Review Article

Animal Model for Type II Diabetes with Cardiometabolic Complication

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ABSTRACT

Animal models have been used extensively in diabetes research. Rat is extensively used as a suitable animal model for understanding the metabolic profile and pathology involved in different stages of type II diabetes. Many animal models have been developed and studied to elucidate molecular mechanisms functional alterations associated with metabolic diseases. Appropriate characterized and clinically relevant experimental models are considered as essential tools for testing new agents, understanding the molecular basis, their pathogenesis and mechanism of actions. In this review, we collate and discuss the various animal models of Diabetes with cardiometabolic complication. The review also be discussed to provide the readers with a comprehensive overview on the selection of the best animal models to meet their research purpose.

Keywords: Animal model, Rat, Type II Diabetes, metabolic profile.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder in which the body does not produce or properly use insulin that affects more than 100 million people worldwide (6% population) and principally characterized by elevated blood glucose levels and by microvascular and macrovascular complications that considerably increase the morbidity and mortality related to the disease [1,2,3]. It causes disturbances in carbohydrate, protein, lipid metabolism leading to metabolic and cardiovascular complication. In practical terms, diabetes mellitus is a condition in which cells are starving in the sea of glucose. During diabetes, a profound alteration in concentration & composition of lipids occurs [1].

Historically, animal models have played a critical role in exploring and describing malady pathophysiology and recognizable proof of targets and surveying new remedial specialists and in vivo medicines. In the present study, we reviewed the experimental models employed for diabetes and for its related complications [4].

Many animal models such as hereditary models, chemical- or diet induced models, and gene-engineered models have been developed and studied to elucidate molecular mechanisms and functional alterations associated with metabolic diseases. Appropriate characterized and clinically relevant experimental models are considered as essential tools for testing new agents, understanding the molecular basis, their pathogenesis and mechanism of actions. Streptozotocin (STZ) and Alloxan (ALX) combination of High Fat Diet model have successfully mimicked natural progress to development of diabetes as well as metabolic features in human type II diabetes [5,6]. Similarly for the study of metabolic syndrome, several investigators have used carbohydrate (Fructose, sucrose) and fat-rich dietary components in rodents. Combinations of carbohydrate and fat-rich dietary components have been used in rodents to mimic these signs and symptoms of human metabolic syndrome [7].

Even though a number of in vitro and in silico studies are available and are improved in the last decades, animal models still remains the effective one in understanding the complex etiology and multi-systemic interactions present in diabetes [8]. Many of the diabetes trials are performed in rodents while some studies are also done in larger animals. The experimental animal used in the study of diabetes mellitus can be categorized into three types such as genetically diabetic animals, miscellaneous models and other models based on the methods to induce experimental diabetes mellitus. In general, animal model study is essential for the development of new and effective means of treating diseases like diabetes. The review also highlights the experimental animals employed for studying the diabetes related complications like metabolic syndrome and Myocardial Infraction.

ANIMAL MODEL

Type II diabetes model

The Streptozotocin and the Alloxan models of chemically induced diabetes are commonly used to screen antidiabetic drugs [9,10]. However, these methods cause marked destruction of the pancreatic mass and may therefore mimic changes closer to Type I diabetes rather than Type II diabetes mellitus. Animal models of type II diabetes are currently the first line for investigating disease mechanisms and pharmacological therapies. For relevance to humans, animal models must replicate the phenotype seen in patients as closely as possible, but it is also desirable that they mimic the developmental process of the disease. From a practical perspective, models that are easy to generate, cheap and develop in a timely manner will be favoured over expensive and time-consuming models. The db/db mouse,

ob/ob mouse and Zucker fatty rat have been extensively studied in the literature [11-14], and are generated by genetic abnormalities in the leptin signalling pathway, whereas, in patients, type II diabetes usually results as a consequence of multiple gene polymorphisms in combination with environmental factors. Similarly, the Goto- Kakizaki GK rat is insulin resistant but remains lean [15,16], making comparisons to the human condition and its association with obesity difficult. Similarly, high-fat diet alone isn't effective at modifying cardiac and systemic metabolism unless fed over an extended period [17]. A relatively new rat model was proposed first by Reed et al[18], with modifications by Srinivasan et al [19], which aimed to induce type II diabetes by using high-fat feeding to induce peripheral insulin resistance, followed by a low dose of the pancreatic β-cell toxin, streptozotocin (STZ). STZ is traditionally used at high doses to induce type 1 diabetes, as it results in impaired insulin secretion from the β-cell [8,20]. Reed et al proposed that if a low dose of STZ was used after high-fat feeding, the function of the β-cell mass would be modestly impaired without completely compromising insulin secretion, resulting in a moderate impairment in glucose tolerance. This would mimic the human disease process resulting in a metabolic phenotype similar to that in late stage type II diabetic patients. This model has become increasingly popular in recent years, both for investigating the mechanisms involved in type II diabetes and for testing potential therapies [19,20,21]. However, the degree of diabetes induced, the amount of STZ used, background strain and starting body weight vary considerably between these studies.

Type II Diabetes with Myocardial Injury Model

In, Various animal models of myocardial infarction have been developed by using either acute occlusion by ligation of coronary arteries or massive injection of catacolamine; Isoproterenol. The surgical method of occlusion of a coronary artery and reperfusion for the development of consequent myocardial infarction has been performed in many species. First developed by Pfeffer and coworkers, consists of ligating the left coronary artery.[22] left coronary artery ligation is the most common method used to induce acute myocardial damage in rat. Rona et al (1959) [23] reported for the first timed that isoproterenol is a chemical that can induce myocardial necrosis in experimental rats. Isoproterenol administration before ischemia exerts a cardioprotective action in rats, but at the right dose it induces cardiac myocyte necrosis and extensive LV dilatation and hypertrophy. Isoproterenol treatment and left coronary artery ligation in rats are efficient and reproducible methods that provide valuable information about the underlying mechanisms.

Myocardial infarction can be induced chemically and non-invasively in small laboratory animals like rats. Commonly used non-invasive techniques for induction of rat myocardial necrosis are those with the use of catecholamines; a sympathomimetic β-adrenergic receptor agonist Isoproterenol (L-B-(3,β dihydroxyphenyl)-α-isopropylaminoethanol hydrcholride) causes severe stress to the myocardium resulting in a infarct like necrosis of heart muscles. Rona and coworkers published the first results about ISP induced cardiotoxic effects.[23] ISP model is characterized by an extraordinary technical simplicity, an excellent reproducibility as well as an acceptable low mortality. [24] Catecholamines are also known to produce a wide variety of direct and indirect pharmacologic action on cardiovascular heamodynamics and metabolism. Low concentrations of catecholamines exert positive inotropic action on the myocardium and thus are considered to be beneficial in regulating cardiac function. On the other hand, high concentrations of catecholamines over a prolonged period produce deleterious effects on the myocardium. It has been known for many years that epinephrine, norepinephrine and isoproterenol can cause cardiac hypertrophy and/or myocardial lesions.[25] These myocardial lesions have been considered to represent catecholamine-induced myocardial cell damage, catecholamine-induced myocardial infarction, or myocarditis. ISP induced necrosis is maximal in the subendocardial region of the left ventricle and in the interventricular septum.[26] Several mechanisms for the cardiotoxic effect of high level of ISP has been suggested. These mechanisms include functional hypoxia and ischemia, coronary insufficiency, alteration in metabolism, decrease level of high energy phosphate level, intracellular Ca^{2+} overload, changes in electrolyte content and oxidative stress. ISP produces biochemical and electrophysiological alteration which precede the histological changes in the heart. The primary disturbances of ISP induced myocardial infarction have been reported to enhance adenyl cyclase activity, resulting in increased cAMP formation, which in turn would lead to the higher lipid accumulation in the myocardium. Several early events, such as ultrastructural changes, histological, biochemical, electrolyte and membrane changes, have been shown to occurs within 48 h after the injection of isoproterenol. Glycogen depletion and fat deposition have been reported. Histological changes induced by excessive amounts of isoproterenol include degeneration and necrosis of myocardial fibers, accumulation of inflammatory cells, interstitial edema, lipid droplets and endocardial hemorrhage.[27,28] Similarly, ISP significantly decreases levels of endogenous myocardial antioxidants CAT, SOD and GSH and increases the levels of cardiac markers (LDH, CPK, SGOT and Troponin I).[29]

Type II Diabetes with Metabolic syndrome Model

The Study documented model capable of promoting the highest hypercholesterolemia without affecting the development of the rats. The rats were fed hypercholesterolemia diets with cholesterol and different contents of soybean oil, starch, casein, micronutrients and fiber and, consequently, different caloric values. After eight weeks animals were evaluated in relation to growth, fecal excretion, liver weight and fat, cholesterol and its fractions, serum biochemical parameters and systolic pressure.[30]The high fat diet in rats produced hypercholesterolemia, which led to an increase in the body weight total cholesterol,

triglycerides and attenuation in the levels of HDL as well as changes in body temperature of animals. temperature as compared to the HFD induced obesity [31].R. Buettner et al. studied the metabolic and molecular effects of olive oil, cocoa oil, lard and cod-liver oil using HFD, and found that the highest level of obesity, insulin resistance and hepatic steatosis as well as activation of sterol response element-binding protein 1c – the main transcriptional regulation of hepatic synthesis of fatty acids, resulted from the ingestion of lard [32].S. Woods et al. found that in rats a ten-week diet rich in of synthetic, semi-refined lipids led to a significant increase of body mass and body fats, development of hyperleptinemy and insulin resistance. The authors recommend HFD as suitable for research of the mechanisms by which food intake affects the regulation of energy balance [33]. Diet plays an important role in growth and development as a source of nutrition, but the composition of the diet decides its nutritional status. The increased calorific intake has been associated with many diet-induced complications including metabolic syndrome, cardiovascular diseases and nonalcoholic fatty liver disease. Some of the effects of diet on signs and symptoms of metabolic syndrome animal models have been described in Table 2. Characterized and clinically relevant type II diabetes animal models are required to achieve this aim of testing new and better therapeutics. Both genetic spontaneous diabetes models and experimentally induced non-spontaneous diabetes models exist. An example of an experimentally induced animal model of diabetes is the High Fat Diet/Streptozotocin treated (HFD/ STZ) rat model. This model involves a combination of a diet high in fat, and in some cases sugar, to bring about hyperinsulinemia, insulin resistance and/or glucose intolerance followed by treatment with the b-cell toxin STZ, which results in a severe reduction in functional b-cell mass [34,35]. Together, these two stressors are designed to mimic the pathology of type II diabetes, though on a shorter time scale than found in the human condition. Latt mansoor et al[36] characterised cardiac metabolic abnormalities, and investigated the optimal experimental approach for inducing disease, in a new model of type II diabetes. Male Wistar rats were fed a High Fat Diet for three weeks, with a single intraperitoneal injection of low dose Streptozotocin (STZ) after fourteen days at 15, 20, 25 or 30 mg/kg body weight. Compared with chow-fed or High Fat Diet fed control rats, a High Fat Diet in combination with doses of 15–25 mg/kg STZ did not change insulin concentrations and rats maintained body weight. In contrast, 30 mg/kg STZ induced hypoinsulinaemia, hyperketonaemia and weight loss. There was a dose-dependent increase in blood glucose and plasma lipids with increasing concentrations of STZ. cardiac and hepatic triglycerides were increased by all doses of STZ, in contrast, cardiac glycogen concentrations increased in a dose-dependent manner with increasing STZ concentrations. High fat feeding in combination with a low dose of STZ induced cardiac metabolic changes that mirror the decrease in glucose metabolism and increase in fat metabolism in diabetic patients. There are studies documented that High fatty diet with Streptozotocin induce diabetes and metabolic complication. As per samira et al, Diabetes was induced by high-fat/high fructose diet for eight weeks followed by a sub diabetogenic dose of Streptozotocin and induced obesity, hyperglycemia and insulin resistance accompanied by depletion in liver glycogen and dyslipidemia [37]. The study documented, MetS was induced in rats by high carbohydrate, high fat diet and administration of low dose Streptozotocin [38,39].

The following parameter is evaluated for animal model for type II diabetes with metabolic syndrome

Central Obesity

Various anthropometric parameters such as body weight, thoracic circumferences (TC), abdominal circumference (AC), and their ratios (AC/TC) were evaluated in the healthy normal control (NC) and High Fat Diabetic control (HF-DC) groups. The HF-DC group showed significant increase in body weight at 4th and 7th week as compared with NC group rats. The increase in body weight of HF-DC group rats was not sustained till the end of 10th week. Similarly, the AC and TC of the HF-DC group rats also increased significantly only at 4th and 7th week as compared to the NC rats at similar time points. The AC/TC ratio of HF-DC group rats was not statistically different form NC rats. These anthropometric finding are in contrast to other study results in published literature. A previous study by E L B Novelli et al [40] (2007) showed an increase in all anthropometric parameters till the end of the study duration in rats induced with metabolic syndrome. The difference observed in the anthropometric results may be attributed to the diabetic state that is known to cause weight loss as shown by Dieudonne Kuate et al [38] (2015). Therefore, this unique model of metabolic syndrome co-existing with diabetes would differ in the anthropometric results which are typically seen in various models of metabolic syndrome. Challenge with Streptozotocin causes loss of body weight which is typically seen in type II diabetes but not metabolic syndrome.

Hyperglycemia

The present study evaluated several metabolic parameters such as blood glucose, glycosylated hemoglobin (HbA1c), serum insulin and C-Peptide. The Blood glucose levels in the HF-DC group rats were significantly higher as compared to NC group rats at 4th, 7th and 10th week. Results do not coincide with the observations made in various animal models of metabolic syndrome as overt diabetes is not an essential requirement for this syndrome. Dieudonne Kuate [36] (2015) also demonstrated that high carbohydrate and fat diet does not induce frank diabetes in experimental rats. Results of Latt S Mansor [36] (2013), Yanwen wang [41] (2011) are also in contrast to the findings of the present study as they also did not record significant hyperglycemia. The previous study by Latt S Mansor [36] (2013) and Yanwen wang[41] (2011) have reported the diabetes related changes 3-4 weeks subsequent to Streptozotocin administration. However, in the present study the long term effects of diabetes. i.e 7 weeks after Streptozotocin administration have been studied. It may be hypothesized

that the metabolic changes of diabetes are chronic changes manifested after a relatively long duration. Therefore the present model is more suitable to study the metabolic syndrome in the setting of diabetes.

In addition to hyperglycemia, the present study results also found poor glycemic control as indicated by increased HbA1c levels in HF-DC group as compared with NC. Kehkashan Parveen [42] (2011) also determined HbA1c in diabetic rats and showed elevated glycosylated hemoglobin levels; similar to present study results. However, hyperglycemia and glycemic control have not been established so far in an animal model of metabolic syndrome. A deficiency of insulin and a decline in pancreatic function was evidenced by reduced serum insulin levels, C-peptide and HOMA-β respectively in HF –DC group as compared to NC group rats. The HOMA-IR was raised in HF-DC group as compared with NC at the end of the study though the results were not statistically significant. The C-peptide determined by Nora M.et el, Sheikh [43](2012) and Kamal [44] (2011) showed reduced level of C-peptide in diabetic rats similar to present study. The study by Latt S Mansor [36] (2013) and Yanwen wang[41] (2011) estimated serum insulin levels in High Fat Diet and STZ challenged diabetic rats. Results showed reduced serum insulin levels as observed in the present study. These results do not concur with the various models of metabolic syndrome induced with High Fat Diet. In contrast to the present study results, Mohammd Reza Shahraki [45] (2011) demonstrated that the High Fat Diet resulted in insulin resistance causing increase in serum Insulin levels. However, in the study, administration of STZ reduced Insulin secretion because it damages the pancreas. Thus, deficiency of insulin and insulin resistance (though statistically insignificant) was the hallmark of this animal model developed to study metabolic syndrome in the setting of diabetes mellitus.

The biochemical results showed increase in blood glucose levels with concomitant decrease in insulin, C-peptide levels in conformity with histopathological and immunohistochemical findings. The pancreas of HF-DC group rats demonstrated damaged islets of langerhans, atrophy of beta cells and reduced beta cell mass as compared to NC. Immunohistochemical results with insulin showed increased secretion of insulin in the NC as compared to HF-DC group. This suggests that beta cells are functional in the NC group, secreting insulin as compared to HF-DC group. HF-DC caused beta cell dysfunction and loss of beta cell mass resulting in decrease in insulin localization.

Dyslipidemia

The triglycerides levels in the HF-DC group rats were significantly higher as compared to NC group rats at 4th, 7th and 10th week. Dyslipidemia is a hallmark of metabolic syndrome. These results concur with studied undertaken by Dieudonne Kuate [38] (2015), Latt S Mansor [36] (2013) and Yanwen wang[41] (2011).

The present study also determined total cholesterol (TC) and high density lipoprotein (HDL) at the end of the 10th week (end parameter). Abnormal lipid profile as reflected by raised TC, reduced HDL levels were observed in the HF-DC group as compared with NC group. The previous studies by Renuka P. Munshi [46] (2014), Diedonne kuate [38] (2015), Mohammd Reza Shahraki [45] (2011) and Norshalizah Mamikutty [47] (2014) evaluated the metabolic parameter in high carbohydrate/Fat, Fructose diet induced metabolic syndrome. The Investigators showed similar results ie raised level of TC and reduced level of HDL in control groups. However, STZ was not administered to induce diabetes in the above-mentioned studies.

Atherogenic index (TC-HDL-C/HDL-C) of plasma, assessing the risk of developing atherosclerosis, was also calculated. Universally, atherogenic index has been used by researchers as a significant predictor of atherosclerosis and as an independent cardiovascular risk factor. In the present study increase in the atherogenic index was observed in the HF-DC group as compared with NC group. Atherogenic dyslipidemia as evidenced by elevated serum triglyceride levels and decreased HDL-C levels was observed in the HF-DC suggesting that the HF-DC rats are more prone to developing coronary artery diseases. The histology of the aorta of HF-DC group rats also showed atherosclerotic deposition in the vessel wall. Renuka P. Munshi [46] (2014) reported similar fatty deposition in tunica intima of aorta and myocardial injury in hyperlipidemic rats.

Raised blood pressure

Individuals with metabolic syndrome and diabetes have a twofold elevated risk of having a heart attack or stroke. Thus, it is critically important that the cardiovascular complication of metabolic syndrome and diabetes are also replicated in the experimental models. The systolic and diastolic blood pressures were measured at 10th week of study and were found to be significantly raised in HF-DC group as compared with NC. Hypertension one of the important components of metabolic syndrome was mimicked successfully in the experimental model of diabetes and metabolic syndrome induced by high fat diet and STZ. The study by Dieudonne Kuate [38] (2015) and Norshalizh Mamikutty[47] (2014) also showed increase in systolic blood pressure in metabolic syndrome induced in rats by high carbohydrate and fructose diet.

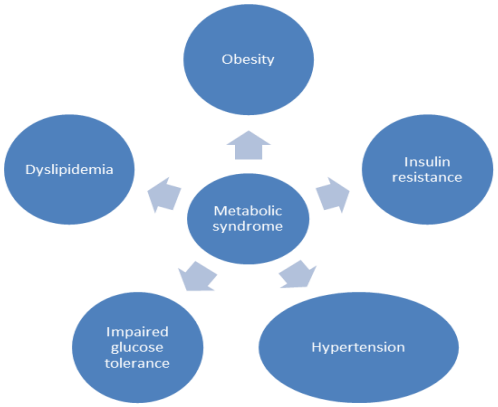

Figure 1: Metabolic syndrome and associated complications.

Table 1: Criteria Proposed for Clinical Diagnosis of Metabolic Syndrome

Clinical measure	World Health Organization	International Diabetes federation	American Heart association
Criteria	Insulin resistance + any other 2	Increased waist circumference + any other 2	Any 3 of 5
Insulin resistance	Impaired glucose tolerance/Impaired fasting glucose + Insulin resistance	-	-
Blood glucose	Impaired glucose tolerance/Impaired fasting glucose Type 2 diabetes	≥100 mg/dL	≥100 mg/dL
Dylipidemia	Triglyceride≥1.69mmol/L and high-density lipoprotein Men≤0.90 mmol/L, women≤1.01 mmol/L	Triglyceride ≥1.69mmol/L and high-density lipoprotein Men ≤1.03mol/L, women≤1.29 mmol/L or high density lipoprotein treatment	Triglyceride ≥1.69mmol/L and high-density lipoprotein Men≤1.03mol/L, women<≤1.29 mmol/L or high density lipoprotein treatment
Blood pressure	≥140/90 mmHg	≥130/85 mmHg or on antihypertensive medication	≥130/85 mmHg or on antihypertensive medication
Obesity	waist :hip ratio Men ≥0.9, Women≥0.85 and or Body mass index 30kg/m^2	waist circumference≥ 94 cm	waist circumference Men≥102cm Women≥88cm
Other	Microalbuminurea		

Table 2: Effects of diet model on the development of Metabolic Syndrome

Types of diet	Strains of animal	Study duration	Component of metabolic syndrome				Reference
			Obesity	Hyperglycemia	Hypertension	Dylipidemia	
Sucrose drinking water	Male wistar rats	21 weeks	√	-	√	√	Aguilera et al (48)
Fructose drinking water	Male wistar rats	12 weeks	√	√	√	√	Mahmoud and Elshazly et al (49)
High fructose diet	Male Sprague-dawley rats	8 weeks	-	-	√	√	Sanchez-Lozada et al (50)
High fructose diet	Male wistar albino rats	16 weeks	√	√	-	√	Mansour et al (51)
High sucrose diet	Male spontaneously hypertensive rats	7 weeks	x	√	√	x	Oron herman et al (52)
High fat diet	Male Sprague-Dawley rats	10 weeks	√	-	√	√	Dobrian et al (53)
High fat diet	Male Sprague Dawley weaning rats	24 weeks	√	√	-	√	Ghilbaudi et al (54)
High fat diet	Male Sprague-Dawley rats	24 weeks	√	√	-	√	Davidson et al(55)
High fat diet	Female C57BL/6NTac mice	12 weeks	√	√	-	√	Podrini et al (56)
High fat diet (60%)	Male & female C57BL/6 j Mice	20 weeks	√	√	-	√	Gallou-kabani et al (57)
High fat high fructose	Male C57BL/6 mice	32 weeks	√	√	X	√	Dissard et al (58)
High sucrose high fat diet	Male Sprague Dawley rats	48 weeks	√	√	-	√	Zhou et al (59)
High fat high sucrose diet	Male C57BL/6 j mice	4 weeks	√	√	-	√	Yang et al (60)
High carbohydrate high fat diet	Male Sprague dawley rats	16 weeks	x	√	√	√	Senaphan et al (61)
High carbohydrate high fat diet	Male wistar rats	14 weeks	√	√	√	√	Hao et al (62)

Table 2 represents the effects of diet on each component of metabolic syndrome. The (√) and (x) indicate the presence and absence of significant effects of the sign of metabolic syndrome, while (-) indicate the effects on the component not being evaluated in the study.

CONCLUSIONS

The advantage of using animal models to study Diabetes with other cardiometabolic complication is the ability to monitor histological, functional and biochemical changes which is difficult to conduct in humans. Subsequent studies are encouraged using combination or modification of existing established methods in order to successfully develop an animal model of type II diabetes.

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