [28]. High technical knowledge and a suitable operating room setting limit this approach. Pancreatectomy has been used to achieve mild to moderate hyperglycemia,; necessary substantial resection is required [28].

2.6. *In vitro* Techniques

2.6.1. Assay of Amylase Inhibition

By first incubating the test sample with the amylase enzyme and then adding starch solution, in vitro amylase inhibition can be studied. After incubation, the dinitrosalicylic acid reagent was used on both the control and the test. Place this mixture in a pot of boiling water for a few minutes. By measuring the absorbance at 540 nm with a spectrophotometer, the amount of inhibition of the α-amylase enzyme was estimated [29].

2.6.2. Inhibition of α-glucosidase Activity

By incubating the glucosidase enzyme solution with phosphate buffer containing test samples from various connections at 37°C for one hour in maltose solution, it was possible to measure the inhibitory activity of the -glucosidase enzyme. After a brief boiling period, the reaction mixture should be made cool. By mixing in glucose reagent and measuring its absorbance at 540 nm, the amount of glucose released from maltose by the-glucosidase enzyme should be calculated. Utilization of glucose to determine the IC_{50} and the percentage of inhibition [30].

2.6.3. Insulin secretion and glucose uptake

Oral antidiabetic medications may impact some glucose metabolic processes, including insulin production, glucose uptake by target organs, and meal absorption. The primary targets of current therapy are incretins, and transcription factors like peroxisome proliferator-activated receptors (PPAR). No diabetes medications have been created that precisely target insulin receptors and glucose transporters [31]. Obesity and Type 2 diabetes, as well as higher intracellular lipid concentrations and insulin resistance, are thought to be linked to adipose tissue [32]. Insulin resistance in either adipocytes or skeletal muscle results in hyperglycemia. To explore insulin resistance pathways, adipocyte cell lines like marine 3T3-L1 cells and rat L6 muscle engineered to overexpress $GLUT_4$ can be employed. Animal Models for Diabetic Microvascular Complications.

Models for screening diabetic complications are enlisted in Table **4**.

2.7. Animal Models of Diabetic Retinopathy

In affluent countries, DR is a diabetes-specific microvascular consequence that continues to be the largest cause of vision loss in middle-aged and economically active persons [33]. A third of diabetics who have DR symptoms, such as severe retinopathy and macular edoema, pose a threat to their ability to see. More than one third of diabetics develop DR symptoms. Around 25% of people with Type 1 Diabetes Mellitus (T1DM) will acquire retinal disease within 5 years after their diagnosis, compared to 20% of people with Type 2 Diabetes Mellitus (T2DM), who will have some form of DR after 20 years of diabetes [34]. Animal models for diabetic retinopathy are mention in Table **1** [35-41].

2.8. Animal Models of Diabetic Neuropathy

Around half of all people with diabetes get diabetic peripheral neuropathy (DPN), the most prevalent type of neuropathy in the world [42]. The clinical course, symptoms, and nerve fiber patterns vary, with symmetrical length-dependent sensorimotor polyneuropathy being the most prevalent variety [43]. Because affected individuals may feel both negative and positive sensory symptoms, including reduced sensitivity, numbness and/or discomfort, motor weakness, impaired proprioception, and abnormal gait patterns, a dichotomous phenotype is frequently observed [44]. Animal models for diabetic neuropathy are shown in table **2** [45-48].

2.9. Animal Models of Diabetic Nephropathy

T2DM is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) globally [49]. Diabetic nephropathy (DN), a long-term primary microvascular consequence of T1DM and T2DM, affects a significant population in the United States and Western Europe, affecting roughly one-third of diabetics [50]. The early stage of DN is characterized by glomerular hypertrophy, mild meningeal matrix enlargement, and thickening of the glomerular capillary walls. Glomerulosclerosis, characterized by thickness of the glomerular basement membrane (GBM),

growth of the mesangial cells, and loss of podocytes, develops as the situation progresses. The following symptoms include fluid retention, tubulointerstitial fibrosis, progressive albuminuria, a lower glomerular filtration rate (GFR), and high blood pressure [51]. Increased urine albumin excretion (UAE) is also a feature of DN, which is split into micro and macro albuminuria [52]. Animal's models for diabetic nephropathy are shown in Table **3** [53-57].

CONCLUSION

Numerous in vitro procedures and animal models have been demonstrated in this review, and each exhibits traits and qualities comparable to those of human diabetics. In studies on diabetes, a variety of experimental animal models has been employed. No species or animal can accurately simulate diabetes in humans. Researching the endocrine, metabolic, genetic, and underlying causes of human diabetes requires using each model. Above mentioned important diabetic models were developed by several eminent researchers to investigate diabetic complications. For novel diabetes treatments requires the use of these animal models and *in-vitro* methods. For diabetes research to advance, new software, techniques, and animal models can be developed.

Table 1. Animal models of diabetic retinopathy.

Species	Type of Diabetes	Mechanism	Retinal Lesions	Time Duration	References
Rabbit	Type-1	STZ	Moderate vascular disease with soft or firm exudates Venous embolism Vascular lesions, retinal and preretinal haemorrhage	135 days	[35]
Rabbit	Type-2	Diet induces	Increase number of microaneurysms	12 weeks	[36]
Rats	Type-1	Alloxan induce	Retinal microvascular cell death	18 months	[37]
Zebra fish	Type-1	High glucose treatment	Thinning of the inner nuclear layer and high plexiform layer and deterioration of the photoreceptor layer	28 days	[38]
Rat/Mice	Type-1	STZ-*ip*	Vascular permeability is increased, while total retinal thickness is decreased	12 Months	[39]
Dog	Type-2	Feeding 30% galactose diet	Retinal dot and blot hemorrhage	5 years	[40]
Cat	Type-1	Pancrecatectomy	Intraretinal hemorrhage	5 Years	[41]

Abbreviation: STZ: Streptozotocin, ip: Intra-peritoneal

Table 2. Animal models of diabetic neuropathy.

Species	Type of Diabetes	Mechanism	Neuronal Lesions	Time Duration	References
Mice	Type-2	BSK-db/db spontaneous	Lowered neurotransmitter levels, elevated thermal delay, and a lack of big myelinated fibre	28 weeks	[45]
Rat	Type-2	ZDF	Reduced blood supply to the muscles and senses and thermal hypoalgesia	6-7 month	[46]
Chinese Hamster	Type-1	Genetic	Reduced conduction velocity bothe sensory and motor nerve	2 weeks	[47]
Monkey	Type-1	STZ induced	Reduced motor nerve conduction velocity	2 years	[48]
Swiss albino mouse	Type-1	STZ treatment	Thermal hypoalgesia	5 weeks	[45]

Abbreviation: BSK:Black Soybean Koji, ZDF: Zucker diabetic Fatty, STZ: Streptozotocin

Table 3. Animal models of diabetic nephropathy.

Species	Type of Diabetes	Mechanism	Lesions	Time Duration	References
Rat/mice	Type-2	STZ	Albuminurea,	15 weeks	[53]
Rabbit	Type-2	Diet induced	Increase perfusion and lip deposition	3-6 months	[53]
Dog	Type-1	Alloxan	Glomerular lesion, hyperfiltration, albunurea	3-4 weeks	[54]
Zebrafish	Type-2	STZ-*ip*	Edema and disruption in filter barriers, thickening of glomerular membrane	4 weeks	[55]
Drosophila	Type-1	High Sucrose Diet	Nephrocyte dysfunctions	15 days	[56]
Mice	Type-1	HD-STZ	Renal hypertrophy	10 weeks	[57]

Abbreviation: STZ: Streptozotocin, HD-STZ: High Diet Streptozotocin.

Table 4. Models for screening the diabetes.

S. No.	Models	References
	in-vivo animal models	
1	Chemical Induced Diabetes Models	
	Alloxan Induced Diabetes	[6]
	Streptozotocin (STZ) Induced Diabetes	[8]
	Dithizone Induced Diabetes	[9]
2	Hormone Induced Diabetes	
	Growth hormone induced diabetes	[11]
	Corticosteroid induced diabetes	[12]
3	Spontaneous Diabetic Obese Rodent Models	
	Obese mouse (Ob/ob mouse)	[14]
	Diabetes induced by db/db mouse model	[16]
	Diabetes induced by Kuo Kondo mouse (KK mouse)	[17]
	Zucker Diabetic Fatty (ZDF) rat model	[18]
	New Zealand Obese (NZO) mouse	[19]
	Otsuka Long-Evans Tokushima Fatty (OLETF) rat	[20]
	Diabetes induced Nagoya-Shibata-Yasuda (NSY) mouse model	[21]
	Tsumura Suzuki Obese Diabetes (TSOD) mouse model	[22]
	Diabetes induced by M16 mouse model	[24]
4	Spontaneous Diabetic Non Obese Rodent Models	
	Goto Kakizaki (GK) rat model	[24]
	Cohen diabetic rat model	[25]
	Spontaneously Diabetic Torii (SDT) rat model	[27]
5	Surgical procedures for Diabetes Mellitus	[28]
	in-vitro models	
	Assay of amylase inhibition	[29]
	Inhibition of α-glucosidase activity	[30]
	Insulin secretion and glucose uptake	[31]

LIST OF ABBREVIATIONS

DN = Diabetic Nephropathy

CKD = Chronic Kidney Disease

ESRD = End-Stage Renal Disease

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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