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**ORIGINAL ARTICLE****Comparison of Indices of Insulin Resistance and Islet Beta-Cell Dysfunction across Rat Models of Diabetes Mellitus Induced by Modified Diets or Streptozotocin**

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**Abstract:**

*Background:* Induction of insulin resistance in rodents involves the use of Streptozotocin (STZ) or diets high in sucrose, fat or fructose; but the relative degrees of insulin resistance induced by each of these approaches are unclear. *Aim and Objectives:* We therefore compared the degree to which intraperitoneal STZ with or without high-fat or high-fructose diet would induce insulin resistance, glucose intolerance and islet  $\beta$ -cell dysfunction in Wistar rats. *Materials and Methods:* Subsets of STZ-injected rats administered streptozotocin at 30 mg/kg body weight for five successive days were fed normal diet (STZ), or diets high in fat or fructose for 30 or 60 days. Normoglycaemic rats on normal rodent chow, High Fat Diet (HFD) or High Fructose Drink (HFrD) constituted the Control (CTR), HFD or HFrD groups, respectively. Rats were anaesthetized and sacrificed at 30 or 60 days of high fat or fructose feeding followed by measurement of fasting plasma glucose and insulin; and calculation of the HOMA-IR and HOMA-% $\beta$ . Oral Glucose Tolerance Test (OGTT) was done 48 hours prior to killing the animals. *Results:* Glucose tolerance and islet  $\beta$ -cell function were most severely perturbed in the STZ-injected hyperglycaemic rats fed diets high in fructose or fat, as indicated by the significantly increased ( $p<0.05$ ) HOMA-IR or decreased HOMA-% $\beta$  ( $p<0.05$ ) at 30 or 60 days compared with the CTR, STZ or diet-only groups. Weekly blood glucose was

most markedly and significantly ( $p<0.05$ ) elevated in these same (STZ+diet) groups, with impaired OGTT. *Conclusion:* The profound impairment of glucose tolerance and  $\beta$ -cell function in the STZ-induced hyperglycaemic rats fed high-fat or high-fructose diet support the continued use of such models in the characterization of the molecular events associated with insulin resistance, and the testing of novel therapeutic interventions.

**Keywords:** Insulin Resistance,  $\beta$  Cell, High Fat Diet, Wistar rats, Streptozotocin

**Introduction:**

Impaired metabolic activity of insulin and poor glucose tolerance underlie a number of clinical conditions that include Type 2 Diabetes Mellitus (T2DM), polycystic ovarian syndrome, obesity, and cardiometabolic syndrome, among others [1-3]. Cardiometabolic syndrome is characterized by a combination of metabolic and cardiovascular abnormalities that include hypertension, atherosclerosis, dyslipidaemia, fasting hyperglycaemia and obesity [4].

Being heterogeneous in its pathogenesis, a number of hypotheses has been proposed and confirmed as underpinning the inability of the otherwise insulin-sensitive issues such as adipose

tissue, skeletal muscle and liver to respond to the normal plasma levels of insulin. Among others, metabolic, inflammatory and molecular changes were recognized. The seminal findings of Hotamisligil *et al.* [5] showed elevated Tumor Necrosis Factor alpha (TNF- $\alpha$ ) levels in adipose tissue from obese fa/fa rats, with evidence that neutralization of TNF- $\alpha$  in the obese paradigm would improve insulin resistance. From the metabolic point of view, excessive fatty acids could trigger intracellular pathways that interfere with insulin receptor signaling [6]. Jornayvaz and Shulman [7] demonstrated how fat metabolism could trigger insulin resistance; besides this lipotoxicity theory, glucotoxicity is also a risk factor for the development of impaired beta cell function and insulin resistance [8]. Moreover, perturbed insulin receptor signaling may underlie insulin resistance, including defects at the level of the transmembrane insulin receptor, Insulin Receptor Substrate 1 (IRS-1), and the downstream signaling molecules, such as Phosphatidylinositol 3 Kinase (PI3K), Protein Kinase B (PKB or Akt) and glycogen synthase kinase 3 beta [9,10].

As outlined in the foregoing, much of our present understanding of the aetiopathogenesis of insulin resistance and beta-cell function arise from clinical observations as well as preclinical research in animal models. Insulin-resistant states in laboratory animals have been induced with either of chronic high-fat diet [11,12], high fructose diet [13,14] or multiple injections of a low dose of the diabetogenic drug streptozotocin [15]; or even different combinations of these regimens [16,17]. However, the rapidity and degrees to which such diets, with or without streptozotocin, perturb insulin activity and beta-

cell functions do vary. Here, we compared indices of insulin activity, glucose homeostasis, and beta-cell function across rodent models of insulin resistance induced by diets, STZ or a combination of these substances for variable durations.

## **Materials and Methods:**

### **Chemicals**

Streptozotocin, fructose and pentobarbital sodium were products of Sigma-Aldrich (St. Louis, MO, USA). Other reagents are available commercially and were of analytical grade.

### **Animals**

Male Wistar rats (250 g) were sourced from Ladoko Akintola University of Technology, Ogbomoso, Nigeria. Rats were acclimatized to the animal house condition of the College of Health Sciences, University of Ilorin, and were kept in plastic cages under 12-hour light/12-hour dark cycle at a room temperature of 22-25°C. They had free access to rat chow (Ogo-Oluwa Feeds, Ilorin, Nigeria) and water prior to the administration of modified diets. Ethical approval was obtained from the Ethical Review Committee of the University of Ilorin (approval number UERC/ASN/2016/358).

### **Preparation of high-fat diet and high-fructose drink**

High Fat diet (HFD) was compounded by a commercial vendor (Ogo-Oluwa Feeds, Ilorin). The diet was prepared according to the method of Woods *et al.* [18] with some modifications. The composition of the modified HFD is presented in Table 1. High Fructose drink (HFrD) was prepared as 15% fructose solution in drinking water [19].

**Table 1: The Nutritional Composition of High-Fat Diet**

Composition	High Fat Diet (kg)	Normal Diet (kg)
Maize	5.5	5.5
Wheat offal	0.5	0.5
Groundnut cake	5.5	Nil
Soya meal	12.5 (toasted)	10
PKC	5	10
Bone meal	0.5	0.5
Fish meal	0.5	0.5
Methionine	0.025	0.025
Lysine	0.025	0.025
Industrial salt	0.0625	0.0625
Broiler premix	0.0625	0.0625

[Modified from Woods et al. (2003)]

### Induction of hyperglycaemia

Hyperglycaemia was induced in a sub-set of rats after an over-night fast, using low dose (30 mg/kg) of intraperitoneal Streptozotocin (STZ) (Sigma-Aldrich, St. Louis, USA) in cold sodium citrate buffer (0.1 M, pH 7.4) for five consecutive days. At 72 hours post-STZ injection, fasting blood glucose levels were measured by the glucose oxidase method using a glucometer (Accu-Check, Roche, Belgium). Animals with fasting blood glucose concentrations not less than 7 mmol/L were included in the study.

### Study Design

Control rats (n=6) were administered normal rat chow and non-sweetened water only. Two subsets of normoglycaemic rats (n=6 each) were fed HFD (Table 1) or administered HFrD (15% fructose in water) *ad libitum* for 30 or 60 days. Moreover, two

groups of STZ-induced hyperglycaemic rats were placed freely on either HFD (STZ+HFD; n=6) or HFrD (STZ+HFrD; n=6) for the same durations. The remaining hyperglycaemic rats were maintained on normal rat chow and non-sweetened water as STZ group. Blood glucose levels were monitored weekly with the aid of a glucometer by obtaining blood from the tail veins. Forty-eight hours prior to euthanasia, all rats (including controls) were fasted overnight to conduct an Oral Glucose Tolerance Test (OGTT). Fasted rats were challenged with oral glucose (2 g/kg body weight) [20] and blood was collected from the tail veins at 0, 30, 60, and 90 minutes post-glucose load to measure glucose concentrations using a glucometer (Accu-Chek, Roche, Belgium). Thereafter, at 30 or 60 days post-feeding with HFD or HFrD, all rats were subjected to over-night fast

and anaesthetized with pentobarbital sodium (60 mg/kg body weight) [21]. Thoracotomy was performed and blood was collected into heparinized tubes by cardiac puncture; and centrifuged at 2500 x g for 10 minutes at 4°C. The plasma was analyzed for fasting glucose and insulin.

**Fasting plasma insulin and glucose assays:**

Fasting plasma insulin concentrations were quantified using rat insulin ELISA kit (Merckodia, Sweden), according to the manufacturer's instruction, with rat insulin as standard. Moreover, fasting plasma glucose was measured by using a kit from Span Diagnostic Chemicals (India), in accordance with the manufacturer's manual.

**Homeostatic model assessment of insulin resistance and β-cell function**

From the data obtained for fasting plasma insulin and glucose, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and β-cell function

(HOMA-%β) were calculated as previously described [22], using the following formulae (with glucose concentrations in molar unit):

$$\text{HOMA-IR} = (\text{FPI} \times \text{FPG}) / 22.5$$

$$\text{HOMA-\%}\beta = (20 \times \text{FPI}) / \text{FPG} - 3.5$$

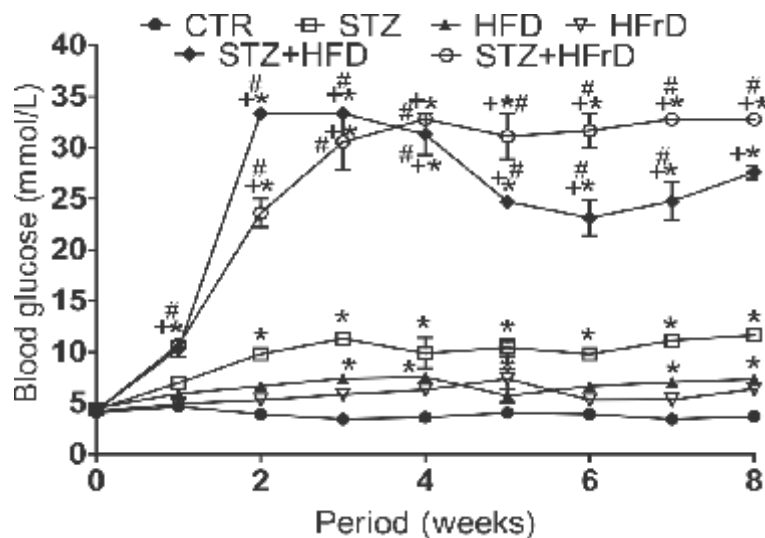
**Data analysis**

Data was analyzed using two-way analysis of variance (2-way ANOVA), followed by Bonferroni *post hoc* test, with the aid of the GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA). Results are presented as mean ± standard error of mean (mean ± SEM). P-value of less than 0.05 (p<0.05) was taken as statistically significant.

**Results:**

**Changes in blood glucose in diet- or STZ-induced rats**

Rats treated with intraperitoneal STZ, with or without different diets, developed marked increases in fasting blood glucose as monitored by the glucometer over 8-week period (Fig. 1).



**Fig. 1: Weekly Fasting Blood Glucose in the Control Rats and Those Administered STZ with or without High Fructose or High Fat Diet; showing Marked Elevation of Weekly Blood Glucose in the STZ+HFD and STZ+ HFrd Rats. \*p<0.05 Compared with Controls (CTR), +p<0.05 compared with Streptozotocin (STZ) group, #p<0.05 Compared with High Fat Diet (HFD) or High Fructose Drink (HFrd) Groups.**

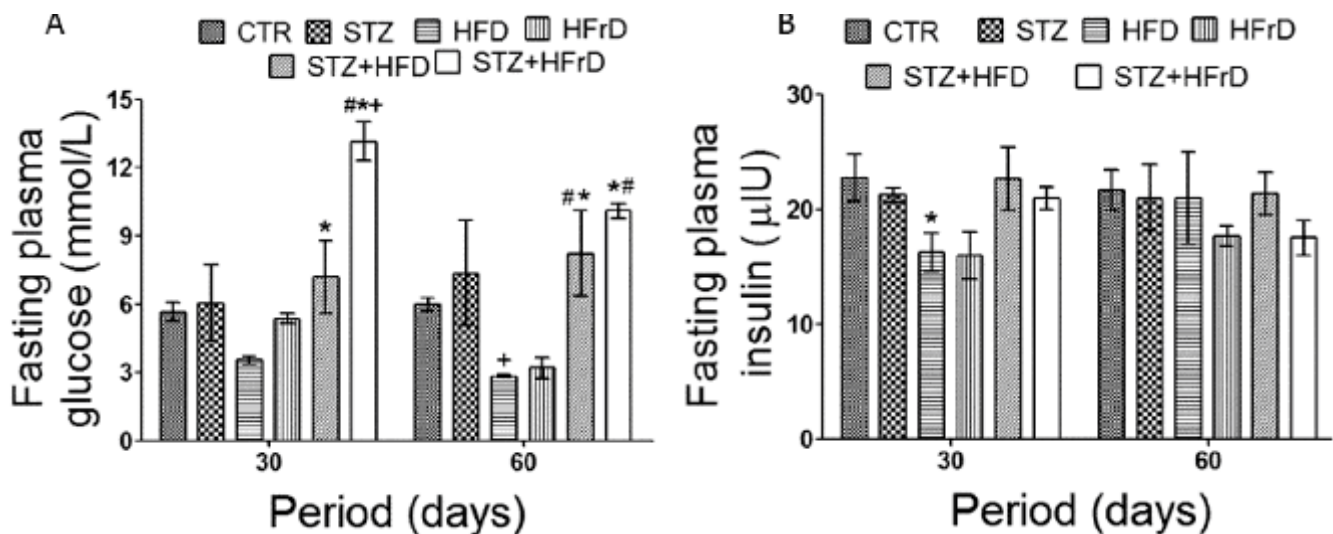
STZ-injected rats fed a high fat or high fructose diet had the maximal increases in blood glucose from week 1 of feeding to week 8. Such increases were significantly ( $p < 0.05$ ) higher each week compared with the controls or rats treated with STZ, HFD or HFrD only.

**Fasting plasma insulin and glucose**

Fasting plasma glucose concentrations were significantly ( $p < 0.05$ ) and markedly increased in STZ-injected rats fed HFD or HFrD for 30 or 60 days compared with the controls or rats on STZ or diet only (Fig. 2A). Conversely, fasting plasma insulin concentrations were not significantly different between most of the STZ- or diet-treated groups compared with the controls (Fig. 2B).

**Impaired glucose tolerance in the diet or STZ-treated rats**

The impaired glucose tolerance seen in the STZ-injected rats was exacerbated by diets high in fat or fructose at 30 or 60 days of such feeding. Such impairment was most pronounced in the STZ rats administered high fructose in the drinking water (Fig. 3A and 3B). Furthermore, insulin activity, as assessed by the HOMA-IR method, was most adversely affected in the STZ-injected hyperglycaemic rats maintained on high fructose drink or high fat diet (Fig. 4A). In these same groups (STZ+HFD and STZ+HFrD), the percentages of functional islet  $\beta$  cells, as assessed by the HOMA-% $\beta$  method) were markedly reduced compared with the non-diabetic controls ( $p < 0.05$ ), or with the STZ, HFD or HFrD groups ( $p > 0.05$ ) (Fig. 4B).



**Fig. 2:** Fasting Plasma Glucose Levels (A) and Insulin Concentrations (B) in the Control (CTR), Streptozotocin (STZ), or Diet-Treated Rats at 30 or 60 Days. \*  $p < 0.05$  Compared with CTR, <sup>+</sup> $p < 0.05$  compared with STZ group, # $p < 0.05$  compared with High Fat Diet (HFD) or High Fructose Drink (HFrD) groups.

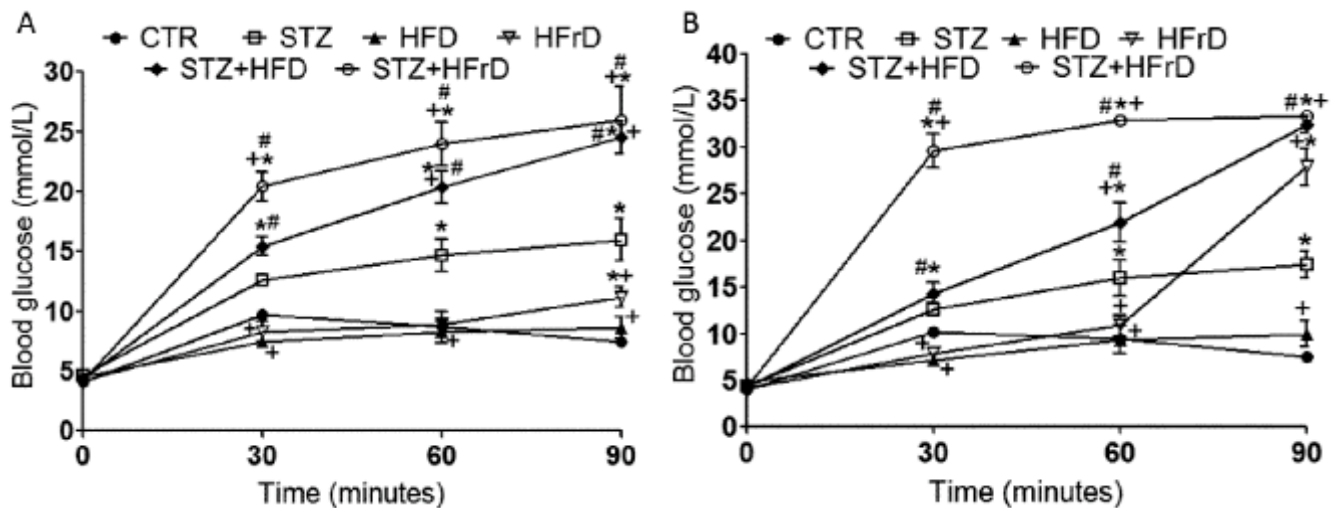


Fig. 3: Oral Glucose Tolerance Test in the Control (CTR) Rats and those Treated with Streptozotocin (STZ), High Fat Diet (HFD) or High Fructose Drink (HFrD) at 30 Days (A) or 60 days (B). \*p<0.05 Compared with CTR, +p<0.05 Compared with STZ group, #p<0.05 Compared with HFD or HFrD Groups.

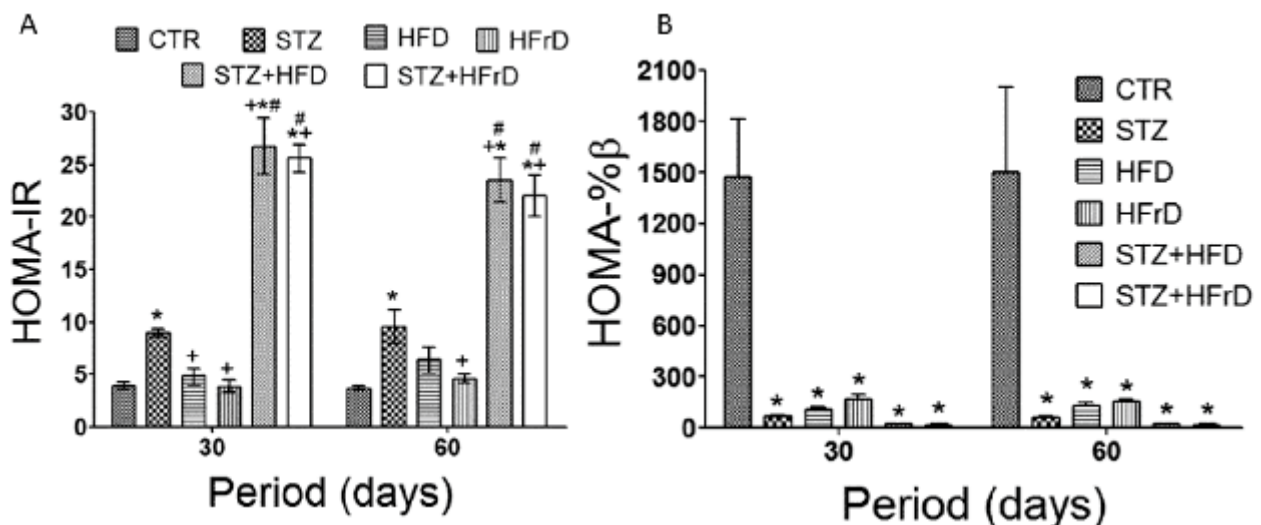


Fig. 4: Indices of Insulin Resistance and Islet Beta-cell Function as Assessed by the HOMA-IR (A) and HOMA-%β (B) Methods in the Control (CTR) Rats and those Treated with Streptozotocin (STZ), High Fat Diet (HFD) or High Fructose Drink (HFrD) at 30 or 60 Days. \*p<0.05 Compared with the CTR, +p<0.05 Compared with STZ Group, #p<0.05 Compared with HFD or HFrD Groups.

**Discussion:**

Transgenic and non-transgenic rodent models have variously been used in the study of metabolic syndrome and related morbidities, such as

diabetes mellitus and obesity. Here, we compared the degree to which glucose tolerance and beta-cell function would be impaired in non-transgenic

rodent model of insulin-resistant diabetes mellitus induced by multiple low-dose STZ with or without high-fructose or high-fat diets. Among these models, insulin activity and beta-cell function were most adversely impacted in the STZ-injected hyperglycaemic rats maintained on high fructose or high fat diet for 30 or 60 days compared with normal controls, STZ-only or diet-only groups.

The pioneering work of Rakieta *et al.* [23] and Junod *et al.* [24] showed the diabetogenic effect of STZ in rodents. STZ, given as a single large dose largely mimics type 1 diabetes in its action; however, when used in a low dose over a few successive days, it is capable of inducing some metabolic changes typical of insulin resistance that characterizes metabolic syndrome and type 2 diabetes [16, 17]. In the present study, rats injected with intraperitoneal multiple low-dose STZ for five successive days showed poorer metabolic outcomes compared with normoglycaemic rats on HFD or HFrD for 30 or 60 days. These showed that multiple injection of low-dose STZ is more effective than either HFD or HFrD alone for the induction of insulin resistance in rats over a relatively short period. STZ induces hyperglycaemia in rodents by mechanisms that include DNA methylation and oxidative damage, leading to  $\beta$ -cell death by apoptosis or necrosis; insulinopenia and fasting hyperglycaemia [25].

Although consistent feeding with HFD or HFrD is a confirmed means of inducing insulin resistant type 2 diabetes in rodents, relatively longer time might be required for this to happen [26,27] compared with models that combine STZ with either high fat or high fructose diet as observed in the present study, and as previously characterized [28]. In the latter, metabolic perturbations typical of insulin resistance occurs relatively early [29].

Meanwhile, the mechanisms by which HFD induces insulin resistance varies and include inflammatory changes [30], oxidative stress in muscle [31], hepatic endoplasmic reticulum and oxidative stress [32], and perturbed insulin receptor signaling [33].

Similarly, high fructose diet produces an insulin-resistant state comparable to the effects of high fat diet. High-fructose feeding promotes hypertriglyceridaemia [34], hyperinsulinaemia and hypertension in rats [35] by altering the early stages of insulin action in insulin-responsive tissues [36]; and by promoting oxidative stress [37], among other mechanisms. Therefore, high-fat or high-fructose-mediated metabolic dysregulation, when coupled with cellular and molecular perturbations induced by STZ [25], could explain the high degree and rapidity of insulin resistance induction and relatively poor beta cell function in the STZ-induced hyperglycaemic rats fed high fat or high fructose diet.

#### **Conclusion:**

Thus, a regimen of multiple low-dose STZ, coupled with high-fat or high-fructose feeding, does not only offer a relatively robust means of inducing insulin resistance and beta cell dysfunction compared with either STZ, HFD or HFrD only; such metabolic changes also occur over a relatively short period. This makes the STZ+HFD or STZ+HFrD models an excellent non-transgenic approach in rodents for the continued characterization of the cellular and molecular mechanisms of insulin resistance, as well as the testing of putative therapeutic interventions when compared with models that employ STZ, HFD or HFrD alone.

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