Diabetes is a multi-factorial disease with diverse pathogenesis affecting millions of people in the world. Although it is mainly classified in two major classes: (a) type 1 or insulin dependent diabetes mellitus (IDDM) and (b) type 2 or non-insulin dependent diabetes mellitus (NIDDM), the types of diabetes is expanding due to its rapidly changing pathogenesis, particularly for type 2 diabetes (T2D). T2D is a heterogeneous disorder characterized by insulin resistance followed by inability of pancreatic β-cells to compensate for insulin resistance or partial pancreatic β-cell dysfunction (1). Although these are considered as two major factors for the development of T2D, the order of their existence on the development of T2D is still controversial. The question has been arisen in 1970 whether the diabetes begins with insulin resistance (2) or β-cell failure (3), when the answer of the question is still not clear and it has been considered as an unresolved controversy (3). Further question has been raised that whether insulin resistance or β-cell failure comes first in NIDDM or not (4). This question has been apparently answered from the results of a number of studies done on normal glucose-tolerant individuals with a first degree NIDDM relative where pancreatic β-cell dysfunction was found as a primary genetic lesion rather than insulin resistance with no evident insulin sensitivity (5). On the other hand, from the results of completed United Kingdom Prospective Diabetes Study (UKPDS), it has been suggested that the declining β-cell function is the major cause for the progression of T2D (6) when in more recent studies, the insulin resistance has been reported as a primary cause for T2D. It has been also mentioned that T2D develops as the compensation of insulin production is failed by the pancreatic β-cell due to defective β-cell function and impaired β-cell mass (7, 8). Although the first appearance of ‘insulin resistance’ or ‘β-cell failure’ is an ongoing controversy till today, there is no doubt that both of these two factors play major role in the progression of T2D. Although there is no officially approved definition of prediabetes, it is an existence of one or more of the following conditions such as: impaired fasting glucose (IFG), impaired glucose tolerance (IGT),
insulin resistance (IR) and/or partial pancreatic β-cell dysfunction/failure. Fasting blood glucose (FBG) <100 mg/dL is considered as normoglycemia in humans (9). On the other hand, according to the definition of American Diabetes Association (ADA), fasting plasma glucose (FPG) >100 mg/dL but <126 mg/dL is considered as IFG, blood glucose >140 mg/dL but <200 mg/dL at 2 h post-glucose load is considered as IG2, when FPG >140 mg/dL and/or 2 h post-glucose load >200 mg/dL is considered as diabetes (10). So the existence of any of the above-mentioned diabetes associated conditions before the confirmation of frank diabetes can be considered as prediabetes. However, in a recent study, Buysschaert and Bergman (11) defined prediabetes as the existence of IFG and/or IGT. They have also added that an increased risk of developing diabetes have been observed in the normoglycemic individuals - those who have the history of IFG and/or IGT. Although IFG and/or IGT are considered as the major conditions as the signs of prediabetes, the insulin resistance and partial pancreatic β-cell failure are considered as the major pathogenesis of T2D. Hence, prevention of insulin resistance and/or pancreatic β-cell failure could be an excellent alternative on the way of the development of T2D. To know more about the origination of all of the above-mentioned factors such IFG, IGT, insulin resistance and partial pancreatic β-cell failure more authentic animal models with all features of human prediabetes and insulin resistance are very crucial.

Although a number of animal models of type 1 and T2D are available in the market, the numbers of animal models of prediabetes and/or insulin resistance are very scanty. Some genetically or spontaneously induced model of diabetes are used as a model for prediabetes and insulin resistance in the early stage of their lives such as prediabetic SHROB rats (12), Zucker Diabetic Fatty (ZDF) rats (13, 14), Goto Kakizaki rats (15), Otsuka Long Evan Tokushima Fatty Rats (OLETF) (16, 17), non-obese prediabetic model (18), prediabetic BB-DP rats (19) and prediabetic Chinese hamster (non-genetic model) (20, 21), however these models are relatively expensive, not widely available compared experimentally-induced non-genetic models, hence not suitable for routine pharmacological screening of anti-diabetic agents. In order to understand the origin of the disease animal models of prediabetes and/or insulin resistance can be the better models compared to frank hyperglycemic T2D model. Since the prediabetic stage is a relatively milder stage of diabetes compared to frank diabetic stage, so prediabetic or insulin resistance model can also be used to study the disease reversal effects of various antidiabetic materials. Recently, no review has been published on this particular topic. Although Velez et al. (22) recently published a review on animal models of insulin resistance and heart failure, there focus was not generalized but completely on the association between insulin resistance and heart failure. In the present review, we carefully discussed the induction method, advantages, disadvantages and suitability of various non-genetic or experimentally-induced animal models prediabetes and insulin resistance. We have also summarized the key factors of different models to give a quick overview to the diabetes researchers in order to more appropriately select an authentic animal model of prediabetes and/or insulin resistance to achieve their specific research outcomes (Table 1).

LITERATURE SEARCH METHOD

A systematic review of the published literature has been conducted using key words: prediabetes, pre-diabetes, pre diabetes, insulin resistance along with or without animal model in Pubmed, Google Scholar, Science Direct, Scopus and other relevant databases. The reference lists of the selected articles have also been scrutinized to retrieve additional articles in the area of our review.

PREDIABETES MODELS

High-fat/high-calorie diet-fed rodent models

In 2007, high-fat diet induced prediabetes as well as prediabetic neuropathy has been induced in C57BL/6J mice by feeding high-fat diet for a 16-week period (23). The prediabetes was characterized by obesity, increased plasma free fatty acids (FFA) and insulin concentrations, and IGT. The prediabetic neuropathy was characterized by motor and sensory nerve conduction deficit, tractile allodynia, and thermal hypoalgesia with the absence of intraepidermal nerve fiber loss or axonal atrophy, which have been further confirmed by another subsequent study in the same animal strain with same experimental setup (24). Subsequently, Shevalye et al. (25) fed high-calorie/high-fat diet (58% calorie from fat) to C57BL/6J mice for a 16-week period to develop a prediabetic model. At the end of the experimental period, the model was characterized by increased body weight, IGT, hyperinsulinemia and polyuria. Prediabetic nephropathy has also been confirmed by 2.7 fold increase in 24-h urinary albumin excretion, 20% increase in renal glomerular volume, 18% increase in renal collagen deposition, and 8%
decrease in glomerular podocytes. Although some other diabetic nephropathy and neuropathy related parameters were measured in the above-mentioned experiments, the model induction time was relatively long (16 weeks) and this model has not been evaluated by using any anti-diabetic, anti-nephropathic or anti-neuropathic drugs.

Jin et al. (26) developed a prediabetic model using high fat diet (24.5% lard + 2.5% soybean oil) in 4-week old C57BL/6J mice. After 12 week feeding, prediabetes was characterized by non-significantly higher blood glucose, glucose intolerance, but significantly higher serum triglyceride, total cholesterol and lower HDL-cholesterol concentrations in high-fat diet-fed mice. Serum insulin, insulin resistance or β-cell functions were not measured in this model and this model was not evaluated by using any anti-diabetic drugs. Although this model has been evaluated by using anti-diabetic plant extract, which was significantly effective in improving glucose tolerance level, the other parameters were not influenced at all. Hence, more detail study is needed to confirm the efficacy of this model for prediabetes.

Table 1. List of prediabetes models with their method of characterization, advantages and disadvantages.

<table>
<thead>
<tr>
<th>Mode of induction/induction time</th>
<th>References/induction time</th>
<th>Characterizations</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-fat/high-calorie diet-fed rodent models</td>
<td>Obrosova et al. (23)/Watcho et al. (24)/16-week</td>
<td>Obesity, Increased plasma fatty acids and insulin, Impaired glucose tolerance (IGT)</td>
<td>Can be used for prediabetic nephropathy.</td>
<td>Relatively longer induction period. Not validated by any anti-diabetic drug.</td>
</tr>
<tr>
<td></td>
<td>Shevalye et al. (25)/16-week</td>
<td>Increased body weight, Polyuria, IGT, Hyperinsulinemia</td>
<td>Can be used for prediabetic nephropathy and neuropathy.</td>
<td>Relatively longer induction time. Not validated by any relevant drug.</td>
</tr>
<tr>
<td></td>
<td>Jin et al. (26)/4-week</td>
<td>Non significantly higher blood glucose, Glucose intolerance, Dyslipidemia</td>
<td>Evaluated by anti-diabetic plant extract and found effective for improving glucose tolerance.</td>
<td>Serum insulin, insulin resistance and β-cell functions were not measured. Not evaluated by any anti-diabetic drug.</td>
</tr>
<tr>
<td>High-fat diet-fed STZ-injected canine models</td>
<td>Ionut et al. (27)/10-week</td>
<td>Increased visceral and subcutaneous fat, Reduced insulin sensitivity, Impaired fasting glucose</td>
<td>Can be a proper model for mild T2D and IGT.</td>
<td>Not validated using anti-diabetic drug. Bigger body size of the animal.</td>
</tr>
<tr>
<td>Sucrose-fed rodent models</td>
<td>Soares et al. (28)/9-week</td>
<td>Hyperinsulinemia, Hypertriglyceridemia with normoglycemia</td>
<td>Can be used as a model for prediabetic nephropathy.</td>
<td>Not validated by using any anti-diabetic or anti-neuropathic drug.</td>
</tr>
<tr>
<td></td>
<td>Nunes et al. (29)/16-week</td>
<td>Hyperinsulinemia, Insulin resistance, IGT, Hypertriglyceridemia with normoglycemia, Obesity, Hypertension</td>
<td>Can be used as a model for prediabetic nephropathy and cardiomyopathy.</td>
<td>Not validated using any relevant drug.</td>
</tr>
<tr>
<td>High saturated fat/cholesterol/sugar-fed swine model</td>
<td>Te Pas et al. (30)/10-week</td>
<td>Dyslipidemia, Hyperglycemia</td>
<td>Can be used as a model for metabolic syndrome.</td>
<td>Insulin resistance or glucose intolerance has not been analyzed. Not validated by using any relevant drug.</td>
</tr>
</tbody>
</table>
entire 22 weeks experimental period including 12 weeks after the STZ injection. The model has been characterized by significantly increased visceral and subcutaneous fat, reduced insulin sensitivity. The animals injected with moderate dose (22.5 mg/kg b.w.) of STZ had mild T2D with normal or IFG when prediabetes with normal FBG was observed in the low STZ (15 mg/kg b.w.) injected group. Animals with no frank hyperglycemia had significantly higher body fat, lower β-cell function and serum insulin level even after 12-week experimental period. Although from the data of this study it has been suggested that the feeding high-fat diet followed by the injection of low to moderation dosages of STZ may induced proper models of mild T2D and IGT, the models have not been evaluated using any anti-diabetic drugs. The relatively higher body size compared to small rodents like rats and mice will make it less popular to the scientists for routine pharmacological screening of anti-diabetic drugs due to higher maintenance cost.

Sucrose-fed rodent models
Soares et al. (28) developed a prediabetic model in adult Wistar rats by feeding them 35% sucrose solution ad libitum for 9 weeks. The prediabetes was characterized by hyperinsulinemia and hypertriglyceridemia with normoglycemia at fed state. Although some prediabetic neuropathy related parameters were measured in this model, the induction time of model was relatively higher (9 weeks) and it has not been evaluated by using any anti-diabetic or anti-neuropathic drugs (28). Using exactly the same approach, Nunes et al. (29) developed a prediabetic model in 16-week-old Wistar rats and the model has been characterized by hyperinsulinemia, insulin resistance, impaired glucose tolerance, hypertriglyceridemia with the absence of hyperglycemia, obesity and hypertension. Additionally, the elevated levels of liver weight/body weight ratio and brain natriuretic peptide (BNP) mRNA expression along with upregulation of fibrosis, hypertrophy, angiogenesis and endothelial lesions and oxidative stress suggest this as a better model to evaluation the cardiac issues in prediabetic condition. However, this model has not been evaluated using any anti-diabetic or anti-cardiomyopathic drug.

High saturated fat/cholesterol/sugar (cafeteria diet) fed swine model
It has been reported in many studies that westernized and cafeteria diets are responsible for the induction of insulin resistance, prediabetes as well as metabolic syndrome. In a recent study, Te Pas et al. (30) fed either high unsaturated fat containing Mediterranean diet or high saturated fat/cholesterol/sugar containing diet to 11 weeks old pigs (BW 30 kg) for 10 weeks as two one-hour-long ad libitum meals per day in the morning (08:00 – 09:00) and afternoon (15:00 – 16:00). The prediabetic condition was characterized by the overexpression of proteins of several prediabetes related parameters such as total cholesterol, VLDL-cholesterol, LDL-cholesterol, non-esterified fatty acids and glucose in high saturated fat/cholesterol/sugar fed pigs compared to Mediterranean diet fed pigs. At the end of the study, high saturated fat/cholesterol/sugar fed pigs were recommended as a better model of prediabetes or metabolic syndrome. However, this model has not been evaluated by using any anti-diabetic drugs.

INSULIN RESISTANCE MODELS

High-fat diet-fed rat models
Ai et al. (31) developed an insulin resistance model by oral ingestion of a high fat emulsion in 180-220 g weighing Wistar rats for a 10 days period. The 100 mL emulsion was prepared by emulsifying 20 g lard, 1 g thyreostat, 1 g cholesterol, 1 g sodium glutamate, 5 g sucrose, 5 g saccharose, 20 mL Tween 80, 30 mL propylene glycol when the final volume was made up by distilled water. The model has been characterized by insulin resistance, insulin tolerance test, larger adipocyte and pancreatic islets, increased GLUT2 and α-glucosidase mRNA expression in high fat emulsion ingested group. Although no lipidogenic parameters (except adipocyte) were measured and the model has not been evaluated by using any relevant drug, this can be suitable and cost effective model for its very short induction time. However, researchers must be careful about the resemblance of the pathogenesis of this quickly induced model with the slowly induced insulin resistance of humans.

In another study, Viswanad et al. (32) fed high-fat diet ad libitum to Spargue-Dawley rats for a period of 4 weeks and the insulin resistance was characterized by obesity, hyperinsulinemia, mild hyperglycemia, hypertriglyceridemia, hypercholesterimia, glucose intolerance and hypertension. Although a number of vascular related parameters were studied in the isolated thoracic aorta of high-fat diet-fed insulin resistance rats and evaluated by relevant drug (Tempol 30-300 mM), the model has not been evaluated by using any anti-diabetic drug in this study. In a subsequent study by the same research group, the efficacy of this insulin resistance model has been evaluated by using two but similar anti-diabetic drugs (pioglitazone and rosiglitazone) (33).
Since this model developed almost all the symptoms of insulin resistance and prediabetes and evaluated by relevant anti-diabetic drugs so it can be a suitable model to study the anti-prediabetic and insulin sensitizing effects of various synthetic or natural anti-diabetic agents.

### Table 2. List of insulin resistance models with their method of characterization, advantages and disadvantages.

<table>
<thead>
<tr>
<th>Mode of induction/ induction time</th>
<th>References/ induction time</th>
<th>Characterizations</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| High-fat diet-fed rat models     | Ai et al. (31)/ 10 days   | ● Insulin resistance  
● Glucose intolerance  
● Larger adipocyte and pancreatic islets  
● Increased GLUT2 and α-glucosidase mRNA expression | Very short induction period (10 days) so it will be cost effective. | No lipid related parameters were analyzed. Not validated using any anti-diabetic drug. |
|                                 | Viswanad et al. (32), Gaikwad et al. (33)/ 4-week | ● Obesity  
● Hyperinsulinemia  
● Mild hyperglycemia  
● Hypertriglyceridemia  
● Hypercholesterimia  
● Glucose intolerance  
● Hypertension | Can be used as model for prediabetic cardiomyopathy. | |
| High fructose-fed models        | Pooranaperundevi et al. (38)/ 30 days | ● Insulin resistance  
● Increased lipid peroxidation | Very similar model to human (rhesus monkey). | Not validated by using any anti-diabetic drug. |
|                                 | Bremer et al. (39)/ 12 months | ● Insulin resistance  
● Central obesity  
● Dyslipidemia  
● Inflammation | Relatively shorter induction period (8 weeks). | Not validated using any relevant drug. |
|                                 | Amin and Gilani (40)/ 8-week | ● Hyperglycemia  
● Hyperinsulinemia  
● Hypertension  
● Dyslipidemia  
● Endothelial dysfunction | Relatively shorter induction period (8 weeks). | Not validated using any relevant drug. |
|                                 | Zaman et al. (41)/ 10-week | ● Higher body weight and body fat mass  
● Lower insulin sensitivity  
● Dyslipidemia | Suggested that high-fat model is better than high-fructose fed model. | Not validated by using any anti-diabetic drug. |
|                                 | Charlton et al. (42) / 6 months | ● Obesity  
● Insulin resistance  
● Liver fibrosis  
● Inflammation  
● Endoplasmic reticulum stress  
● Lipopaposis | Data suggested that combination of high-fat and high-fructose diet may be suitable to induce insulin resistance. | Originally developed for NASH but not for insulin resistance. Not validated using relevant drug. |
|                                 | Munshi et al. (43)/ 6-week | ● Hyperglycemia  
● Hyperinsulinemia  
● Dyslipidemia | Shorter induction time (6 weeks) so cost effective. Suggested as a better model to study dyslipidemia and insulin resistance. | |
|                                 | Severino et al. (44)/ 4-week | ● Lower insulin sensitivity or higher insulin resistance  
● Hyperinsulinemia  
● Dyslipidemia  
● Hypertension | Evaluated by using relevant drugs. Shorter induction time (4 weeks). | |
High-fructose fed models

A number of previous studies reported that high-fructose diet is one of the major contributors for the development of overweight, obesity, insulin resistance, type 2 diabetes as well as metabolic syndrome (34-37). Pooranaperundevi et al. (38) developed an insulin resistance model by feeding 60% (w/w) high fructose diet for 30 days in rats. The model has been characterized by insulin resistance, declined insulin resistance status and increased lipid peroxidation. Although the suitability of this model has been tested by using hepatotoxic drug (thioacetamide), this model has not been evaluated by using any anti-diabetic drugs. Due to the metabolic difference between rodents and humans, Bremer et al. (39) developed a high fructose (15% fructose containing 500 mL/monkey/day) fed primate (rhesus monkey, 12-20 years old, 16.3 ± 0.4 kg) model which has been characterized by insulin resistance along with central obesity, dyslipidemia, and inflammation in a period of 12 months. The fructose containing beverage was supplied along with diet contained 30% energy as protein, 11% energy as fat, and 59% energy as carbohydrate. Although this model has not been evaluated by using any relevant drugs and body size of the animals are significantly larger than rodents, it can be a better animal model of insulin resistance due to its more similarity with humans.

In a more recent study, Amin and Gilani (40) developed a rat model of metabolic syndrome along with insulin resistance by dietary manipulation. A 60% fructose containing diet has been provided to Sprague-Dawley rats for an 8-week experimental period along with fiber free refined wheat flour. The model was characterized by hyperglycemia, hyperinsulinemia, hypertension, reduced HDL-cholesterol level at 4-week period hypertriglyceridemia when endothelial dysfunction was observed at 8-week period. Although this model has not been evaluated using any anti-diabetic or relevant drugs, the model induction time was relatively shorter than many other models and can be suitable for routine pharmacological screening of newly developed anti-diabetic drugs, functional and medicinal foods and natural products.

High-fat high-fructose diet-fed rodent models

Although both high-fat and high-fructose diets are usually used for the development of insulin resistance in animals, it could be better to know, which dietary components are more effective for the development of insulin resistance in animals. To answer this question, Zaman et al. (41) conducted a comparative study in rats by feeding either a high-fat (65% calorie from fat) or high-fructose (65% calorie from fructose) diet for a 10-week period. Each model has been characterized by higher body weight, body fat mass, lower insulin sensitivity and dyslipidemiam after 10-week feeding period. Although these models have not been evaluated by using any relevant drugs, from the data of this study, it has been concluded that high-fat diet-fed rats can be better than high-fructose fed rats as an animal model of insulin resistance.

The high-fat high-fructose diet-fed approach of the induction of insulin resistance is further supported by the study conducted by Charlton et al. (42) where they fed either high fat (60% calorie from fat) or fast food (40% calorie from fat including 12% saturated fatty acids and 2% cholesterol) diet along with fructose containing drinking water (23.1 g/L) to mice for a 6 months period. In both cases, animals become obese and insulin resistance was evident. Apart from obesity and insulin resistance, the combination of high fat and high fructose diet induced liver fibrosis, inflammation, endoplasmic reticulum stress and lipoaapoptosis when inflammation was minimal and no fibrosis was observed in the high fat diet fed animals. Although this model has been originally developed for the nonalcoholic steatohepatitis (NASH) and not validated by any relevant drugs, the combination of high fat and high fructose diet can be an excellent approach for the development of insulin resistance model with some other associated features of metabolic syndrome.

In a very recent study, Munshi et al. (43) developed a rat model of insulin resistance along with hyperlipidemia in 200-270 g weighing male Wistar rats by feeding 3 : 1 ratio of animal fat : coconut oil containing diet along with 25% fructose in drinking water for a 6 weeks period. The model was characterized by hyperglycemia, hyperinsulinemia, increased total cholesterol, LDL-cholesterol and triglycerides with decreased HDL-cholesterol. This model has been further evaluated by using relevant drugs and suggested as a cost-effective model to study at least two cardiovascular biomarkers such as dyslipidemia and insulin resistance. Due to the shorter induction time and better response to relevant test drug with the existence of all major symptoms this model can be a suitable tool for routine pharmacological screening of anti-dyslipidemic and insulin sensitizing drugs.

Dexamethasone induced rat model

Severino et al. (44) developed a model of insulin resistance by injecting (s.c.) a low dose (2 mg/day) of dexamethasone for 4 weeks in Wistar rats. This model was characterized by lower insulin sensitivity or higher insulin resistance, high blood
pressure, higher serum triglyceride, insulin and hematocrit level. This model has also been evaluated by using three relevant drugs, two of which have been successfully reduced dexamethasone-induced insulin resistance and related abnormalities in rats. The induction time of this model was also relatively shorter compared to many other models so it can be a cost-effective model of insulin resistance for routine pharmacological screening of anti-diabetic drugs and natural products.

Zymosan-induced mice model

Wang and colleagues (45) used zymosan, a mixture of cell-wall particles from the yeast named Saccharomyces cerevisiae, to induce zymosan in mice. Although this model has been found as a better insulin resistance model compared to high-fructose diet-fed insulin resistance model, it has been reported that this model is not sustainable without the zymosan treatment. Hence, it cannot be used as proper animal model of insulin resistance.

CONCLUSIONS

According to our review, a number of different approaches have been used to develop the animal models of prediabetes and insulin resistance such as high-fat or high-calorie diet-fed models, high-fat diet-fed STZ-injected models, high sucrose-fed model, high saturated fat/ cholesterol/ sugar-fed models, high fructose-fed models, high-fat high-fructose diet-fed models, dexamethsone-induced models and zymosan-induced models. Although many of these models have been successfully developed either for prediabetes or insulin resistance or both, all of them did not receive similar appreciation for several reasons. Some of them showed very similar pathogenesis of prediabetes or insulin resistance but took very long time to develop. Although some of them developed in a very short period of time but they did not completely reproduce the pathogenesis of either prediabetes or insulin resistance or both. Some models did analyze very fewer parameters from which no conclusion can be drawn regarding their suitability as a model for either prediabetes or insulin resistance. Finally, most of these models have not been validated by any anti-diabetic or relevant drugs which reduced the suitability of these models. Although high-fat diet-fed STZ-injected model has been found suitable to study prediabetes, it has been developed in bigger rodent (dog) hence it may not be popular to scientist not only due to bigger body size but also due to higher housing and maintenance costs. On the other hand, although most of them are not validated by relevant drugs, the high-fat/ high-calorie/high sucrose diet fed models were found to be most suitable to study the prediabetes and associated complications such as diabetic neuropathy and nephropathy and cardiomyopathy with almost similar induction period, when all of these approaches almost required similar induction time (9-16 weeks). Although a number of approaches have been used for the development of insulin resistance model, either high-fat or high-fructose or both fed was found to meet the most major pathogenesis of insulin resistance model. Adding high-fructose with high-fat diet did not make any significant difference in terms of pathogenesis or model induction time when feeding high-fat diet alone has been recommend as a better approach for the development of insulin resistance model rather than with high fructose diet or with the combination of them (41). Although most of the insulin resistance models have been developed in 4-12 weeks of time, a couple of models have been taken significantly longer time (6-12 months or 24-48 weeks) (39, 42) and another model taken only 10 days to induce insulin resistance (31). Since naturally it takes considerably longer period of time to induce insulin resistance in humans, it is not clear how similar will be the quickly developed model with the human pathogenesis of insulin resistance. Hence, high-fat diet fed insulin resistance models developed in 4-12 weeks period could be considered as the models of choice for insulin resistance.

Acknowledgment

This work was supported jointly by the Department of Science and Technology (DST) and Federation of Indian Chambers of Commerce and Industries (FICCI), New Delhi, India and Research Reward from the University of KwaZulu-Natal, Westville Campus, Durban 4000, South Africa. First author received CV Raman Visiting Research Fellowship for African Researchers during the period of this work.

Disclosure

There is no conflict of interest within this article.

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Received: 13. 06. 2015