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Review Article

Efficient and Safe Induction of Diabetes in Experimental Animals: A Review of Alternative Models and Techniques

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ABSTRACT

Diabetes Mellitus (DM) is a multitudinous metabolic disorder that can occur due to insufficient or inefficient levels of insulin that leads to hyperglycemia. In many conditions, diabetes can also directly or indirectly lead to other functional disorders such as dyslipidemia and hypertension making them more severe and life-threatening. It is believed that Type 1 Diabetes can be caused by the process of auto-immune destruction of beta-cells of Islet of Langerhans of the pancreas responsible for the production of insulin whereas Type 2 diabetes is because of resistance against insulin along with the futilities of beta-cells to compensate the body with the required amount of insulin. The animal models are considered an essential component in the experimental studies and drug discovery process. Animal models provide safety, effectiveness, and dose of the test substance that needs to be extrapolated to human use. There are several methods for the induction of diabetes in experimental animal models. The present review aimed to discuss and explore currently used approaches including models from streptozotocin-induced diabetes to transgenic models for reproducible and safe diabetes induction in different experimental animals (rats, mice, guinea pigs, and dogs) and sex. Additionally, some genetically modified animal models are also included and discussed in this review which will pave the way for further studies.

1. Introduction

Diabetes mellitus is a complex metabolic abnormality believed to occur because of decreased insulin production or the development of autoimmune resistance against insulin which is a regulatory hormone to digest glucose molecules and maintain its concentration in blood. It is majorly categorized into two categories, Type-1 [Insulin-dependent diabetes mellitus(IDDM)] and Type-2 [Non-Insulin-dependent diabetes mellitus (NIDDM)][1]. All over the world, the prevalence of diabetes is approximately ten percent (10%) of the total population and 90% of those are affected by T2DM[2]. Asia has a greater rate of diabetes prevalence, especially in China and India. These two nations were found to have the highest numbers of diabetics In China it is around 109.6 million and in India, it is 69.2 million[3]. The treatment of diabetes takes up almost 10% of the health care budget in affluent nations[4]. By 2040, there will be up to 642 million cases of diabetes mellitus worldwide, according to predictions[5]. Diabetes is responsible for the progression and development of heart attacks, strokes, kidney failure, blindness, and amputations of lower limbs. Despite the current availability of more advanced techniques, the animal model remains the major useful strategy for comprehending the intricate pathophysiology, etiology, and intricate interconnections associated with diabetes[6]. Experimental diabetes mellitus is induced in animals primarily because it is useful in shedding light on the pathophysiology and genesis of the illness. Both larger animals and rodents are used in diabetes-related research[7]. To understand the various stages of diabetes rodents are commonly used as an acceptable animal model. Rodents provide an animal model of human disease advantageous over other species in several ways[8]. The insulin resistance mechanism of diabetes mellitus and prospective treatments of

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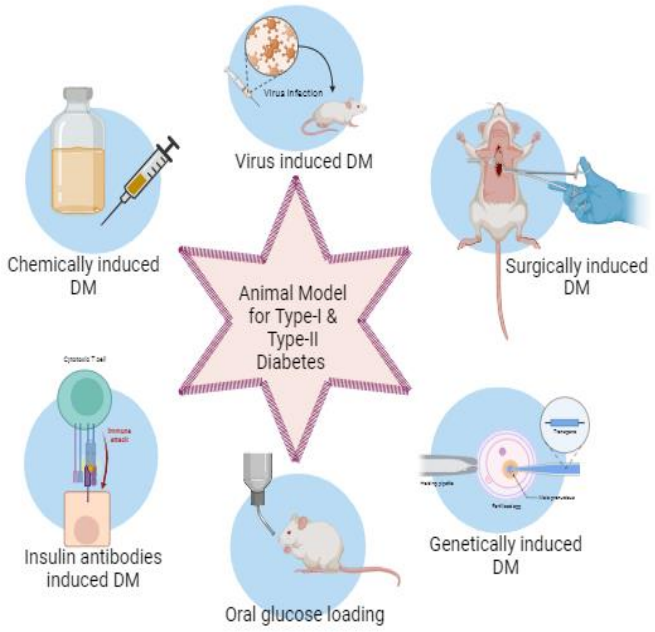


Figure 1. Diagrammatic representation of various animal models for diabetes induction. DM: Diabetes mellitus

diabetes mellitus and its effects must be better understood through rodent-based experimental research. The research outcomes are accurately applied to individuals suffering from the illness (Figure 1). Other non-rodents used in research on diabetes and its complications include zebrafish, pigs, rabbits, and rhesus monkeys[9].

Induction of Diabetes using various animal models

Diabetes research often uses animal models for understanding diabetes mechanisms, testing new treatments, and developing preventive strategies. Each model has its strengths and limitations, and the choice of model depends on the specific research objectives. Some of the common animal models used for inducing diabetes are:

a) Chemically Induced Diabetes

Chemically induced diabetes refers to diabetes that results from exposure to certain chemicals or drugs that impair the body's ability to regulate blood glucose levels. There are many chemicals such as streptozotocin (STZ), alloxan, Nicotinamide, etc. used to induce reversible diabetes in experimental animals[10]. These chemicals and drugs are valuable tools in diabetes research, helping scientists understand the disease's mechanisms and test new treatments. Each has different properties and effects, making them useful for studying various aspects of diabetes as shown in Table 1.

Table 1. Chemicals or drugs used for the induction of diabetes in rat models

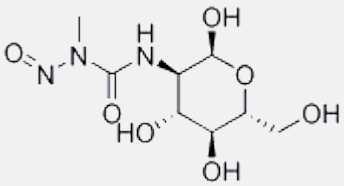
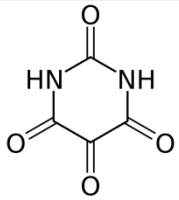
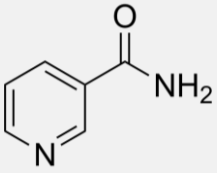
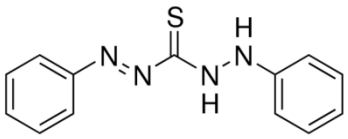
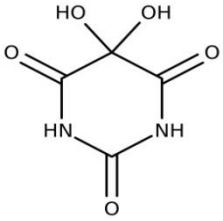
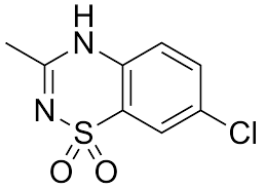
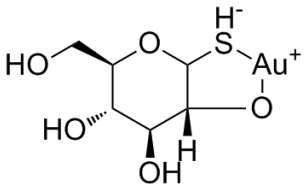
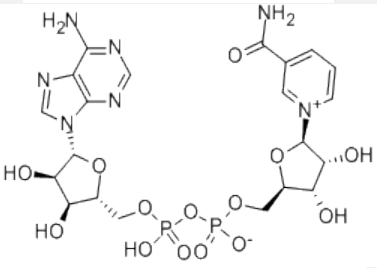
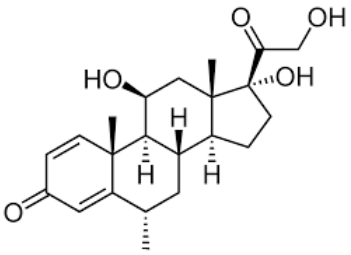
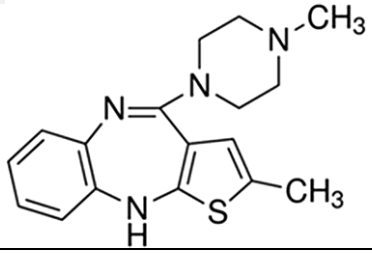
No.	Chemical Name	Chemical Structure	Mechanism of Action	Dose (mg/kg) body weight	Ref.
1	Streptozotocin		This chemical specifically targets and destroys insulin-producing beta-cells in the pancreas. STZ is used to induce type 1 diabetes in animal models because it mimics the autoimmune destruction of beta-cells seen in human type 1 diabetes.	40-60 mg (i.p. or i.v.)	11
2	Alloxan		This compound also causes diabetes by selectively destroying pancreatic beta-cells. Alloxan induces oxidative stress and damage to these cells, leading to decreased insulin production and subsequent hyperglycemia.	50-75 mg (i.p.)	12
3	Nicotinamide		It is often used in combination with STZ, nicotinamide can help modulate the severity of diabetes induced by STZ. It is thought to have protective effects on beta-cells but can also contribute to diabetes under certain conditions.	100-120 mg (i.p.)	13

Table1 Continue

4	Dithizone		This chemical is used to selectively destroy pancreatic beta-cells, similar to STZ and alloxan. It's less commonly used than STZ and alloxan but serves as another tool for creating diabetes models.	32 mg (i.p.)	14
5	Alloxan Monohydrate		Similar to alloxan, this form is used to induce diabetes by selectively damaging pancreatic beta-cells.	125 mg (i.p.)	15
6	Diazoxide		This causes diabetes by inhibiting insulin secretion and increased glucagon secretion. Prolonged use of diazoxide can lead to beta-cell toxicity, causing permanent damage and diabetes-like symptoms.	300 mg (i.p. or p.o.)	16
7	Gold Compounds		Goldthioglucose is a compound which leads to significant reduction in insulin availability, resulting hyperglycemia and diabetes in animal models.	150-350 or 200 mg (i.p.)	17
8	Nicotinamide Adenine Dinucleotide (NAD+)		While it is primarily used in combination with other agents, altering NAD+ levels (mainly decreasing) can impact beta-cell function and induce diabetes in some experimental setups.	1-10 mg	18
9	Methyl-prednisolone		This corticosteroid can induce insulin resistance and diabetes-like symptoms in animal models, useful for studying the impact of steroids on glucose metabolism.	75 mg (i.p.)	19
10	Olanzapine		This Atypical antipsychotic drug quickly reduce insulin sensitivity and increased glucose production by suppressing the insulin receptor signaling pathway within muscle cells, hepatocytes, and adipocytes.	2.5-10 mg (i.v.)	20

Most commonly used chemicals

Streptozotocin (STZ) induced diabetes

STZ [2-deoxy-2-(3-(methyl-3-nitrosoureido)-D glucopyranose] is produced by Streptomycetes achromogenes. Following administration of intravenous or intraperitoneal injection, it makes its way into the pancreatic beta-cell via the Glut-2 transporter, where it induces DNA alkylation[21]. Rakieten and colleagues (1963) documented the ability of the antibiotic streptozotocin to cause diabetes. The substance was found to be particularly harmful to the beta-cells in the pancreas[22].

Mechanism of Streptozotocin-induced diabetes

Upon injection or intravenous infusion, STZ enters the pancreatic beta-cells through the Glut-2 receptor, leading to DNA alkylation. This triggers the activation of PARP, which in turn leads to a decrease in NAD+, a reduction in cellular ATP levels, and a halt in insulin synthesis. Moreover, STZ releases free radicals that could also play a role in DNA damage and lead to cell death. STZ is typically administered in either a single high dose or in several low doses[21, 23].

Procedure of streptozotocin-induced diabetes

Wistar albino rats (Male) weighing 200 ±10% gm that are fed with a standard diet are taken and injected with 40-60 mg/kg streptozotocin (STZ) intravenously. Initially, blood glucose level increases, peaking at 150–200 mg/dl within three hours[22]. Following a period of six to eight hours after the administration of streptozotocin, there is a significant increase in blood insulin levels, leading to a phase of low blood sugar (hypoglycemia) that is then followed by a prolonged period of high blood sugar (hyperglycemia). The intensity and timing of diabetic symptoms are influenced by the amount of streptozotocin given. After injection of 40-60 mg/kg i.v., symptoms begin to appear between 24 and 48 hours, with blood sugar levels reaching as high as 800 mg/dl along with the presence of glucosuria and ketonemia[23]. Histologically, the beta-cells of the pancreas either release their contents or are even destroyed. A stable condition is achieved within a period of 10 to 14 days, at which point the animals can be utilized for pharmacological tests[24]. Following are some diabetes induction models used in rats in combination with STZ.

Nicotinamide-Streptozotocin (NAD-S) induced diabetic model

Type-2 diabetes is developed in rats by injecting STZ (60mg/kg) and NAD (120mg/kg) [25].

Sucrose-challenged streptozotocin-induced diabetic rat model (S-STZ)

A solution of sucrose loaded with 2.5 g/kg of body weight is administered to the rats 30 minutes after the STZ injection[26].

Neonatal- Streptozotocin-induced diabetes rat model (n-STZ)

Administering a single dose of STZ at a concentration of 100 mg/kg by injection to a one-day-old puppy, leads to the development of diabetes[27].

Low dose of STZ with high fat diet-fed model

The rodents receive a high-calorie diet containing 20% sucrose and 10% fat, in addition to a single dose of STZ (30mg/kg body weight) [28].

Alloxan induced diabetes

Frerichs and Creutzfeldt (1968, 1971) were the first to give a survey on chemically induced diabetes in animals[29]. Hyperglycemia and glucosuria caused by alloxan administration have been observed in dogs, rabbits, and rats. Guinea pigs show resistance. Generally, a three-phase pattern is seen with an initial glucose rise, a subsequent decrease, potentially caused by insulin depletion, and finally a sustained increase in blood glucose levels[30].

Mechanism of alloxan-induced diabetes

Alloxan (also known as 2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil) is primarily associated with diabetes due to its rapid uptake by beta-cells and its role in generating free radicals, which the beta-cells struggle to counteract with their limited defense mechanisms. A redox reaction occurs when alloxan is converted to dialuric acid and then converted back to alloxan. This reaction leads to the formation of superoxide radicals, which subsequently dismutate into hydrogen peroxide and highly reactive hydroxyl radicals, which damage the DNA of beta-cells. Despite being absorbed by the liver at a similar rate, alloxan is less susceptible to damage due to its higher resistance to reactive oxygen species[31].

Procedure of alloxan-induced diabetes

New Zealand rabbits that weigh between 2.0 to 3.5 kg undergo a treatment where they are administered 150 mg/kg alloxan monohydrate through their ear veins, leading to 70% of them experiencing hyperglycemia and an increase in uric acid levels for 10 minutes[32]. Rats of the Wister or Sprague-Dawley strain, with weights ranging from 150 to 200 g, receive a SC injection of 100-175 mg/kg alloxan[33]. Adult male Beagle dogs, weighing between 15 to 20 kg, receive an injection directly into their veins with 60 mg/kg alloxan. Following this, they are supplied with a 1,000 ml solution of 5% glucose and 10 IU of Regular insulin daily for seven days, in addition to having unlimited access to canned food. Subsequently, they are administered a single injection of 28 IU of insulin daily via the subcutaneous route (Ultratard HM) [34].

Advantages of chemically induced diabetes

Alloxan/STZ specifically targets and destroys pancreatic beta-cells, while the alpha and delta-cells remain unaffected. This process allows for the continued production of insulin in animals, which in turn, helps them survive by lowering ketosis and decreasing death rates, all while being a cost-efficient method[23, 24, 31].

Disadvantages of chemically induced diabetes

Chemical-induced diabetes can be unstable and reversible with beta-cell regeneration, requiring beta-cell function monitoring. Potential toxicity to other organs is a drawback of this method as P450 isozyme changes were observed in several organs after using STZ or alloxan[22, 24, 34].

b) Surgically induced diabetes

Surgically induced diabetes refers to diabetes that is artificially created in an animal model through surgical procedures for research purposes. This method allows researchers to study diabetes and its complications under controlled conditions. The experimental animals used are anesthetized to ensure no pain during the surgery[35]. There are a few common surgical techniques used to induce diabetes in animal models (Table 2):

Pancreatectomy in dogs

Banting and Best (1922), using pancreatectomized dogs, were the first scientists to provide a logical demonstration for the presence of a hormone in the pancreas that was later characterized as insulin. Their classical studies involving pancreatectomized dogs revolutionized our understanding of the pathophysiology and causes of diabetes mellitus. The method of total pancreatectomy in dogs has been employed by numerous researchers as a key animal model for studying diabetes mellitus in humans[36].

Table 2. Surgical methods that affect insulin secretion in Experimental Animals

No.	Surgical Model	Purpose	Surgical Procedure	Ref.
1	Total Pancreatectomy	To study the effects of complete insulin deficiency and to test insulin replacement therapies and other diabetes treatments.	• Animals are placed under general anesthesia. • A midline abdominal incision is made. • The entire pancreas is excised. This may involve careful dissection to avoid damaging other organs. • This method leads to severe insulin deficiency, mimicking type 1 diabetes. • The animal becomes dependent on external insulin for survival.	36
2	Partial Pancreatectomy	The aim is to study diabetes with residual pancreatic function. It is also beneficial in evaluating the interventions that might help preserve pancreatic function or manage partial insulin deficiency.	• The animal is put under general anesthesia. • A midline abdominal incision is performed but only a portion of the pancreas is removed. • The extent varies based on the desired outcome. • Animals are monitored for changes in glucose metabolism and insulin sensitivity.	37
3	Pancreatic Islet Removal	To test therapies aimed at preserving or regenerating pancreatic islets and studying the specific effects of beta-cell loss.	• The animal is anesthetized. • An abdominal incision is made to access the pancreas. • Islets are isolated from the pancreas using a combination of enzymatic digestion and mechanical separation. • The isolated islets are removed or destroyed, leaving behind the non-functional pancreatic tissue. • Animals are monitored for the onset of diabetes and manage glucose levels.	38
4	Intra-abdominal Adipose Tissue Transplantation	Its aim is to evaluate the impact of obesity on insulin sensitivity and glucose metabolism. And studying obesity-related diabetes and metabolic syndrome.	• The animal is put under general anesthesia. • An abdominal incision is made. • Adipose tissue (often from a donor animal) is transplanted into the abdominal cavity. • Animals are monitored for changes in weight, glucose metabolism, and insulin resistance.	39
5	Ovariectomy-Induced Diabetes	This model is useful for studying the impact of sex hormones on diabetes development and for evaluating hormone-related therapies.	• The animal is placed under general anesthesia. • An incision is made to access and remove the ovaries. • Animals are monitored for metabolic changes and diabetes onset.	40
6	Glycoprotein Induced Diabetes with Surgical Intervention	To study the effects of beta-cell destruction. Testing the potential treatments for beta-cell protection or regeneration.	• The animal is put under general anesthesia. • Chemicals like STZ or alloxan are administered, often intraperitoneally. • Sometimes combined with surgery, such as partial pancreatectomy, to enhance the effect. • Animals are monitored for diabetes development and managed accordingly.	41
7	Pancreatic Duct Ligation	It is beneficial in investigating the effects of pancreatic duct obstruction on insulin production and diabetes development.	• The animal is anesthetized. • An incision is made to access the pancreas. • The pancreatic duct is ligated (tied off) to obstruct pancreatic secretions. • Animals are monitored for symptoms of diabetes and pancreatic damage.	42
8	Duodenal-jejunal bypass (DJB) surgery	It is often used to explore the mechanisms behind weight loss and improved glucose control following gastrointestinal bypass surgery. This procedure can be used to model aspects of bariatric surgery, particularly to understand its effects on diabetes and metabolic syndrome.	• The animal is placed under general anesthesia. • An abdominal incision is made to access the gastrointestinal tract. • The duodenum is bypassed, and the jejunum is anastomosed (connected) directly to the stomach or another part of the gastrointestinal tract. • This rerouting changes the digestive pathway, affecting nutrient absorption and hormonal signaling. • Animals are monitored for changes in weight, glucose metabolism, and overall health.	43

Procedure of pancreatectomy in dogs

Beagle dogs (Male) weighing 12 to 16 kg are anesthetized with pentobarbitone sodium and positioned on their back. The abdomen is opened, and the pancreas is isolated from the duodenum, carefully cauterizing or tying off any vessels.

The small vessels that link to the pancreas are ligated, and the pancreatic duct is irrigated and sectioned. Following this, the splenic and pyloric parts of pancreas are isolated. The blood supply to the pancreatic inner tissue is then secured twice and sectioned away from the splenic vessels. The pyloric segment of the pancreas is finally sectioned. Every section of pancreas tissue is then carefully extracted. After the surgery, the dog receives retroperitoneal injections of 1% procaine and 2,50,000 IU of penicillin G. The abdominal wall and skin are sutured. Post-operative care includes daily intravenous injections of 10% glucose with 10 IU of insulin, cotrimoxazole, metamizol, and secretin for two days. On the third day, the dog is given milk and gradually returns to a normal diet. Insulin (34 IU Retard Insulin) is then administered via a single subcutaneous injection[36, 44].

Duodenal-jejunal bypass

The duodenal-jejunal bypass (DJB) procedure for non-obese individuals with type-2 diabetes mellitus (T2DM) involves rerouting a portion of the small intestine to impact nutrient absorption and hormonal regulation (shown in Figure 2). This surgical intervention aims to improve glucose metabolism and insulin sensitivity. Sham operations are operated in Goto-Kakizaki and non-diabetic Wistar-Kyoto rats. After two weeks of post-duodenal-jejunal bypass, the ability to tolerate glucose (oral glucose tolerance) through oral means is evaluated, and then, after an additional three weeks, the process of insulin-triggered signal transmission and the uptake of glucose by skeletal muscle are assessed[43].

The research showed that bypassing of the proximal small intestine does not boost the uptake of glucose by skeletal muscles. The absence of insulin resistance in skeletal muscles in Goto-Kakizaki rats challenges if this specific animal model is suitable for studying its causes and potential therapies for type 2 diabetes[43].

Procedure of duodenal-jejunal bypass

The first step of this procedure is the construction of the bypass. The surgeon creates a connection between the duodenum and jejunum, bypassing a section of the small intestine. By redirecting the digestive pathway, the procedure modifies the flow of nutrients, impacting their absorption and metabolism. The bypassed section of the intestine plays an essential role in hormonal regulation linked to glucose metabolism. Significant changes in this pathway can lead to altering in insulin sensitivity and glucose control[43, 45].

Advantages of surgically induced diabetes

It prevents the harmful effects of diabetogens (an agent that causes a persistent increase in blood glucose level) on organs and mimics human type-2 diabetes[43, 44].

Disadvantages of surgically induced diabetes

This procedure has complex technical and post-operative steps and can lead to digestive issues due to a lack of amylase. It also affects the production of glucagon and insulin, increasing the risk of mortality[36, 43, 44].

c) Genetically induced diabetes models

Genetically induced diabetes models are valuable tools in diabetes research, used to study the genetic, molecular, and physiological mechanisms underlying diabetes and to test potential treatments. These models involve manipulating the genome of animals, typically mice or rats (Elaborated in Table 3), to mimic various forms of diabetes or to investigate specific genetic factors that contribute to the disease[46]. Usually, diabetes is passed down to animals from a single gene or from multiple genes, as observed in animals like the KK mouse, db/db mouse, or Zucker fatty rat. The unique metabolic traits arise from a single gene mutation, which can be caused by a dominant gene (for example, Yellow obese mouse or KK/A mouse), a recessive gene (such as diabetic or db/db mouse, Zucker fatty rat), or it might be due to a combination of genes (like Kuo Kondo (KK) mouse, New Zealand obese mouse) [47].

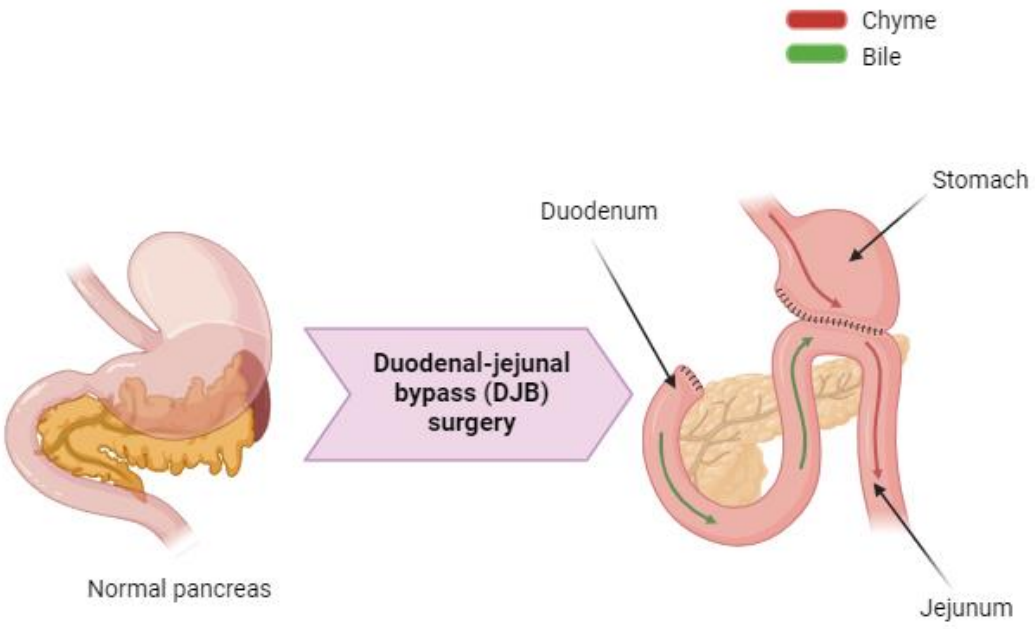


Figure 2. The duodenal-jejunal bypass (DJB) involves rerouting a portion of the small intestine to impact nutrient absorption and hormonal regulation

Table 3. Genetically modified Rodent models highly susceptible to diabetes

S. No.	Diabetic Models	Discovered/ Developed by	Description	Ref.
		Rat Models		
1	BioBreeding (BB) Rat	Dr. Arvid Lernmark et al. (1974)	The BB rat is created through natural selection and inbreeding rather than genetic engineering.	48
2	WBN/KOB Rat	Dr Oichiro Kobori et al. (1977)	The strain's tendency to spontaneously develop chronic pancreatitis in males, along with other degenerative conditions, makes it particularly valuable for investigating human diseases with similar characteristics.	49
3	Cohen Diabetic Rat	A. M. Cohen (1990)	This rat was created by selective breeding of rats that exhibited high blood sugar levels and insulin resistance, similar to human type-2 diabetes.	50
4	Goto-Kakizaki (GK) Rat	Goto and Kakizaki (1973)	The GK rat is a non-obese, spontaneous model of type 2 diabetes, meaning that it naturally develops the disease without any genetic manipulation or dietary interventions.	51
5	Komeda Diabetes Prone (KDP) Rat	Komeda K et al. (1998)	The Long-Evans Tokushima Lean strain was genetically modified to create two rat sub strains: one with a high risk of developing diabetes- Komeda Diabetes Prone (KDP) and one without- Komeda Non-diabetic (KND).	52
6	Zucker-Fatty Rat (ZDF/DRT-FA)	Zucker et al. in 1961	The Zucker fatty rat has a mutation in the leptin receptor gene (Lepr), leading to a deficiency in leptin signaling. Leptin is a hormone that regulates energy balance, body weight, and glucose metabolism.	53
7	WDF/TA-FA Rat	Velasquez MT et al. (1990)	The WDF/Ta-fa rat is a type of rat that has been genetically modified to be obese and hyperglycemic rat. This modification was achieved by moving the fatty (fa) gene from the Zucker rat to the Wistar Kyoto rat.	54
8	Otsuka Long-Evans Tokushima Fatty (OLETF) Rat	Shinichi Otsuka et al. (1984)	The OLETF rat has a mutation in the CD36 gene, which plays a role in fatty acid metabolism and insulin signaling. This mutation leads to impaired insulin secretion and insulin resistance, making it a valuable model for researching type 2 diabetes.	55
9	Early Senescence Syndrome (ESS) Rat	Kobayashi M et al. (1992)	The ESS rat has a mutation in the Werner syndrome helicase (Wrn) gene, which leads to premature aging and age-related diseases including diabetes.	56
10	Obese SHR Rat	Koletsky S (1973)	The Obese SHR rat has a spontaneous mutation in the leptin receptor gene, leading to obesity and related metabolic disorders. This model combines the characteristics of two popular research models: the SHR (Spontaneously Hypertensive Rat) and the obese Zucker rat.	57
11	SHR/N-CP RAT	Michaelis et al. (1986)	The SHR/N-CP rat has a genetic background that predisposes it to developing hypertension, obesity, and cancer, making it a valuable tool for researchers to investigate the complex relationships between these diseases.	58
12	BHE Rat	Berdanier CD et al. (1991)	The BHE rat colony was initially developed by breeding black and white hooded rats from the Pennsylvania State College lineage with albino rats from the Yale (Osborne Mendell) strain. The BHE rat serves as a model where diabetes only becomes evident in maturity.	59
		Mice Models		
1	KK Mouse	Dr. Kiyoshi Kondo (1967)	The KK mouse model was developed through a natural mutation in the gene encoding the leptin receptor (Lepr). The mutation is a point mutation that leads to a substitution of glutamine for arginine at position 105 (R105Q) in the extracellular domain of the leptin receptor.	60
2	KK-A^y Mouse	Iwatsuka et al. (1970)	The KK-A^y mouse is created by crossbreeding KK mice (which are naturally prone to diabetes) with mice carrying the A^y mutation (agouti yellow). The A^y mutation causes obesity by increasing appetite through overexpression of the agouti signaling protein, which blocks melanocortin receptors in the brain.	61
3	NOD Mouse	Makino S. et al. (1974)	The NOD mouse strain serves as a model for insulin-dependent diabetes mellitus, exhibiting hypoinsulinemia resulting from autoimmune destruction of pancreatic β cells.	62
4	Akita mouse	Yoshioka M et al. (1997)	The Akita mouse carries a point mutation in the Ins2 gene (encoding insulin), which leads to misfolding of proinsulin and results in pancreatic beta-cell dysfunction.	63
5	Diabetes Mouse (db/db)	Hummel et al. (1966)	These mice carry a mutation in the Lepr gene disrupts leptin signaling, leading to an inability to regulate food intake properly. db/db mice become extremely obese due to hyperphagia. The mice develop insulin resistance as a result of their obesity, closely mimicking the early stages of type 2 diabetes in humans.	64
6	CBA/J Mice	Leonell C. Strong (1920)	CBA/J mice, a strain have been used in autoimmune diabetes studies, often in conjunction with other strains to understand the genetic and immunological factors involved in type-1 diabetes.	65

Advantages of genetically induced diabetes

Inbred animal models resembling human type-2 diabetes offer a genetically controllable and environmentally stable resource for research, providing consistent results with small sample sizes[59, 62].

Disadvantages of genetically induced diabetes

Inbred, homogeneous, and mostly monogenic, they have limited availability and are expensive. Mortality from ketosis is high in animals with brittle pancreas (db/db, ZDF rat, P. obesus, etc.), requiring insulin for survival. Their genetic

determinism sets them apart from humans, and they demand sophisticated maintenance[53, 63, 64].

d) Virus-induced diabetes model

Emerging evidence from animal models supports the hypothesis that viruses cause disease through mechanisms related to innate immune regulation. In bioengineered diabetic-resistant mice, parvovirus infection induces islet destruction through upregulation of the Toll-like receptor 9 (TLR9) signaling pathway. The virus causes diabetes by destroying and infecting the beta-cells of the pancreas. A less infectious or cellular variant would cause equivalent damage by inducing an auto-immune response to beta-cells. Viruses have been associated with type-1 Diabetic pathogenesis.66. Consequently, viruses have been used to destroy beta-cells in a number of animal models. Damage may be caused by direct beta-cell infection or by the initiation of an autoimmune response against beta-cells. Cochsackie B virus, encephalomyocarditis virus, reovirus, RNA picornavirus, lymphocytic choiriomeningitis and Kilham rat virus are the viruses used for inducing diabetes in animal studies. The mechanism includes, in susceptible individuals, this immune response can become dysregulated, leading to autoimmune destruction of pancreatic beta-cells. Some viruses have proteins on their surface that share structural similarities with proteins present in pancreatic beta-cells, particularly in the islets of Langerhans where insulin is produced. This resemblance can lead to a phenomenon called molecular mimicry, where the immune system, while targeting the virus, also attacks the beta-cells, mistaking them for the viral particles[66, 67].

Encephalomyocarditis virus

Juvenile diabetes (type I) can be caused by viral infections and β-cell-specific autoimmunity. The D-variant of the encephalomyocarditis virus (EMC-D) is particularly good at infecting and destroying the cells in the pancreas that make insulin in certain mouse models, similar to the way it affects humans with insulin-dependent diabetes. Male mice of the ICR Swiss strain are more likely to develop diabetes when exposed to the D-variant of EMC-D compared to male mice of the C3H/HeJ strain, which are less affected. However, giving these susceptible mice cyclosporin A, a strong drug that suppresses the immune system, makes their diabetes worse and more frequent. On the other hand, cyclosporin A does not seem to have the same effect on the resistant C3H/HeJ mice[68].

Coxsackie viruses

The Coxsackie virus has been found to lead to diabetes in mice by disrupting pancreatic acinar cells. Specifically, the Coxsackie B4 strain of the virus is closely linked to the development of type 1 diabetes in humans. Infected diabetes stimulates the release of stored islet antigen, which in turn causes the activation of auto-reactive T-cells[69].

Advantages of virus-induced diabetes

Diabetes induced by viruses can be stable and irreversible[66].

Disadvantages of virus-induced diabetes

It is comparatively costlier for development. It develops Type-1 diabetes. Technical experts are required for the handling of viruses[67, 69].

e) Hormone induced diabetic model

Diabetes is a multifaceted metabolic disorder that has been observed to interact with a variety of endocrine disorders. The dysglycemia can be induced by hormonal disorders, such as excessive glucocorticoids, epinephrine, and growth hormone[70].

Mechanism of action of glucocorticoids

Growth hormone-induced diabetes

Cotes et al. (1949) outlined how the growth hormone from the anterior pituitary can cause diabetes in cats. In adult dogs and cats that are still in good health, giving them growth hormone repeatedly leads to a severe form of diabetes, characterized by severe ketonuria and ketonemia. However, rats of any age given the same treatment do not develop diabetes but do experience accelerated growth and show a notable increase in the size of the pancreatic islets (Figure 3)[71].

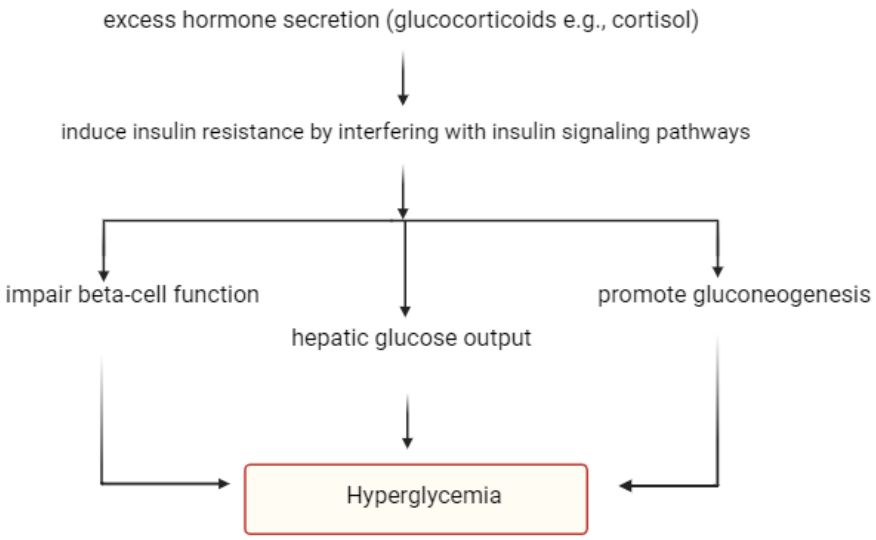


Figure 3. Mechanism of action of Glucocorticoids

Corticosteroid induced diabetes

Ingle (1941) described the hyperglycemia and glucosuria in rats that were administered with cortisone as part of a study. However, in both guinea pigs and rabbits, it was possible to induce diabetes related to corticosteroids without the need for additional feeding. In rats, the adrenal glands, when triggered by the hormone corticotrophin, have the ability to release sufficient levels of hormones that lead to steroid diabetes[72].

Advantages of hormone-induced diabetes

It is an efficient way to study hormone-driven glucose dysregulation and insulin resistance, particularly for stress-induced or endocrine-related diabetes[70].

Disadvantages of hormone-induced diabetes

Their limitations include systemic toxicity, lack of autoimmune mechanisms, and difficulty in mimicking the chronic, progressive nature of human diabetes[70].

f) Oral glucose loading animal model

This technique is commonly known as the physiological induction of diabetes mellitus because it temporarily raises the blood sugar of the animal without harming the pancreas. At the same time, checking the levels of glucose in the blood and insulin in the plasma helps in calculating measures of insulin release and insulin sensitivity[73]. This model involves administering a fixed amount of glucose orally and measuring blood glucose levels over time to observe how efficiently the animal's body processes the glucose. It is analogous to the Oral Glucose Tolerance Test (OGTT) used in humans to diagnose diabetes or prediabetes[74].

Oral glucose tolerance test for diabetes model in rodents

Animals (commonly rodents like rats or mice) are typically fasted overnight to establish baseline blood glucose levels. A specific dose of glucose (usually 1–2 grams per kilogram of body weight) is administered orally, either through feeding or via a gavage (a tube inserted into the esophagus). Blood glucose levels are measured at various time points (e.g., 0, 30, 60, 90, 120 minutes) after glucose administration to track how quickly and efficiently the glucose is cleared from the bloodstream. In diabetic or insulin-resistant animals, glucose levels remain elevated for an extended period compared to non-diabetic, indicating impaired glucose clearance and insulin function[74, 75].

Advantages of Oral Glucose Loading Animal Model

The model involves a simple oral administration of glucose and is non-invasive, making it easy to conduct without the need for complex surgeries or genetic manipulations[73].

Disadvantages of oral glucose loading animal model

While it provides a quick snapshot of how glucose is metabolized, it may not capture the full spectrum of long-term metabolic dysfunctions related to diabetes[75].

g) Insulin antibodies-induced diabetes model

The Insulin Antibodies Induced Diabetes Model is a specialized model used in research to explore the development of diabetes mediated by autoimmune responses, specifically through the generation of antibodies against insulin.76. In this model, diabetes is induced by triggering an immune response that generates antibodies against insulin. These antibodies interfere with the normal activity of insulin, impairing its ability to regulate blood glucose levels, which ultimately results in hyperglycemia and diabetes[77].

Mechanism of insulin antibodies-induced diabetes

In mice and rats, an excessive amount of pro-insulin II within the thymus organ slows down the development of diabetes, whereas a reduced presence of pro-insulin II speeds up the onset of the disease. The thymus secretes immune cells that target insulin, occurring before the emergence of auto-antibodies for insulin and can accurately forecast diabetes in the body. These insulin-targeting immune cells then penetrate the islets and carefully eliminate the cells responsible for producing insulin[77, 78].

Procedure of insulin antibodies-induced diabetes

Mice (e.g., BALB/c, C57BL/6) or rats (Wistar or Sprague-Dawley) are used of the same age group to ensure uniformity in response. Animals should be healthy and young (6-8 weeks old), as they have an active immune system, ideal for antibody generation. Insulin from a different species (human or bovine) is commonly used to elicit an immune response in the animal since endogenous insulin may not be recognized as foreign. Insulin is usually prepared in sterile saline at a concentration appropriate for inducing antibody production[78,79]. A subcutaneous or intraperitoneal injection of insulin (1-5 IU/kg) is given to the animal. Insulin injections should be prepared in adjuvants like Freund's complete adjuvant (CFA) to boost the immune response. The insulin injection is repeated multiple times (weekly or bi-weekly) to boost the immune response and promote the formation of insulin-specific antibodies[79, 80]. Blood samples are collected to measure the presence of insulin antibodies by using Enzyme-Linked Immunosorbent Assay (ELISA) or Radioimmunoassay (RIA).

Advantages of insulin antibodies-induced diabetes model

It is useful for studying the mechanisms underlying autoimmune diabetes. It is useful for testing immunosuppressive drugs or vaccines designed to prevent the production of insulin antibodies, offering potential strategies to treat or prevent Type 1 diabetes[77, 78].

Disadvantages of insulin antibodies-induced diabetes model

The development of insulin antibodies can take time, and repeated insulin administration may be needed, making the model time-consuming and costly compared to other methods of inducing diabetes in animals[77, 79].

Complications of diabetes mellitus induction

Diabetes induced in experimental animals, particularly rodents like mice and rats are frequently used models in research to study the disease and its complications due to their similarities to humans in terms of physiology and genetics (as shown in Figure 4). These complications that come along with diabetes are classified as microvascular, caused by blood vessel damage, and macrovascular disease resulting from artery damage[81]. Diabetes-

induced complications in experimental animals are extensively studied to understand the pathophysiology of the disease and to develop potential treatments. Numerous complications observed in experimental animals with induced diabetes include neuropathy, retinopathy, nephropathy, cardiovascular diseases, and cerebrovascular diseases[82].

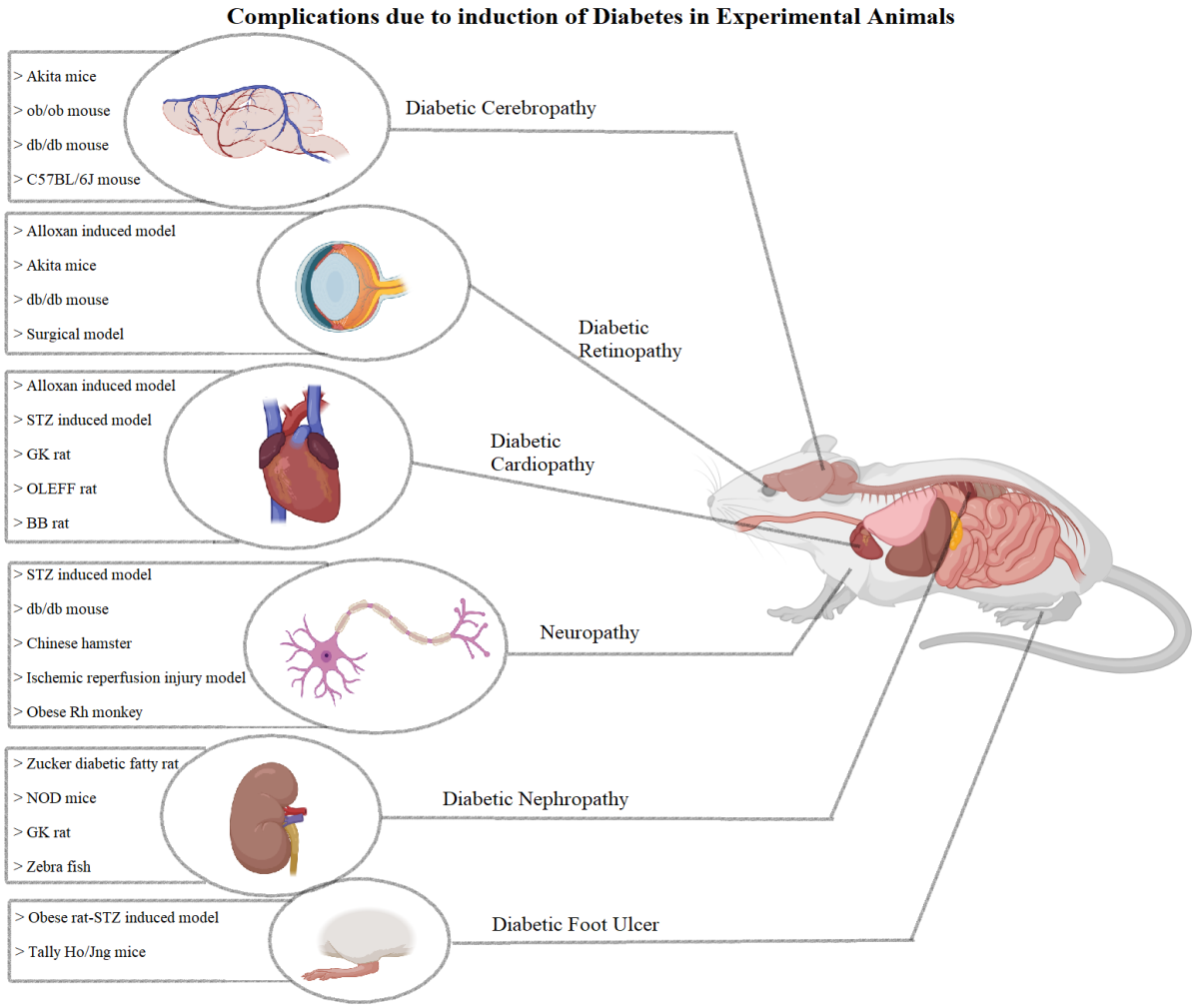


Figure 4. Diagrammatic representation of Diabetes-induced animal models that are at the risk of diseases/ complications mentioned above

Cerebropathy/ cerebrovascular disease

Induction of diabetes in animals, particularly rodents, can lead to cerebrovascular disease, characterized by damage to blood vessels supplying the brain. It can occur in breeds like Akita mice, ob/ob mice, db/db mice, and C57BL/6J[83].

Diabetic retinopathy

Diabetic retinopathy is a common complication of diabetes affecting the eyes. It can occur due to elevated blood glucose levels in diabetic animals contributing to the development of retinopathy. Chronic hyperglycemia causes damage to the small blood vessels (microvasculature) in the retina[84].

Cardiomyopathy/ Cardiovascular disease

The induction of diabetes in animals can lead to the development of diabetic cardiomyopathy, a condition characterized by structural and functional abnormalities in the heart muscle. Diabetes can lead to microvascular dysfunction in the heart, impairing coronary perfusion and exacerbating myocardial damage[85].

Diabetic neuropathy

In animal models of diabetes, including those induced by streptozotocin (STZ), neuropathy refers to damage to the peripheral nerves that occurs as a complication of diabetes mellitus. Chronic hyperglycemia causes metabolic changes that directly damage nerves and disrupt nerve function contributing to neuropathy development. Diabetes affects small blood vessels supplying nerves, leading to reduced blood flow (microvascular changes). Poor blood flow deprives nerves of oxygen and nutrients, further damaging nerve tissues86.

Diabetic nephropathy

Nephropathy in animal models of diabetes involves complex interactions between hemodynamic changes, cellular responses, inflammation, and oxidative stress, leading to structural and functional alterations in the kidney resembling diabetic nephropathy in humans.87. Diabetes activates the RAS within the kidney, leading to increased Angiotensin II levels. Angiotensin II promotes vasoconstriction, inflammation, and fibrosis, further contributing to renal damage. Diabetes damages the glomerular filtration barrier, comprising endothelial cells, basement membrane, and podocytes[88].

Diabetic foot ulcer

Diabetes-induced foot ulcers in animal models resemble those seen in diabetic patients, providing valuable insights into the pathophysiology of diabetic complications and potential therapeutic interventions. Diabetes compromises the immune system, impairing the body's ability to fight infections. Even minor injuries to the foot can develop into non-healing ulcers due to impaired immune response[89].

2. Conclusion

Different animal models that are similar to human diabetes have been discussed but each model possesses its own characteristics. Although inducing agents are different for each model overall all model targets precipitate human diabetes by the destruction of beta-cells in the pancreas. These animal models are not only helpful for the pharmacological screening of new compounds but they will be useful for the mechanism underlying the disease (diabetes). The selection of the model generally depends on the study protocol (purposes of the study). In most of the cases, Type-2 animal models are used rather than Type-1 (autoimmune type). In type-2 human similar diabetes, the mechanisms can include insulin resistance and/or beta-cell failure. During the research, the investigator determines whether a drug intervention causes improvement of symptoms in any suitable model or not. The selection of species and strains of experimental animals is the most important concern during research because different species and strains show susceptibilities to diabetes and treatments in a different manner. It is always advisable to use different species; strain as well as gender to screen a particular compound to avoid errors in the research output. In this review we have discussed many mice models that do not exist in humans for example; NOD Mouse, KK mouse, Akita mouse. Consideration of gender bias is also an important factor during using animal models for screening purposes. It has also been suggested by many researchers that, in some cases, this is due to the effects of sex hormones, where the exact mechanism of gender bias has not been elucidated. Eventually, gender bias may be due to the involvement of mitochondria and stress responses. The authors indicate that when choosing an animal model for human-similar type-1 or type-2 diabetes, it is highly recommended that a variety of different animal models (species and different strains) are needed to be used to represent the diversity seen in human-similar diabetes.

Declarations

Competing interests

The author declares no conflict of interest.

Authors' contributions

Kalpana Sen prepared the content of the Manuscript and Diagram. Trilochan Satapathy did the revising and Proofreading. All the authors read and approved the final version.

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The authors have reviewed all ethical problems, including plagiarism, consent to publish, data fabrication, and falsification.

Availability of data and materials

The data from this trial could be available with the agreement of the corresponding author.

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