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INSIGHT INTO THE EMERGING AND COMMON EXPERIMENTAL INVIVO MODELS OF DIABETES MELLITUS

***Akansha Rathore, Seema Sharma, Devshree Gayakwad and Sampat Singh Tanwar**

Acropolis Institute of Pharmaceutical Education & Research, Indore, Madhya Pradesh 452003

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****Corresponding author: Akansha Rathore***

ABSTRACT

Diabetes mellitus stands as a chronic metabolic disorder marked by elevated blood sugar levels due to deficiencies in insulin secretion, insulin action, or both. Experimental in vivo models serve as crucial tools in comprehending the onset, progression, and potential treatments for this condition. This paper offers insights into a range of experimental in vivo models, both established and emerging, utilized in diabetes research. Commencing with well-established models such as chemically induced diabetes using agents like streptozotocin (STZ) and alloxan, as well as genetic models like leptin-deficient (ob/ob) and insulin-deficient (Akita) mice, this review delineates how these models replicate specific facets of diabetes pathophysiology, thereby enabling researchers to delve into underlying mechanisms and evaluate therapeutic interventions. Moreover, emerging models including dietary-induced obesity and diabetes, alongside transgenic models targeting particular genes within insulin signaling pathways, are explored. These models shed light on the intricate interplay between genetic predispositions and environmental influences contributing to diabetes progression. Additionally, the review underscores advancements in employing non-traditional animal models such as zebrafish and Drosophila, offering unique prospects for studying conserved metabolic pathways and facilitating high-throughput drug screening. Furthermore, the integration of cutting-edge technologies like CRISPR/Cas9 gene editing and optogenetics into experimental models enhances their utility in elucidating the molecular intricacies underlying diabetes pathogenesis and identifying novel therapeutic targets. In summary, this review emphasizes the significance of experimental in vivo models in advancing our comprehension of diabetes mellitus, showcasing a diverse range of models accessible to researchers. Leveraging these models can expedite the development of innovative therapeutic strategies aimed at enhancing the management and treatment of diabetes mellitus.

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INTRODUCTION

Diabetes is a major global health concern. The underlying cause of it is persistently elevated blood glucose levels due to either insufficient insulin production by beta cells (β cells) in the pancreas or inefficient insulin uptake by body tissues(Alberti *et al*., 1998).Two main forms of diabetes exist: type 1 diabetes (T1D) and type 2 diabetes (T2D). Diabetes is a chronic illness that negatively affects several organs, including the kidney, heart, brain, and eyes. It also tends to raise the risk of other diseases brought on by macrovascular and microvascular degeneration. (Idf Diabetes Atlas Group, 2015). In addition, diabetic patients are more susceptible to infection. Several studies have reported the increased risk of lower respiratory tract infections such as pulmonary tuberculosis(Idf Diabetes Atlas Group, 2015) and pneumonia (Benfield *et al*., 2007; Kornum *et al*., 2007, 2008), urinary tract infections(Saliba *et al*., 2015) (Boyko *et al*., 2002) and skin and soft skin tissues infections(Dryden *et al*., 2015; Jenkins *et al*., 2014; Suaya *et al*., 2013) in people with diabetes. Patients with diabetes typically have poor outcomes from infection treatments.(Carey *et al*., 2018; Jia *et al*., 2011; Leibovici *et al*., 1996; Ruslami *et al*., 2010; Saliba *et al*., 2015). Diabetes patients who have an infection have greater financial burdens because of the high cost of therapy, length of treatment, and associated complications.(Kornum *et al*., 2007). The International Diabetes Federation estimated that 425 million people globally had diabetes in 2016(Cho *et al*., 2018). Both developed and developing nations are expected to see an increase in this number. By 2045, there will likely be 629 million diabetics worldwide if the condition is not properly managed and controlled. 850 million USD were spent on diabetic care in 2017, and 5 million people globally lost their lives to the disease(Cho *et al*., 2018). Naturally, the incidence of infectious diseases and the associated cost burdens would rise in low-

and middle-income nations due to the growing number of diabetics, particularly in tropical regions where the communicable disease is highly prevalent.

Type 2 diabetes mellitus: One of the most prevalent metabolic diseases in the world, Type 2 Diabetes Mellitus (T2DM) is mainly brought on by a combination of two main factors: insufficient insulin secretion by pancreatic β-cells and the tissues' incapacity to respond to insulin (Roden & Shulman, 2019).The synthesis, release, and molecular mechanisms of insulin, as well as the tissue's response to insulin, must all be tightly controlled in order for insulin to perfectly fulfil the metabolic demand. Consequently, malfunctions in any of the underlying systems may result in a metabolic dysregulation that triggers the development of type 2 diabetes. The main features of Type 2 Diabetes (T2DM), the molecular pathways and mechanisms linked to insulin metabolism, and the connections between T2DM and cardiovascular pathology are all examined in this study. The global trends of type 2 diabetes (T2DM) are discussed in this study, along with the contributions of main risk factors, including lifestyle factors, obesity, genetic predispositions, gut dysbiosis, epigenetics, and mitochondrial dysfunction. We highlight the molecular and physiological pathways that cause type 2 diabetes and its consequences.

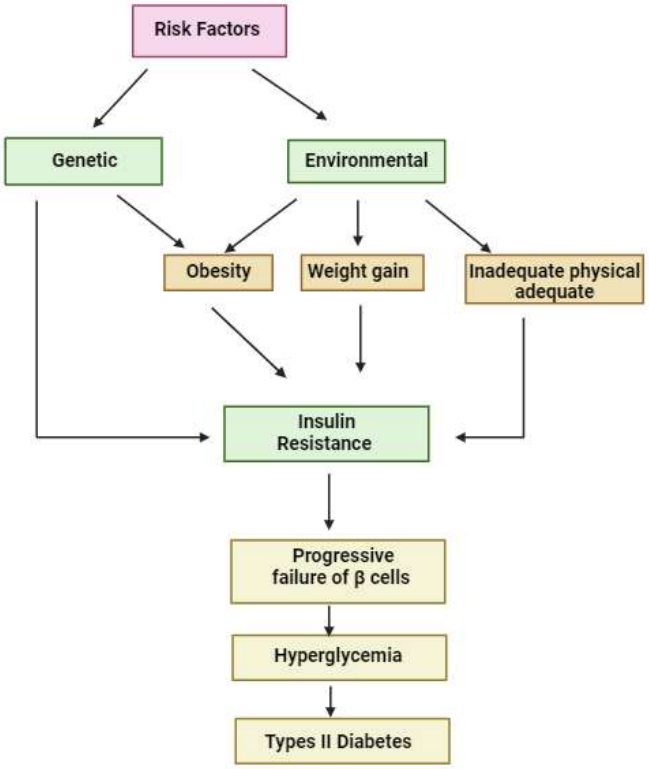

Fig. 1. Mechanism of Type Two Diabetes Mellitus

Type 2 Diabetes Mellitus: Background and Epidemiology: The World Health Organisation (WHO) describes diabetes mellitus as a chronic metabolic disease marked by high blood glucose levels. Over time, this condition can cause damage to the heart, blood vessels, eyes, kidneys, and nerves. T2DM, which is characterised by insufficient insulin secretion by pancreatic islet β-cells, tissue insulin resistance (IR), and insufficient compensatory insulin secretory response, accounts for more than 90% of cases of diabetes mellitus.(Stumvoll *et al*., 2005; Weyer *et al*., 1999). Hyperglycemia results from insulin secretion's inability to maintain glucose homeostasis as the disease progresses. The main characteristic of T2DM patients is obesity or a greater body fat percentage, which is primarily distributed in the abdominal area. Adipose tissue in this disease induces IR through a number of inflammatory pathways, such as elevated production of free fatty acids (FFA) and dysregulation of adipokines. Sedentary lifestyles, high-calorie meals, population ageing, and the global rise in obesity are the main causes of the T2DM epidemic, which has tripled the incidence and prevalence of T2DM. (Chatterjee *et al*., 2017; Zhou *et al*., 2016). The organs implicated in the development of type 2 diabetes include the brain, small intestine, liver, skeletal muscle, kidneys, and adipose tissue (DeFronzo, 2009). An major pathophysiological aspect that has emerged is the involvement of immunological dysregulation, inflammation, and alterations in gut microbiota, as suggested by evolving research (Schwartz *et al*., 2016).The epidemiological data indicate concerning trends that point to a concerning future for type 2 diabetes. The International Diabetes Federation (IDF) estimates that 463 million persons between the ages of 20 and 79 have diabetes, a number that is expected to increase to 700 million by 2045. In 2019, diabetes was reported to be the cause of 4.2 million fatalities. At least 720 billion USD in medical expenses in 2019 were related to diabetes. Furthermore, 1 in 3 diabetics, or 232 million people, had an underdiagnosis, suggesting that the actual disease burden of T2DM is probably underreported. The age group between 40 and 59 is the one with the highest percentage of diabetic patients. Geographical differences in the incidence and prevalence of type 2 diabetes arise from the fact that over 80% of patients reside in low- to middle-income nations, which makes treatment even more difficult. With cardiovascular disease (CVD) being the main cause of morbidity and death associated with T2DM, patients with the condition have a 15% higher chance of dying from all causes when compared to those without the disease (Gæde *et al*., 2003). A meta-analysis revealed that diabetes was associated with a higher risk of coronary heart disease (hazard ratio [HR] 2.00; 95% CI 1.83–2.19), ischemic stroke (HR 2.27; 1.95–2.65), and other vascular disease-related fatalities (HR 1.73; 1.51–1.98)(The Emerging Risk Factors Collaboration, 2010). Environment and heredity both have an impact on the epidemiology of type 2 diabetes. Once exposed to a setting that encourages sedentary behaviour and a high calorie intake, genetic factors start to take influence. Genome-wide association studies have shown common glycaemic genetic variations for type 2 diabetes, however these only explain 10% of the variance in the trait, indicating the significance of uncommon variants and their contribution (Grarup *et al*., 2014). Individuals with distinct phenotypes that heighten susceptibility to clusters of cardiovascular disease risk factors, such as insulin resistance, dyslipidemia, and hypertension, may come from different ethnic backgrounds (Wong *et al*., 2016).

Animal Models of Type 2 Diabetes Mellitus

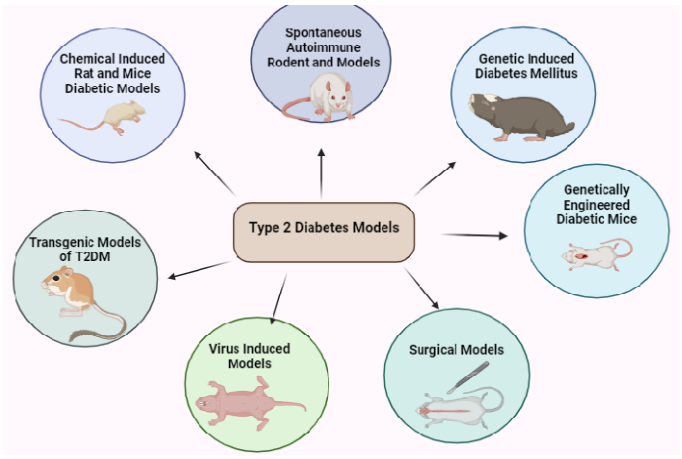

Fig. 2. Animal Models

Chemical induced animal model of Diabetes Mellitus T2DM: Most often, animals are used to induce experimental diabetes mellitus(Roep & Atkinson, 2004). because studying the pathophysiology of the disease using animal models is effective(Arndt *et al*., 2013). The most effective method for comprehending the intricate a etiology and multi-systemic interactions associated with diabetes is still using animal models, despite the availability and advancement of numerous in vitro and in silico research in recent decades(Graham & Schuurman, 2015a). While some research are conducted on larger animals, rodents are used in many diabetes trials. The three types of

experimental animals employed in the research of diabetes mellitus are genetically diabetic animals, various models, and other models based on the techniques used to create experimental diabetes mellitus (Kumar *et al*., 2012a). Diabetes can occur spontaneously or with the use of chemical agents in experimental animals (Chatzigeorgiou *et al*., 2009). There are two main methods for creating animal models: genetic alteration or illness induction (e.g., by using specific medicines). In order to comprehend the pathogenesis and course of the disease and to extrapolate to humans, both are significant since they allow the examination of specific pathways associated to the illness. Selecting the appropriate animal model for use in various in vivo research requires careful thought because T1DM and T2DM are metabolic disorders that reflect complex integration of bodily systems (Vieira *et al*., 2019). In order to accomplish this, selecting an animal model for diabetes mellitus requires a thorough examination of the unique features of the condition as well as the unique information that each study aims to address(Rees & Alcolado, 2005a).The type of diabetes that the experimental animal models genuinely imitate as well as the technique of induction—such as spontaneous or induced—are used to categorise the models(Graham & Schuurman, 2015b; Perlman, 2016). T1DM is typified by insufficient insulin production, which is obtained in lab animals by either chemically eliminating pancreatic β-cells or by producing rats with autoimmune diabetes that arises on its own. Conversely, there are many more T2DM animal models available, including models of both obesity and nonobesity with varying degrees of β-cell loss and insulin resistance. Furthermore, transgenic and knockout mouse models are available; however, their application in the research field is still debatable(Rees & Alcolado, 2005b).

Mice and Rats: Utilising mice as test subjects has greatly advanced our knowledge of human biology(Peltonen & McKusick, 2001). Because of the genetic similarity between the two species, mouse models are widely used to investigate human diseases (Heydemann, 2016).The basic understanding of human disease is mostly gained through the use of mouse models, and this understanding is then applied to preclinical research using the same mice models(Islam, M.S. & Loots, D.T., 2009). In experimental studies on obesity and type 2 diabetes, mice are a valuable tool for determining the role of inflammation, insulin resistance, and other possible treatments. The knowledge gained from these studies is faithfully applied to humans who have been diagnosed with the same disease(Iannaccone & Jacob, 2009).Rats provide a number of advantageous conditions and benefits over mice and other species when used as an experimental animal model for human disease(Bryda, 2013).The rodent's physiology is easier to understand, and over time, a lot of information has gathered that the mouse will take a very long time to replicate(Skovsø, 2014). Rats are widely employed as an appropriate animal model to comprehend the pathophysiology and metabolic profile associated with various phases of type 2 diabetes (Kottaisamy *et al*., 2021). Many experimental models, including those using rats and mice (Table 1), are used to study diabetes and are covered in the sections that follow.

Chemical Induced Rat and Mice diabetic models: The experimental animals are given certain drugs to make them diabetic. We refer to these substances as diabetogenic agents. When given parenterally, two widely used chemicals that cause diabetes include streptozotocin and alloxan(Federiuk *et al*., 2004).The dosage of the two medications may differ based on the kind of animal and the mode of delivery(Ighodaro *et al*., 2017).

Alloxan Induced models: An chemical substance called alloxan (5,5-dihydroxyl pyrimi-dine-2,4,6-trione) is a cytotoxic glucose analogue (Rohilla & Ali, 2012). It is employed to chemically cause diabetes mellitus through two potential processes(Lenzen, 2008). By broadly inhibiting glucokinase, the pancreatic glucose sensor found in beta cells, alloxan specifically prevents glucose-induced insulin emission, according to one investigation (Katoh *et al*., 2002a). Additionally, it triggers the production of reactive oxygen species (ROS), which starts a redox cycle that produces superoxide radicals(Szkudelski, 2001). Alloxan is reduced to a dialuric corrosive and then reoxidized to alloxane. This process produces superoxide radicals, which undergo dismutation (by superoxide dismutase) to produce hydrogen peroxide; moreover, hydroxyl radicals can be produced as a side reaction. These extremely reactive oxygen species can break apart the DNA of β-cells, which would result in apoptosis(King, 2012a). Although the liver also absorbs alloxan, alloxan-induced hepatotoxicity is negligible or unfounded because the liver has more effective ROS defence mechanisms than β-cells(Eileen Dolan, 1997).and they possess many methods for the biotransformation and removal of xenobiotics. Alloxan also promotes basic oxidation—SH classes, in particular glutathione (GSH) molecules and proteins—and dysregulates intracellular calcium homeostasis, which results in supraphysiological calcium concentrations and, ultimately, cell damage(Eileen Dolan, 1997).The range of alloxan dosages is 50–200 mg/kg in mice and 40–200 mg/kg in rodents, depending on the strain and method of administration chosen (for example, intraperitoneal and subcutaneous administration of alloxane necessitates doses up to multiple times those administered intravenously) (King, 2012b).

Streptozotocin Induced models: Streptozotocin (STZ), also referred to as N-(methylnitrosocarbamoyl)-α-d-glucosamine, is a naturally occurring substance generated by Streptomycetes achromogenes that possesses antibacterial characteristics(Yan & Wu, 2015a). that cause pancreatic β-cells to selectively absorb and destroy them https://pubmed.ncbi.nlm.nih.gov/13990586/. Additionally, it is a cytotoxic glucose analogue(Katoh *et al*., 2002b) like alloxan. According to Rakieten, STZ is used as a diabetogenic. https://pubmed.ncbi.nlm.nih.gov/4921840/. The most widely utilised substance to cause diabetes mellitus in experimental animals is the STZ (Eleazu *et al*., 2013). It is nitrosourea compound(Ventura-Sobrevilla *et al*., 2011) contains a hazardous glucose and a N-acetyl glucosamine analogue that are taken up by the transmembrane carrier protein GLUT-2 transporter and accumulate in the pancreatic β cells. https://pubmed.ncbi.nlm.nih.gov/22330251/. There are two ways that STZ might cause diabetes in rats, mice, and other animals such as rabbits and guinea pigs, depending on the dosage(Dufrane *et al*., 2006). At elevated dosages, STZ selectively targets pancreatic β cells through its alkalyzing characteristic, a typical feature of the cytotoxic nitrosourea compounds (Elsner *et al*., 2000).

Nitrosourea compounds are generally lipophilic, making them easy for cells to absorb. However, the nitrosourea compound STZ, which is a hydrophilic compound because of hexose substitution, is not easily absorbed by cells. As a result, STZ is transported to the β cells by the glucose carrier protein GLUT-2, because the chemical structure of STZ is similar to that of glucose (Paik *et al*., 1980). The chemical compound maintains the pancreatic α cell and extra pancreatic cells intact, without affecting the pancreatic β cell, which typically possesses selective properties of the STZ (Katoh *et al*., 2002b). Similar circumstances apply to humans, where STZ has no effect on any pancreatic cell, including the β cell (Yan & Wu, 2015a). The release of the enzyme glutamic acid decarboxylase causes STZ to cause an immunological and inflammatory response at low doses (typically administered as multiple exposure)(Ellis & Atkinson, 1996). In autoimmune diabetes, this enzyme is a key autoantigen (Kanaani *et al*., 2004). The enzyme interacts with the immunological effector cells after being released from the islet β cell(Deeds *et al*., 2011).This disease promotes the breakdown of β cells and develops a hyperglycemic state linked to inflammatory infiltrates, specifically with pancreatic lymphocytes (Yan & Wu, 2015b). In the high-portion STZ approach, a single dose of STZ is administered intraperitoneally (100–200 mg/kg) or intravenously (35–65 mg/kg) to mice or rats, resulting in significant death of the pancreatic β-cells and little to no insulin production(Furman, 2015). Several low-portion STZ techniques indicate that in order to progress insulitis, small dosages (20 to 40 mg/kg/day) need be administered over an ill-defined period of time (King, 2012a; Thayer *et al*., 2010).

Spontaneous auto-immune rodents and mouse: The most popular animal models of spontaneous diabetes for research on autoimmune diabetes include the NOD mouse, diabetes-prone BB rats, KDP rat, LETL rat, and LEW-iddm rat(Ventura-Sobrevilla *et al*., 2011).One of

the most often used models for studying type 1 diabetes (T1D) is the nonobese diabetic (NOD) mouse. This is because there are some genetic and immunological similarities between the metabolic disease in humans and the NOD mice(Pearson *et al*., 2016). This model can develop a comparable unrestricted illness to people, in contrast to other mice used in autoimmune studies. The use of this model has spurred some advancements in our understanding of the disease, such as the identification of a few human-comparable auto antigens and biomarkers that have aided in the discovery of therapeutic targets(Makino *et al*., 1980).In the pancreatic islets of langerhans area, this NOD mouse's progenitor strain, the Cataract Shionogi (CTS strain), displayed polyuria, glycosuria, and lymphocytic infiltration(Mathews, 2005).The major histocompatibility complex is the most significant genetic component contributing to T1D defenselessness in both NOD mice and humans (MHC). Numerous genes in NOD mice make them prone to type 1 diabetes, just like in people. MHC alleles have a significant impact on how the illness progresses. The combined effect of several MHC alleles and non-MHC genes causes diabetes in both humans and NOD mice(Wallis *et al*., 2009). The most useful experimental animals for examining the genetic foundation of type 1 diabetes are BB rats (Hartoft-Nielsen *et al*., 2009). and also in intervention studies(Holmberg *et al*., 2011; Prins *et al*., 1991). This particular type of rat was produced from outbred Wistar rodents that developed spontaneous hyperglycemia and ketoacidosis during the 1970s. These afflicted mice gave rise to two colonies, one entrenched biobreeding diabetes-prone/worceste (BBDP/Wor) and the other outbreed biobreeding diabetes-prone (BBDP) rodent, which served as the foundation for the creation of all other BB rat colonies (Mordes *et al*., 2004; Yokoi *et al*., 2003a).Ninety percent of biobreeding (BB) rodents develop diabetes between the ages of eight and seventeen. The incidence of diabetes in BB rats is similar in males and females and occurs after puberty. The extremely serious diabetes phenotype is characterised by improved hyperglycemia, hypoinsulinemia, decreased weight, and ketonuria (King, 2012a). These animals are lymphopenic, with a marked drop in CD4+T cells and near nonattendance of CD8+T cells, despite having insulitis with T-cells, B-cells, macrophages, and natural killer (NK) cells. Neither type 1 diabetes (T1D) in humans nor non-obese diabetic (NOD) animals exhibit lymphopenia(Yokoi *et al*., 2003b). One of the best spontaneous animal models for autoimmune type 1 diabetes problem research is the Komeda diabetes-prone (KDP) rat(Yokoi *et al*., 2007). In the study of autoimmune diseases, particularly autoimmune thyroid disease, it is also a crucial experimental model (Komeda *et al*., 1998a).

The KDP rats' phenotypic characteristics include autoimmune destruction of pancreatic β cells, quick onset of diabetes regardless of age or gender, and no discernible thymopenia. The traits are very similar to those of type 1 diabetes in humans (Yokoi *et al*., 1997). The majority of the KDP rats show moderate to severe levels of lymphocyte infiltration into the pancreatic islets, which is linked to insulinitis. Within 220 days of birth, diabetes affects about 80% of the animals (Yokoi *et al*., 1997). The major histocompatibility complex (MHC) on chromosome 20 and the IDDM/KDP 1 locus on chromosome 11 are two examples of susceptible loci that were identified by the genetic investigation of type 1 diabetes in the KDP rats (Yokoi *et al*., 2002). Eventually, a significant susceptibility gene for rat type 1 diabetes was identified as Cblb (Komeda *et al*., 1998b; Kottaisamy *et al*., 2021). Due to their remarkable resemblance to the pathophysiology of human insulin-dependent diabetic mellitus, the Long Evans Tokushima Lean (LETL) rat is one of the most commonly utilised spontaneous animal models of IDDM (Komeda *et al*., 1998b). These 1982 discovery LETL rats were descended from a few pairs of Long-Evans outbred rats that were obtained from Charles River in Canada (Ishida *et al*., 1995). The LETL rats exhibit the following behavioural traits: 1. Sudden beginning of weight loss, hyperglycemia, polyphagia, and polyuria. 2. Pancreatic β cell death and lymphocyte disappearance with the development of diabetes, which follow lymphocyte infiltration into the pancreatic islets (insulitis). 3. The lacrimal and salivary glands are impacted by lymphocytes. The disease's severity, regardless of age or gender. 5. Hyperplastic foci inside the pancreatic islets. 6. Little to no lymphocytopenia. 7. Renal problems, such as nodules, in particular (Kumar *et al*., 2012b). It has been demonstrated that these traits are strongly linked to human IDDM. After eighteen weeks of birth, the animals experience hyperglycemia (Kumar *et al*., 2012c). According to the animal's genetic investigation, the pathophysiology of insulitis requires two recessive genes (Kawano *et al*., 1991). The Lewis congenic mouse model for diabetes (T1D), represented by the characterised MHC Lewis. 1AR1 (LEW.1AR1) haplotype, spontaneously arose in a colony of these rodents. It is one of the popular models used to study type 1 diabetes in humans (T1D). These animals clearly develop diabetes between 60 and 90 days of age, characterised by rapid insulinitis progression leading to widespread β cell apoptosis (Jörns *et al*., 2005; Lenzen *et al*., 2001; Mordes *et al*., 2004). This animal can acquire type 1 diabetes in two ways, each with a distinct incidence rate. It develops autoimmune diabetes both spontaneously at a rate of about 2% and by immunological disruption at a rate of up to 100% (Arndt *et al*., 2013). Diabetes develops in this experimental rat model equally in males and females. Its distinct features set it apart from other naturally occurring animals used to research type 1 diabetes (Weiss *et al*., 2005). The animal's genetic examination revealed an autosomal recessive pattern of inheritance for the genes causing diabetes, opening the door for a thorough identification of the loci causing the disease (Azushima *et al*., 2018).

Genetically induced diabetes mellitus: AKITA mice, GK rats, Zucker diabetic fatty rats, Obese spontaneously hypertensive rats (SHR), ESS rats, and diabetes mouse (db/db) are classified as genetically induced diabetes models. Among them, the most commonly utilized model is AKITA mice. These mice harbor an Ins2+/C96Y mutation that triggers abnormal insulin folding and leads to the destruction of β cells (Kong *et al*., 2013; Todd, 2016). Initially, the Akita mice were originated on the C57BL/6 inbred strain in Akita, Japan. But these experimental animals were nowadays developed with various genetic backgrounds and are made commercially available in the market. This model involves chronic stress on protein processing involving the endoplasmic reticulum and unfolded protein response triggering apoptosis and diabetes. The unfolded protein response tries to compensate and reduce the protein load of the endoplasmic reticulum, increasing its folding capacity(Goto *et al*., 1976). Pancreatic β cells become toxic as a result, which lowers insulin output. In the first four weeks of life, there is a noticeable increase in both the glucose level and albuminuria. The albuminuria tends to increase more rapidly in the tenth week. are therefore used in research on problems associated with diabetes. The Goto-Kakizaki (GK) rats do not have obesity and are insulin-resistant. GK rats are a highly developed strain of Wistar rats that develop type 2 diabetes right away (Movassat *et al*., 2007). This model of type 2 diabetes and its associated consequences is based on genetic research(Portha, 2005; Portha *et al*., 2009). After 56 days after birth, peripheral insulin resistance sets established. The number of pancreatic β cells and their functions have diminished (Nie *et al*., 2011). This rat's disease progression has been linked to chronic inflammation, which is why it is used in type 2 diabetes pathogenesis and treatment research(Garnett *et al*., 2005; Xue *et al*., 2011).One kind of experimental animal model that mimics type 2 diabetes in humans is the Zucker diabetic fatty (ZDF) rat. In Walter Shaw's laboratory in Indianapolis, USA, there was a colony of outbred Zucker rats that gave rise to the tese rats. In 1991, a genetic model of the Zucker diabetic rat was created. This animal's spontaneous mutation of the simple autosomal recessive leptin receptor gene (fa) on chromosome 5 results in insulin resistance, hyperphagia, and obesity (D. Chen & Wang, 2005; M. S. Phillips *et al*., 1996; Slieker *et al*., 1992). The most common use of ZDF male rats is in the research of type 2 diabetes and the transition from prediabetic to diabetic state (Wexler *et al*., 1980). Mutation produces the obese spontaneously hypersensitive rat (SHR), which has genetic obesity, endogenous hyperlipemia, and other problems related to metabolism. This strain is created from the mating of a normotensive Sprague-Dawley male with an unrestrained hypertensive Kyoto-Wistar strain female mouse. These models are frequently used to investigate the connection between metabolic and endocrine disorders and obesity. It is regarded as a crucial animal model for researching the roles played by hyperlipemia and elevated

blood pressure in the arthrosclerosis pathogenesis(Koletsky, 1973).The inbred ESS rat (e Stilman Siagado) strain is kept alive at Rosario University's medical school in Argentina.It is a type of experimental rat that does not develop obesity-related mild diabetes syndrom e (Dumm *et al*., 1990). From the time they are two months old until then, the animals exhibit varying degrees of glucose resistance. The illness is a mild type of diabetes that doesn't shorten an animal's life. Rodents that were six months old showed signs of stroma fibrosis and islet pulverisation(Hummel *et al*., 1966). The Jackson laboratory created the diabetes mouse (db/db), which is caused by an autosomal recessive mutation in the leptin receptor. On chromosome 4, there is a Gly to Tr mutation in the leptin receptor gene. These animals exhibit several symptoms, including hyperglycemia, which is often seen between 4 and 8 weeks of age, obesity, which is evident from 3-5 weeks of age, and hyperphagia, or excessive eating(W. Chen *et al*., 2009; Ikeda, 1994). These mice develop a severe form of diabetes, characterised by initial hypoinsulinemia and hyperglycemia. Changes in leptin receptors result in a wide phenotype that is identical to that of Ob mice. Ob-Ra, Ob-Rb, Ob-Rc, and Ob-Rd are among the five alternative joined forms that the leptin receptor (Ob-R) encodes. If the grafting is uncommon, the Ob-Rb transcript has a supplement with a premature stop codon in the C57BL/KsJ ob/ob mouse strain(M. S. Phillips *et al*., 1996).

Genetically engineered diabetic mice: Obese hyperglycemic mice and KK mice are two of the genetically modified diabetic animals. The KK mouse is frequently used to study diabetes that is linked to obesity. This mouse has polyphagia, polyuria, and moderate obesity as distinguishing characteristics. Since the KK mouse did not exhibit hyperglycemia or glycosuremia, but did exhibit insulin resistance and glucose intolerance, its diabetic state was determined to be chemical diabetes (Berndt *et al*., 2014). The KK mouse can age and have a high-fat diet, which can lead to the development of type 2 diabetes (Bleisch *et al*., 1952). Bleisch *et al*. identified genetically obese hyperglycemic mice as having developed diabetes. Although the non-fasting blood sugar level in these mice is approximately 300 mg%, they are glycosuric and do not exhibit ketonuria or coma (Halaas *et al*., 1995). The langerhans islands have a higher insulin concentration and are hypertrophic. Clearly, the hyperglycemic mice's diabetes and the human diabetic patient's diabetes are not exactly the same. According to Halaas *et al*., leptin substitution completely reverses the phenotype associated with obesity and diabetes (Leahy *et al*., 1988).

Surgical models: These models are frequently used to investigate the regeneration potential of β cells or their progenitors. The paradigm that is more significant for the study of diabetes is partial pancreatectomy, which is the partial or complete removal of the pancreas through surgery. In rat models, diabetes is brought on by removing 95% of the pancreas within three months, and dogs and pigs also exhibit this same process. However, it is a fact that a 60% partial pancreatectomy only results in a slight increase in cell mass level and does not raise blood glucose concentrations (Bonner-Weir *et al*., 1983). Approximately 90% of pancreatectomy patients experience mild hyperglycemia, which is subsequently followed by pancreatic regeneration (Yoon *et al*., 1986).This model is technically insignificant due to its invasiveness, particularly when it comes to healthy tissues instead of the pancreas (King, 2012a).

Virus induced models: Diabetes mellitus is brought on by viruses that damage and infect the pancreatic beta cells. Coxsackie B virus is one of the many RNA picornoviruses that cause diabetes in humans (Guberski *et al*., 1991). Kilham Rat Virus (Yoon *et al*., 1979) Coxsackie virus B4, or CVB4, is the enterovirus that is most frequently detected in people with diabetes. When injected into murine cells, the CVB strain that was isolated from the pancreas of a sick child with diabetic ketoacidosis causes diabetes in the cells (Utsugi *et al*., 1992). Insulin-dependent diabetic mellitus has been linked to the Coxsackie virus. The EMC-D virus can infect and kill mice's pancreatic beta-cells, resulting in insulin-dependent hyperglycemia. The NDK2 virus is identified as an EMC virus clone. Diabetes mellitus that is not insulin dependent is brought on by an intraperitoneal injection of NDK25(Meier & Yerganian, 1961).

Transgenic models of T2DM

Chinese hamster

Meier and Yerganian (Meier & Yerganian, 1961). The manifestation of hereditary diabetes mellitus in Chinese hamsters (Cricetulus griseus) is characterized by notable physiological changes. Diabetic hamsters exhibit a marked elevation in blood glucose levels, soaring from the typical 110 mg to as high as 600 mg per deciliter. Concomitantly, they display pronounced symptoms including excessive urination (polyuria), excretion of glucose in urine (glycosuria), presence of ketones in urine (ketonuria), and excessive protein excretion in urine (proteinuria).The administration of insulin and oral antidiabetic medications has demonstrated efficacy in ameliorating these diabetic symptoms. Histological examination of pancreatic, hepatic, and renal tissues reveals significant pathological alterations over time. Specifically, there is a discernible decline in the number of pancreatic islets, accompanied by abnormalities in the remaining islet cells (Wise *et al*., 1972).

Tuco-Tuco: According to Shrewd *et al*., prickly mice and sand rodents are comparable to Tuco Tucos (Ctenomys talarum) in their diabetes illness. On the other hand, tuco-tucos are less likely to enter ketosis and have lower blood sugar levels. Numerous animals, mostly males, develop hyperphagia. In certain animals, the typical lesion in the pancreas is the degranulation of β cells; nevertheless, amyloid islet hyalinization has also been noted.

Sand rat: Psammomys obesus, the sand rat, inhabits the arid regions of northeastern Africa and eastern Sudan(Ziv *et al*., 1999). The impact and implications of diet and exercise on the development of type 2 diabetes are studied in this rat model(Marquié *et al*., 1991).When the animals are fed laboratory chow instead of a whole vegetable diet, they develop the adverse symptoms of diabetes(Matveyenko & Butler, 2006). Most often, the diabetic condition develops in sand rats in two to three months. Animals with true hyperglycemia snatch at the dust rashly from ketosis. When these animals are given a diet high in cholesterol, they become hyperlipidemic and develop arthrosclerosis (Shafrir *et al*., 2006).

Spiny mouse: The spiny mouse (Acomys cahirinus) is found in semi-arid regions of the eastern Mediterranean. In laboratory conditions, approximately 15 percent of these mice develop diabetes. This diabetes is a result of endocrine-pancreatic hyperplasia. Some mice exhibit obesity, moderate high blood sugar levels, and low insulin levels, while others experience severe glucosuric hyperglycemia, leading to fatal ketosis. Notably, all spiny mice display significant pancreatic islet hyperplasia and increased insulin content in the pancreas("OUP Accepted Manuscript," 2017).

African hamster: The spiny mouse (Acomys cahirinus) inhabits semi-arid areas in the eastern Mediterranean. About 15 percent of these mice develop diabetes under laboratory conditions due to endocrine-pancreatic hyperplasia. While some mice show signs of obesity, moderately high blood sugar, and low insulin levels, others suffer from severe glucosuric hyperglycemia, ultimately resulting in fatal ketosis. Importantly, all spiny mice exhibit notable pancreatic islet hyperplasia and elevated insulin content in the pancreas(Kumar *et al*., 2012d).

Invertebrate animal model- Bombyx mori: The issues surrounding contemporary animal rights can be resolved by substituting an invertebrate animal model for a mammalian one, which will lower the mortality rate of mammals (The International Silkworm Genome Consortium, 2008). Due to their high homologous gene content with humans, silkworms are used as an animal model in life sciences research. In addition, silkworms are reasonably sized, easily dissectable organisms. The capacity to do oral administration and intravenous injection examination tests on silkworms is made

possible by this characteristic (Zhang *et al*., 2012). The human adenylate protein kinase signalling pathway controls blood glucose levels, and in silkworms, the hemolymph glucose levels are also regulated by the same signalling pathway. Furthermore, there is a 40% resemblance between the insulin-like peptide encoded by the silkworms' genes and human insulin. The development of the silkworm as a diabetes model is facilitated by these two characteristics. Transgenic silkworms that express the human insulin receptor (hIR) can do this (R. W. Phillips *et al*., 1982).

Pigs as diabetic models: Pigs are used as a great model for studying diabetes and its associated problems. The reason for this is that the pig's pancreas and its general metabolic state are comparable to those of humans. The Yucatan Peninsula in Mexico is where the Yucatan pig originated. Colorado State University is where the animal was first discovered and described. It's said that selective breeding works well for producing pigs with a lower glucose tolerance(Boullion *et al*., 2003).The quantity of islets of langerhans and β cells in these pigs is determined to be normal, and their response to isoproterenol challenge results in normal insulin secretion.

Primate model-obese Rh monkey: The rhesus monkey was first used as an experimental model for diabetes by Hansen *et al*. The monkeys are divided into successive phases of the metabolic disease according to age, body weight, glucose tolerance, fasting insulin levels, and secretory insulin levels. Sequential variations in blood glucose levels and plasma insulin variability are identified as indicators of the onset of type 2 diabetes and impaired glucose tolerance. After the monkey developed diabetes, a high concentration of islet amyloid gradually developed (Bremer *et al*., 2011). A high-fructose diet causes rhesus monkeys to become insulin resistant, obese, and inflammatory quickly before they eventually develop type 2 diabetes (Zhu *et al*., 2014). Preclinical islet transplantation research identify the rhesus and cynomolgus monkeys as valuable animal models to study the effects of therapeutic arbitrations(Den Broeder *et al*., 2015).

Zebra fish models: Zebra fish are now commonly used in diabetes research. It is a useful model system for researching metabolic abnormalities and is also employed in the diagnosis and development of therapies for certain conditions. Energy homeostasis and cholesterol metabolism are conserved in zebrafish. They are a perfect model for studying lipid metabolism because of these important characteristics (Lieschke & Currie, 2007). Additionally, zebrafish are commonly used in clinical research since they resemble humans in having well-developed organ systems such the digestive system, skeletal muscle, and adipose tissue (Oka *et al*., 2010). When zebra fish are overfed, it is discovered that their plasma triglyceride levels rise and they experience hepatic steatosis (Teame *et al*., 2019). The treatment of diet-induced insulin resistance and glucose intolerance also makes use of it. The great degree of genetic similarities between humans and zebrafish makes them useful for studying metabolic disorders. The zebra fish is recognised as a special model for the study of metabolic problems in humans due to the availability of its fully sequenced genome, ease of genetic manipulation, and greater fertility rates (Papatheodorou *et al*., 2018).

CONCLUSION

The exploration of both established and emerging experimental in vivo models of Diabetes Mellitus (DM) reflects the dynamic nature of research in comprehending this intricate metabolic condition. Through the examination of well-established models such as chemically induced diabetes and genetic models, alongside emerging models like dietary-induced obesity and transgenic models, researchers gain invaluable insights into the complex interplay of genetic and environmental factors contributing to DM's onset and progression. Furthermore, the utilization of non-traditional animal models such as zebrafish and Drosophila broadens the horizons of DM research, facilitating the study of conserved metabolic pathways and enabling innovative approaches to drug screening. Moreover, the integration of advanced technologies such as CRISPR/Cas9 gene editing and optogenetics enhances the precision and depth of our comprehension of DM pathophysiology, opening avenues for the identification of novel therapeutic targets.Overall, the diverse range of experimental in vivo models elucidated in this review underscores the collaborative efforts within the scientific community to advance our understanding of DM and develop more effective treatments. By harnessing these models and technologies, researchers can expedite the development of personalized therapeutic strategies aimed at enhancing the management and outcomes of DM patients, ultimately leading to improved health outcomes for individuals affected by this prevalent metabolic disorder.

REFERENCES

Alberti, K. G. M. M., Zimmet, P. Z., & WHO Consultation. 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. *Diabetic Medicine*, *15*(7), 539–553. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S

Arndt, T., Jörns, A., Weiss, H., Tiedge, M., Hedrich, H.-J., Lenzen, S., & Wedekind, D. 2013. A Variable CD3+ T-Cell Frequency in Peripheral Blood Lymphocytes Associated with Type 1 Diabetes Mellitus Development in the LEW.1AR1-iddm Rat. *PLoS ONE*, *8*(5), e64305. https://doi.org/10.1371/journal.pone.0064305

Azushima, K., Gurley, S. B., & Coffman, T. M. 2018. Modelling diabetic nephropathy in mice. *Nature Reviews Nephrology*, *14*(1), 48–56. https://doi.org/10.1038/nrneph.2017.142

Benfield, T., Jensen, J. S., & Nordestgaard, B. G. 2007. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia*, *50*(3), 549–554. https://doi.org/10.1007/s00125-006-0570-3

Berndt, A., Sundberg, B. A., Silva, K. A., Kennedy, V. E., Richardson, M. A., Li, Q., Bronson, R. T., Uitto, J., & Sundberg, J. P. 2014. Phenotypic Characterization of the KK/HlJ Inbred Mouse Strain. *Veterinary Pathology*, *51*(4), 846–857. https://doi.org/10.1177/0300985813501335

Bleisch, V. R., Mayer, J., & Dickie, M. M. 1952. Familial diabetes mellitus in mice, associated with insulin resistance, obesity, and hyperplasia of the islands of langerhans. *The American Journal of Pathology*, *28*(3), 369–385.

Bonner-Weir, S., Trent, D. F., & Weir, G. C. 1983. Partial pancreatectomy in the rat and subsequent defect in glucose-induced insulin release. *Journal of Clinical Investigation*, *71*(6), 1544–1553. https://doi.org/10.1172/JCI110910

Boullion, R. D., Mokelke, E. A., Wamhoff, B. R., Otis, C. R., Wenzel, J., Dixon, J. L., & Sturek, M. 2003. Porcine model of diabetic dyslipidemia: Insulin and feed algorithms for mimicking diabetes mellitus in humans. *Comparative Medicine*, *53*(1), 42–52.

Boyko, E. J., Fihn, S. D., Scholes, D., Chen, C.-L., Normand, E. H., & Yarbro, P. 2002. Diabetes and the Risk of Acute Urinary Tract Infection Among Postmenopausal Women. *Diabetes Care*, *25*(10), 1778–1783. https://doi.org/10.2337/diacare.25.10.1778

Bremer, A. A., Stanhope, K. L., Graham, J. L., Cummings, B. P., Wang, W., Saville, B. R., & Havel, P. J. 2011. Fructose-Fed Rhesus Monkeys: A Nonhuman Primate Model of Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes. *Clinical and Translational Science*, *4*(4), 243–252. https://doi.org/10.1111/j.1752-8062.2011.00298.x

Bryda, E. C. 2013. The Mighty Mouse: The impact of rodents on advances in biomedical research. *Missouri Medicine*, *110*(3), 207–211.

Carey, I. M., Critchley, J. A., DeWilde, S., Harris, T., Hosking, F. J., & Cook, D. G. 2018. Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study. *Diabetes Care*, *41*(3), 513–521. https://doi.org/10.2337/dc17-2131

Chatterjee, S., Khunti, K., & Davies, M. J. 2017. Type 2 diabetes. *The Lancet*, *389*(10085), 2239–2251. https://doi.org/10.1016/ S0140-6736(17)30058-2

Chatzigeorgiou, A., Halapas, A., Kalafatakis, K., & Kamper, E. 2009. The use of animal models in the study of diabetes mellitus. *In Vivo (Athens, Greece)*, *23*(2), 245–258.

Chen, D., & Wang, M. 2005. Development and application of rodent models for type 2 diabetes. *Diabetes, Obesity and Metabolism*, *7*(4), 307–317. https://doi.org/10.1111/j.1463-1326.2004.00392.x

Chen, W., Zhou, X., Liu, H., Xu, C., Wang, L., & Li, S. 2009. P633H, a novel dual agonist at peroxisome proliferator-activated receptors α and γ, with different anti-diabetic effects in *db/db* and KK-A ^{y} mice. *British Journal of Pharmacology*, *157*(5), 724–735. https://doi.org/10.1111/j.1476-5381.2009.00231.x

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., Da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. 2018. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023

Deeds, M. C., Anderson, J. M., Armstrong, A. S., Gastineau, D. A., Hiddinga, H. J., Jahangir, A., Eberhardt, N. L., & Kudva, Y. C. 2011. Single dose streptozotocin-induced diabetes: Considerations for study design in islet transplantation models. *Laboratory Animals*, *45*(3), 131–140. https://doi.org/10.1258/la.2010.010090

DeFronzo, R. A. 2009. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes*, *58*(4), 773–795. https://doi.org/10.2337/db09-9028

Den Broeder, M. J., Kopylova, V. A., Kamminga, L. M., & Legler, J. 2015. Zebrafish as a Model to Study the Role of Peroxisome Proliferating-Activated Receptors in Adipogenesis and Obesity. *PPAR Research*, *2015*, 1–11. https://doi.org/10.1155/2015/358029

Dryden, M., Baguneid, M., Eckmann, C., Corman, S., Stephens, J., Solem, C., Li, J., Charbonneau, C., Baillon-Plot, N., & Haider, S. 2015. Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: Focus on skin and soft-tissue infections. *Clinical Microbiology and Infection*, *21*, S27–S32. https://doi.org/10.1016/j.cmi.2015.03.024

Dufrane, D., Van Steenberghe, M., Guiot, Y., Goebbels, R.-M., Saliez, A., & Gianello, P. 2006. Streptozotocin-Induced Diabetes in Large Animals (Pigs/Primates): Role of GLUT2 Transporter and β-cell Plasticity. *Transplantation*, *81*(1), 36–45. https://doi.org/10.1097/01.tp.0000189712.74495.82

Dumm, C. L. A. G., Semino, M. C., & Gagliardino, J. J. 1990. Sequential Morphological Changes in Pancreatic Islets of Spontaneously Diabetic Rats: *Pancreas*, *5*(5), 533–539. https://doi.org/10.1097/00006676-199009000-00007

Eileen Dolan, M. 1997. Inhibition of DNA repair as a means of increasing the antitumor activity of DNA reactive agents. *Advanced Drug Delivery Reviews*, *26*(2–3), 105–118. https://doi.org/10.1016/S0169-409X(97)00028-8

Eleazu, C. O., Eleazu, K. C., Chukwuma, S., & Essien, U. N. 2013. Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *Journal of Diabetes & Metabolic Disorders*, *12*(1), 60. https://doi.org/10.1186/2251-6581-12-60

Ellis, T. M., & Atkinson, M. A. 1996. The clinical significance of an autoimmune response against glutamic acid decarboxylase. *Nature Medicine*, *2*(2), 148–153. https://doi.org/10.1038/nm0296-148

Elsner, M., Guldbakke, B., Tiedge, M., Munday, R., & Lenzen, S. 2000. Relative importance of transport and alkylation for pancreatic beta-cell toxicity of streptozotocin. *Diabetologia*, *43*(12), 1528–1533. https://doi.org/10.1007/s001250051564

Federiuk, I. F., Casey, H. M., Quinn, M. J., Wood, M. D., & Ward, W. K. 2004. Induction of type-1 diabetes mellitus in laboratory rats by use of alloxan: Route of administration, pitfalls, and insulin treatment. *Comparative Medicine*, *54*(3), 252–257.

Furman, B. L. 2015. Streptozotocin-Induced Diabetic Models in Mice and Rats. *Current Protocols in Pharmacology*, *70*(1). https://doi.org/10.1002/0471141755.ph0547s70

Gæde, P., Vedel, P., Larsen, N., Jensen, G. V. H., Parving, H.-H., & Pedersen, O. 2003. Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes. *New England Journal of Medicine*, *348*(5), 383–393. https://doi.org/10.1056/NEJMoa021778

Garnett, K. E., Chapman, P., Chambers, J. A., Waddell, I. D., & Boam, D. S. W. 2005. Differential gene expression between Zucker Fatty rats and Zucker Diabetic Fatty rats: A potential role for the immediate-early gene Egr-1 in regulation of beta cell proliferation. *Journal of Molecular Endocrinology*, *35*(1), 13–25. https://doi.org/10.1677/jme.1.01792

Goto, Y., Kakizaki, M., & Masaki, N. 1976. Production of Spontaneous Diabetic Rats by Repetition of Selective Breeding. *The Tohoku Journal of Experimental Medicine*, *119*(1), 85–90. https://doi.org/10.1620/tjem.119.85

Graham, M. L., & Schuurman, H.-J. 2015a. Validity of animal models of type 1 diabetes, and strategies to enhance their utility in translational research. *European Journal of Pharmacology*, *759*, 221–230. https://doi.org/10.1016/j.ejphar.2015.02.054

Graham, M. L., & Schuurman, H.-J. 2015b. Validity of animal models of type 1 diabetes, and strategies to enhance their utility in translational research. *European Journal of Pharmacology*, *759*, 221–230. https://doi.org/10.1016/j.ejphar.2015.02.054

Grarup, N., Sandholt, C. H., Hansen, T., & Pedersen, O. 2014. Genetic susceptibility to type 2 diabetes and obesity: From genome-wide association studies to rare variants and beyond. *Diabetologia*, *57*(8), 1528–1541. https://doi.org/10.1007/s00125-014-3270-4

Guberski, D. L., Thomas, V. A., Shek, W. R., Like, A. A., Handler, E. S., Rossini, A. A., Wallace, J. E., & Welsh, R. M. 1991. Induction of Type I Diabetes by Kilham's Rat Virus in Diabetes-Resistant BB/Wor Rats. *Science*, *254*(5034), 1010–1013. https://doi.org/10.1126/science.1658938

Halaas, J. L., Gajiwala, K. S., Maffei, M., Cohen, S. L., Chait, B. T., Rabinowitz, D., Lallone, R. L., Burley, S. K., & Friedman, J. M. 1995. Weight-Reducing Effects of the Plasma Protein Encoded by the *obese* Gene. *Science*, *269*(5223), 543–546. https://doi.org/10.1126/science.7624777

Hartoft-Nielsen, M.-L., Rasmussen, A. K., Bock, T., Feldt-Rasmussen, U., Kaas, A., & Buschard, K. 2009. Iodine and tri-iodo-thyronine reduce the incidence of type 1 diabetes mellitus in the autoimmune prone BB rats. *Autoimmunity*, *42*(2), 131–138. https://doi.org/10.1080/08916930802438774

Heydemann, A. 2016. An Overview of Murine High Fat Diet as a Model for Type 2 Diabetes Mellitus. *Journal of Diabetes Research*, *2016*, 1–14. https://doi.org/10.1155/2016/2902351

Holmberg, R., Refai, E., Höög, A., Crooke, R. M., Graham, M., Olivecrona, G., Berggren, P.-O., & Juntti-Berggren, L. 2011. Lowering apolipoprotein CIII delays onset of type 1 diabetes. *Proceedings of the National Academy of Sciences*, *108*(26), 10685–10689. https://doi.org/10.1073/pnas.1019553108

Hummel, K. P., Dickie, M. M., & Coleman, D. L. 1966. Diabetes, a New Mutation in the Mouse. *Science*, *153*(3740), 1127–1128. https://doi.org/10.1126/science.153.3740.1127

Iannaccone, P. M., & Jacob, H. J. 2009. Rats! *Disease Models & Mechanisms*, *2*(5–6), 206–210. https://doi.org/10.1242/dmm.002733

Idf Diabetes Atlas Group. 2015. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. *Diabetes Research and Clinical Practice*, *109*(3), 461–465. https://doi.org/10.1016/j.diabres.2015.05.037

Ighodaro, O. M., Adeosun, A. M., & Akinloye, O. A. 2017. Alloxan-induced diabetes, a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. *Medicina*, *53*(6), 365–374. https://doi.org/10.1016/j.medici.2018.02.001

Ikeda, H. 1994. KK mouse. *Diabetes Research and Clinical Practice*, *24*, S313–S316. https://doi.org/10.1016/0168-8227(94)90268-2

Ishida, K., Mizuno, A., Min, Z., Sano, T., & Shima, K. 1995. Which is the primary etiologic event in Otsuka Long-Evans Tokushima Fatty rats, a model of spontaneous non—Insulin-dependent diabetes mellitus, insulin resistance, or impaired insulin secretion? *Metabolism*, *44*(7), 940–945. https://doi.org/10.1016/0026-0495(95)90249-X

Islam, M.S. & Loots, D.T. 2009. Experimental rodent models of type 2 diabetes: A review. *Methods and Findings in Experimental and Clinical Pharmacology*, *31*(4), 249. https://doi.org/10.1358/mf.2009.31.4.1362513

Jenkins, T. C., Knepper, B. C., Jason Moore, S., Saveli, C. C., Pawlowski, S. W., Perlman, D. M., McCollister, B. D., & Burman, W. J. 2014. Comparison of the microbiology and antibiotic treatment among diabetic and nondiabetic patients hospitalized for cellulitis or cutaneous abscess. *Journal of Hospital Medicine*, *9*(12), 788–794. https://doi.org/10.1002/jhm.2267

Jia, Q., Zhao, X., Wang, C., Wang, Y., Yan, Y., Li, H., Zhong, L., Liu, L., Zheng, H., Zhou, Y., & Wang, Y. 2011. Diabetes and Poor Outcomes Within 6 Months After Acute Ischemic Stroke: The China National Stroke Registry. *Stroke*, *42*(10), 2758–2762. https://doi.org/10.1161/STROKEAHA.111.621649

Jörns, A., Günther, A., Hedrich, H.-J., Wedekind, D., Tiedge, M., & Lenzen, S. 2005. Immune Cell Infiltration, Cytokine Expression, and β-Cell Apoptosis During the Development of Type 1 Diabetes in the Spontaneously Diabetic LEW.1AR1/Ztm- *iddm* Rat. *Diabetes*, *54*(7), 2041–2052. https://doi.org/10.2337/diabetes.54.7.2041

Kanaani, J., Diacovo, M. J., El-Husseini, A. E.-D., Bredt, D. S., & Baekkeskov, S. 2004. Palmitoylation controls trafficking of GAD65 from Golgi membranes to axon-specific endosomes and a Rab5a-dependent pathway to presynaptic clusters. *Journal of Cell Science*, *117*(10), 2001–2013. https://doi.org/10.1242/jcs.01030

Katoh, M., Sakurai, K., & Fujimoto, Y. 2002a. Alloxan Radical-Induced Generation of Reactive Oxygen Species in the Reaction System of Alloxan with Ascorbate. *YAKUGAKU ZASSHI*, *122*(10), 831–839. https://doi.org/10.1248/yakushi.122.831

Katoh, M., Sakurai, K., & Fujimoto, Y. 2002b. Alloxan Radical-Induced Generation of Reactive Oxygen Species in the Reaction System of Alloxan with Ascorbate. *YAKUGAKU ZASSHI*, *122*(10), 831–839. https://doi.org/10.1248/yakushi.122.831

Kawano, K., Hirashima, T., Mori, S., Saitoh, Y., Kurosumi, M., & Natori, T. 1991. New Inbred Strain of Long-Evans Tokushima Lean Rats With IDDM Without Lymphopenia. *Diabetes*, *40*(11), 1375–1381. https://doi.org/10.2337/diab.40.11.1375

King, A. J. 2012a. The use of animal models in diabetes research. *British Journal of Pharmacology*, *166*(3), 877–894. https://doi.org/10.1111/j.1476-5381.2012.01911.x

King, A. J. 2012b. The use of animal models in diabetes research. *British Journal of Pharmacology*, *166*(3), 877–894. https://doi.org/10.1111/j.1476-5381.2012.01911.x

Koletsky, S. 1973. Obese spontaneously hypertensive rats—A model for study of atherosclerosis. *Experimental and Molecular Pathology*, *19*(1), 53–60. https://doi.org/10.1016/0014-4800 (73) 90040-3

Komeda, K., Noda, M., Terao, K., Kuzuya, N., Kanazawa, M., & Kanazawa, Y. 1998a. Establishment of Two Substrains, Diabetes-Prone and Non-Diabetic, from Long-Evans Tokushima Lean(LETL) Rats. *Endocrine Journal*, *45*(6), 737–744. https://doi.org/10.1507/endocrj.45.737

Komeda, K., Noda, M., Terao, K., Kuzuya, N., Kanazawa, M., & Kanazawa, Y. 1998b. Establishment of Two Substrains, Diabetes-Prone and Non-Diabetic, from Long-Evans Tokushima Lean (LETL) Rats. *Endocrine Journal*, *45*(6), 737–744. https://doi.org/10.1507/endocrj.45.737

Kong, L., Wu, H., Cui, W., Zhou, W., Luo, P., Sun, J., Yuan, H., & Miao, L. 2013. Advances in Murine Models of Diabetic Nephropathy. *Journal of Diabetes Research*, *2013*, 1–10. https://doi.org/10.1155/2013/797548

Kornum, J. B., Thomsen, R. W., Riis, A., Lervang, H.-H., Schønheyder, H. C., & Sørensen, H. T. 2007. Type 2 Diabetes and Pneumonia Outcomes. *Diabetes Care*, *30*(9), 2251–2257. https://doi.org/10.2337/dc06-2417

Kornum, J. B., Thomsen, R. W., Riis, A., Lervang, H.-H., Schønheyder, H. C., & Sørensen, H. T. 2008. Diabetes, Glycemic Control, and Risk of Hospitalization With Pneumonia. *Diabetes Care*, *31*(8), 1541–1545. https://doi.org/10.2337/dc08-0138

Kottaisamy, C. P. D., Raj, D. S., Prasanth Kumar, V., & Sankaran, U. 2021. Experimental animal models for diabetes and its related complications—A review. *Laboratory Animal Research*, *37*(1), 23. https://doi.org/10.1186/s42826-021-00101-4

Kumar, S., Singh, R., Vasudeva, N., & Sharma, S. 2012a. Acute and chronic animal models for the evaluation of anti-diabetic agents. *Cardiovascular Diabetology*, *11*(1), 9. https://doi.org/10.1186/1475-2840-11-9

Kumar, S., Singh, R., Vasudeva, N., & Sharma, S. 2012b. Acute and chronic animal models for the evaluation of anti-diabetic agents. *Cardiovascular Diabetology*, *11*(1), 9. https://doi.org/10.1186/1475-2840-11-9

Kumar, S., Singh, R., Vasudeva, N., & Sharma, S. 2012c. Acute and chronic animal models for the evaluation of anti-diabetic agents. *Cardiovascular Diabetology*, *11*(1), 9. https://doi.org/10.1186/1475-2840-11-9

Kumar, S., Singh, R., Vasudeva, N., & Sharma, S. 2012d. Acute and chronic animal models for the evaluation of anti-diabetic agents. *Cardiovascular Diabetology*, *11*(1), 9. https://doi.org/10.1186/1475-2840-11-9

Leahy, J. L., Bonner-Weir, S., & Weir, G. C. 1988. Minimal chronic hyperglycemia is a critical determinant of impaired insulin secretion after an incomplete pancreatectomy. *Journal of Clinical Investigation*, *81*(5), 1407–1414. https://doi.org/10.1172/JCI113470

Leibovici, L., Yehezkelli, Y., Porter, A., Regev, A., Krauze, I., & Harell, D. 1996. Influence of Diabetes Mellitus and Glycaemic Control on the Characteristics and Outcome of Common Infections. *Diabetic Medicine*, *13*(5), 457–463. https://doi.org/10.1002/(SICI)1096-9136(199605)13:5<457::AID-DIA83>3.0.CO;2-T

Lenzen, S. 2008. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia*, *51*(2), 216–226. https://doi.org/10.1007/s00125-007-0886-7

Lenzen, S., Tiedge, M., Elsner, M., Lortz, S., Weiss, H., Jörns, A., Klöppel, G., Wedekind, D., Prokop, C.-M., & Hedrich, H. J. 2001. The LEW.1AR1/Ztm-iddm rat: A new model of spontaneous insulin-dependent diabetes mellitus. *Diabetologia*, *44*(9), 1189–1196. https://doi.org/10.1007/s001250100625

Lieschke, G. J., & Currie, P. D. 2007. Animal models of human disease: Zebrafish swim into view. *Nature Reviews Genetics*, *8*(5), 353–367. https://doi.org/10.1038/nrg2091

Makino, S., Kunimoto, K., Muraoka, Y., Mizushima, Y., Katagiri, K., & Tochino, Y. 1980. Breeding of a Non-Obese, Diabetic Strain of Mice. *Experimental Animals*, *29*(1), 1–13. https://doi.org/10.1538/expanim1978.29.1_1

Marquié, G., Hadjiisky, P., Arnaud, O., & Duhault, J. 1991. Development of macroangiopathy in sand rats (Psammomys obesus), an animal model of non-insulin-dependent diabetes mellitus: Effect of gliclazide. *The American Journal of Medicine*, *90*(6), S55–S61. https://doi.org/10.1016/0002-9343(91)90419-X

Mathews, C. E. 2005. Utility of murine models for the study of spontaneous autoimmune type 1 diabetes. *Pediatric Diabetes*, *6*(3), 165–177. https://doi.org/10.1111/j.1399-543X.2005.00123.x

Matveyenko, A. V., & Butler, P. C. 2006. Islet Amyloid Polypeptide (IAPP) Transgenic Rodents as Models for Type 2 Diabetes. *ILAR Journal*, *47*(3), 225–233. https://doi.org/ 10.1093/ilar.47.3.225

Meier, H., & Yerganian, G. 1961. Spontaneous Hereditary Diabetes Mellitus in the Chinese Hamster (Cricetulus Griseus): III. Maintenance of a Diabetic Hamster Colony With the Aid of Hypoglycemic Therapy. *Diabetes*, *10*(1), 19–21. https://doi.org/10.2337/diab.10.1.19

Mordes, J. P., Bortell, R., Blankenhorn, E. P., Rossini, A. A., & Greiner, D. L. 2004. Rat Models of Type 1 Diabetes: Genetics, Environment, and Autoimmunity. *ILAR Journal*, *45*(3), 278–291. https://doi.org/10.1093/ilar.45.3.278

Movassat, J., Calderari, S., Fernández, E., Martín, M. A., Escrivá, F., Plachot, C., Gangnerau, M. N., Serradas, P., Álvarez, C., & Portha, B. 2007. Type 2 diabetes – a matter of failing β-cell neogenesis? Clues from the GK rat model. *Diabetes, Obesity and Metabolism*, *9*(s2), 187–195. https://doi.org/10.1111/j.1463-1326.2007.00786.x

Nie, J., Xue, B., Sukumaran, S., Jusko, W. J., DuBois, D. C., & Almon, R. R. 2011. Differential muscle gene expression as a function of disease progression in Goto-Kakizaki diabetic rats. *Molecular and Cellular Endocrinology*, *338*(1–2), 10–17. https://doi.org/10.1016/j.mce.2011.02.016

Oka, T., Nishimura, Y., Zang, L., Hirano, M., Shimada, Y., Wang, Z., Umemoto, N., Kuroyanagi, J., Nishimura, N., & Tanaka, T. 2010. Diet-induced obesity in zebrafish shares common pathophysiological pathways with mammalian obesity. *BMC Physiology*, *10*(1), 21. https://doi.org/10.1186/1472-6793-10-21

OUP accepted manuscript. 2017. *Journal of Insect Science*. https://doi.org/10.1093/jisesa/iex076

Paik, S. G., Fleischer, N., & Shin, S. I. 1980. Insulin-dependent diabetes mellitus induced by subdiabetogenic doses of streptozotocin: Obligatory role of cell-mediated autoimmune processes. *Proceedings of the National Academy of Sciences*, *77*(10), 6129–6133. https://doi.org/10.1073/pnas.77.10.6129

Papatheodorou, K., Banach, M., Bekiari, E., Rizzo, M., & Edmonds, M. 2018. Complications of Diabetes 2017. *Journal of Diabetes Research*, *2018*, 1–4. https://doi.org/10.1155/2018/3086167

Pearson, J. A., Wong, F. S., & Wen, L. 2016. The importance of the Non Obese Diabetic (NOD) mouse model in autoimmune diabetes. *Journal of Autoimmunity*, *66*, 76–88. https://doi.org/10.1016/j.jaut.2015.08.019

Peltonen, L., & McKusick, V. A. 2001. Dissecting Human Disease in the Postgenomic Era. *Science*, *291*(5507), 1224–1229. https://doi.org/10.1126/science.291.5507.1224

Perlman, R. L. 2016. Mouse Models of Human Disease: An Evolutionary Perspective. *Evolution, Medicine, and Public Health*, eow014. https://doi.org/10.1093/emph/eow014

Phillips, M. S., Liu, Q., Hammond, H. A., Dugan, V., Hey, P. J., Caskey, C. T., & Hess, J. F. 1996. Leptin receptor missense mutation in the fatty Zucker rat. *Nature Genetics*, *13*(1), 18–19. https://doi.org/10.1038/ng0596-18

Phillips, R. W., Panepinto, L. M., Spangler, R., & Westmoreland, N. 1982. Yucatan Miniature Swine as a Model for the Study of Human Diabetes Mellitus. *Diabetes*, *31*(Supplement_1), 30–36. https://doi.org/10.2337/diab.31.1.S30

Portha, B. 2005. Programmed disorders of β-cell development and function as one cause for type 2 diabetes? The GK rat paradigm. *Diabetes/Metabolism Research and Reviews*, *21*(6), 495–504. https://doi.org/10.1002/dmrr.566

Portha, B., Lacraz, G., Kergoat, M., Homo-Delarche, F., Giroix, M.-H., Bailbé, D., Gangnerau, M.-N., Dolz, M., Tourrel-Cuzin, C., & Movassat, J. 2009. The GK rat beta-cell: A prototype for the diseased human beta-cell in type 2 diabetes? *Molecular and Cellular Endocrinology*, *297*(1–2), 73–85. https://doi.org/10.1016/j.mce.2008.06.013

Prins, J. B., Herberg, L., Den Bieman, M., & Van Zutphen, L. F. M. 1991. Genetic variation within and between lines of diabetes-prone and non-diabetes-prone BB rats; allele distribution of 8 protein markers. *Laboratory Animals*, *25*(3), 207–211. https://doi.org/10.1258/002367791780808446

Rees, D. A., & Alcolado, J. C. 2005a. Animal models of diabetes mellitus. *Diabetic Medicine*, *22*(4), 359–370. https://doi.org/10.1111/j.1464-5491.2005.01499.x

Rees, D. A., & Alcolado, J. C. 2005b. Animal models of diabetes mellitus. *Diabetic Medicine*, *22*(4), 359–370. https://doi.org/10.1111/j.1464-5491.2005.01499.x

Roden, M., & Shulman, G. I. 2019. The integrative biology of type 2 diabetes. *Nature*, *576*(7785), 51–60. https://doi.org/10.1038/s41586-019-1797-8

Roep, B. O., & Atkinson, M. 2004. Animal models have little to teach us about Type 1 diabetes: 1. In support of this proposal. *Diabetologia*, *47*(10), 1650–1656. https://doi.org/10.1007/s00125-004-1517-1

Rohilla, A., & Ali, S. 2012. Alloxan Induced Diabetes: Mechanisms and Effects. *Int J Res Pharm Biomed Sci*, *3*.

Ruslami, R., Nijland, H. M. J., Adhiarta, I. G. N., Kariadi, S. H. K. S., Alisjahbana, B., Aarnoutse, R. E., & Van Crevel, R. 2010. Pharmacokinetics of Antituberculosis Drugs in Pulmonary Tuberculosis Patients with Type 2 Diabetes. *Antimicrobial Agents and Chemotherapy*, *54*(3), 1068–1074. https://doi.org/10.1128/AAC.00447-09

Saliba, W., Nitzan, O., Chazan, B., & Elias, M. 2015. Urinary tract infections in patients with type 2 diabetes mellitus: Review of prevalence, diagnosis, and management. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 129. https://doi.org/10.2147/DMSO.S51792

Schwartz, S. S., Epstein, S., Corkey, B. E., Grant, S. F. A., Gavin, J. R., & Aguilar, R. B. 2016. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell–Centric Classification Schema. *Diabetes Care*, *39*(2), 179–186. https://doi.org/10.2337/dc15-1585

Shafrir, E., Ziv, E., & Kalman, R. 2006. Nutritionally Induced Diabetes in Desert Rodents as Models of Type 2 Diabetes: Acomys cahirinus (Spiny Mice) and Psammomys obesus (Desert Gerbil). *ILAR Journal*, *47*(3), 212–224. https://doi.org/10.1093/ilar.47.3.212

Skovsø, S. 2014. Modeling type 2 diabetes in rats using high fat diet and streptozotocin. *Journal of Diabetes Investigation*, *5*(4), 349–358. https://doi.org/10.1111/jdi.12235

Slieker, L. J., Sundell, K. L., Heath, W. F., Osborne, H. E., Bue, J., Manetta, J., & Sportsman, J. R. 1992. Glucose Transporter Levels in Tissues of Spontaneously Diabetic Zucker *fa* / *fa* Rat (ZDF/drt) and Viable Yellow Mouse (*Avy* / *a*). *Diabetes*, *41*(2), 187–193. https://doi.org/10.2337/diab.41.2.187

Stumvoll, M., Goldstein, B. J., & Van Haeften, T. W. 2005. Type 2 diabetes: Principles of pathogenesis and therapy. *The Lancet*, *365*(9467), 1333–1346. https://doi.org/10.1016/S0140-6736(05)61032-X

Suaya, J. A., Eisenberg, D. F., Fang, C., & Miller, L. G. 2013. Skin and Soft Tissue Infections and Associated Complications among Commercially Insured Patients Aged 0–64 Years with and without Diabetes in the U.S. *PLoS ONE*, *8*(4), e60057. https://doi.org/10.1371/journal.pone.0060057

Szkudelski, T. 2001. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. *Physiological Research*, *50*(6), 537–546.

Teame, T., Zhang, Z., Ran, C., Zhang, H., Yang, Y., Ding, Q., Xie, M., Gao, C., Ye, Y., Duan, M., & Zhou, Z. 2019. The use of zebrafish (Danio rerio) as biomedical models. *Animal Frontiers*, *9*(3), 68–77. https://doi.org/10.1093/af/vfz020

Thayer, T. C., Wilson, S. B., & Mathews, C. E. 2010. Use of Nonobese Diabetic Mice to Understand Human Type 1 Diabetes. *Endocrinology and Metabolism Clinics of North America*, *39*(3), 541–561. https://doi.org/10.1016/j.ecl.2010.05.001

The Emerging Risk Factors Collaboration. 2010. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *The Lancet*, *375*(9733), 2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9

The International Silkworm Genome Consortium. 2008. The genome of a lepidopteran model insect, the silkworm Bombyx mori. *Insect Biochemistry and Molecular Biology*, *38*(12), 1036–1045. https://doi.org/10.1016/j.ibmb.2008.11.004

Todd, J. A. 2016. Intolerable secretion and diabetes in tolerant transgenic mice, revisited. *Nature Genetics*, *48*(5), 476–477. https://doi.org/10.1038/ng.3560

Utsugi, T., Kanda, T., Tajima, Y., Tomono, S., Suzuki, T., Murata, K., Dan, K., Seto, Y., & Kawazu, S. 1992. A new animal model of non-insulin-dependent diabetes mellitus induced by the NDK25 variant of encephalomyocarditis virus. *Diabetes Research (Edinburgh, Scotland)*, *20*(4), 109–119.

Ventura-Sobrevilla, J., Boone-Villa, V. D., Aguilar, C. N., Román-Ramos, R., Vega-Avila, E., Campos-Sepúlveda, E., & Alarcón-Aguilar, F. 2011. Effect of varying dose and administration of streptozotocin on blood sugar in male CD1 mice. *Proceedings of the Western Pharmacology Society*, *54*, 5–9.

Vieira, Souto, Sánchez-López, Machado, Severino, Jose, Santini, Fortuna, García, Silva, & Souto. 2019. Sugar-Lowering Drugs for Type 2 Diabetes Mellitus and Metabolic Syndrome—Review of Classical and New Compounds: Part-I. *Pharmaceuticals*, *12*(4), 152. https://doi.org/10.3390/ph12040152

Wallis, R. H., Wang, K., Marandi, L., Hsieh, E., Ning, T., Chao, G. Y. C., Sarmiento, J., Paterson, A. D., & Poussier, P. 2009. Type 1 Diabetes in the BB Rat: A Polygenic Disease. *Diabetes*, *58*(4), 1007–1017. https://doi.org/10.2337/db08-1215

Weiss, H., Bleich, A., Hedrich, H.-J., Kölsch, B., Elsner, M., Jörns, A., Lenzen, S., Tiedge, M., & Wedekind, D. 2005. Genetic analysis of the LEW.1AR1-iddm rat: An animal model for spontaneous diabetes mellitus. *Mammalian Genome*, *16*(6), 432–441. https://doi.org/10.1007/s00335-004-3022-8

Wexler, B. C., Iams, S. G., & McMurtry, J. P. 1980. Pathophysiological differences between obese and non-obese spontaneously hypertensive rats. *British Journal of Experimental Pathology*, *61*(2), 195–207.

Weyer, C., Bogardus, C., Mott, D. M., & Pratley, R. E. 1999. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Journal of Clinical Investigation*, *104*(6), 787–794. https://doi.org/10.1172/JCI7231

Wise, P. H., Weir, B. J., Hime, J. M., & Forrest, E. 1972. The diabetic syndrome in the tuco-tuco (Ctenomys talarum). *Diabetologia*, *8*(3), 165–172. https://doi.org/10.1007/BF01212256

Wong, N. D., Zhao, Y., Patel, R., Patao, C., Malik, S., Bertoni, A. G., Correa, A., Folsom, A. R., Kachroo, S., Mukherjee, J., Taylor, H., & Selvin, E. 2016. Cardiovascular Risk Factor Targets and Cardiovascular Disease Event Risk in Diabetes: A Pooling Project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. *Diabetes Care*, *39*(5), 668–676. https://doi.org/10.2337/dc15-2439

Xue, B., Sukumaran, S., Nie, J., Jusko, W. J., DuBois, D. C., & Almon, R. R. 2011. Adipose Tissue Deficiency and Chronic Inflammation in Diabetic Goto-Kakizaki Rats. *PLoS ONE*, *6*(2), e17386. https://doi.org/10.1371/journal.pone.0017386

Yan, L.-J., & Wu, J. (2015a). Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic β cell glucotoxicity. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 181. https://doi.org/10.2147/DMSO.S82272

Yan, L.-J., & Wu, J. (2015b). Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic β cell glucotoxicity. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 181. https://doi.org/10.2147/DMSO.S82272

Yokoi, N., Hayashi, C., Fujiwara, Y., Wang, H.-Y., & Seino, S. (2007). Genetic Reconstitution of Autoimmune Type 1 Diabetes With Two Major Susceptibility Genes in the Rat. *Diabetes*, *56*(2), 506–512. https://doi.org/10.2337/db06-1027

Yokoi, N., Kanazawa, M., Kitada, K., Tanaka, A., Kanazawa, Y., Suda, S., Ito, H., Serikawa, T., & Komeda, K. (1997). A non-MHC locus essential for autoimmune type I diabetes in the Komeda Diabetes-Prone rat. *Journal of Clinical Investigation*, *100*(8), 2015–2021. https://doi.org/10.1172/JCI119733

Yokoi, N., Komeda, K., Wang, H.-Y., Yano, H., Kitada, K., Saitoh, Y., Seino, Y., Yasuda, K., Serikawa, T., & Seino, S. (2002). Cblb is a major susceptibility gene for rat type 1 diabetes mellitus. *Nature Genetics*, *31*(4), 391–394. https://doi.org/10.1038/ng927

Yokoi, N., Namae, M., Fuse, M., Wang, H.-Y., Hirata, T., Seino, S., & Komeda, K. (2003a). Establishment and Characterization of the Komeda Diabetes-prone Rat as a Segregating Inbred Strain. *Experimental Animals*, *52*(4), 295–301. https://doi.org/10.1538/expanim.52.295

Yokoi, N., Namae, M., Fuse, M., Wang, H.-Y., Hirata, T., Seino, S., & Komeda, K. (2003b). Establishment and Characterization of the Komeda Diabetes-prone Rat as a Segregating Inbred Strain. *Experimental Animals*, *52*(4), 295–301. https://doi.org/10.1538/expanim.52.295

Yoon, J.-W., Austin, M., Onodera, T., & Notkins, A. L. (1979). Virus-Induced Diabetes Mellitus: Isolation of a Virus from the Pancreas of a Child with Diabetic Ketoacidosis. *New England Journal of Medicine*, *300*(21), 1173–1179. https://doi.org/10.1056/NEJM197905243002102

Yoon, J.-W., London, W. T., Curfman, B. L., Brown, R. L., & Notkins, A. L. (1986). Coxsackie Virus B4 Produces Transient Diabetes in Nonhuman Primates. *Diabetes*, *35*(6), 712–716. https://doi.org/10.2337/diab.35.6.712

Zhang, X., Xue, R., Cao, G., Pan, Z., Zheng, X., & Gong, C. (2012). Silkworms Can be Used as an Animal Model to Screen and Evaluate Gouty Therapeutic Drugs. *Journal of Insect Science*, *12*(4), 1–9. https://doi.org/10.1673/031.012.0401

Zhou, B., Lu, Y., Hajifathalian, K., Bentham, J., Di Cesare, M., Danaei, G., Bixby, H., Cowan, M., Ali, M., Taddei, C., Lo, W., Reis-Santos, B., Stevens, G., Riley, L., Miranda, J., Bjerregaard, P., Rivera, J., Fouad, H., Ma, G., … Zuñiga Cisneros, J. (2016). Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4·4 million participants. *The Lancet*, *387*(10027), 1513–1530. https://doi.org/10.1016/S0140-6736(16)00618-8

Zhu, H., Yu, L., He, Y., & Wang, B. (2014). Nonhuman Primate Models of Type 1 Diabetes Mellitus for Islet Transplantation. *Journal of Diabetes Research*, *2014*, 1–9. https://doi.org/10.1155/2014/785948

Ziv, E., Shafrir, E., Kalman, R., Galer, S., & Bar-On, H. (1999). Changing pattern of prevalence of insulin resistance in Psammomys obesus, a model of nutritionally induced type 2 diabetes. *Metabolism*, *48*(12), 1549–1554. https://doi.org/10.1016/S0026-0495(99)90244-5

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