

# Insulin Secretory Dysfunction as the Underlying Mechanism of Diabetogenesis in Neonatal Streptozotocin-Induced Type 2 Diabetes Model Rats

Ramendu Parial<sup>1,\*</sup>, Manisha Das<sup>2</sup>, Masfida Akhter<sup>3</sup>, JMA Hannan<sup>4</sup>, Dwaipayan Sikdar<sup>1</sup>, Liaquat Ali<sup>5</sup>

<sup>1</sup>Department of Biochemistry and Molecular Biology, University of Chittagong, Chattogram, BANGLADESH.

<sup>2</sup>EuGEF Research Foundation, Chattogram, BANGLADESH.

<sup>3</sup>Hamdard Institute of Traditional Medicine and Natural Product Research, Hamdard University Bangladesh, Munshiganj, BANGLADESH.

<sup>4</sup>Department of Pharmacy, Independent University, Bangladesh (IUB), Dhaka, BANGLADESH.

<sup>5</sup>Pothikrit Institute of Health Studies (PIHS), Dhaka, BANGLADESH.

## ABSTRACT

**Background:** Neonatal Streptozotocin (n-STZ) rats are widely used as models for type 2 diabetes mellitus, but the basic defects of diabetes (insulin secretion and resistance) have not yet been adequately characterized in all species of such rats. **Materials and Methods:** In this study, the basic defects were studied in a group of neonatal streptozotocin-induced type-2 (n-2 STZ) diabetic models of *Long Evans* rats. The model rats were produced with a single intraperitoneal injection of streptozotocin to 48 hr old pups. Glucose and lipid levels were measured using the standard method. Insulin was measured by ELISA. The intestinal perfusion method was followed to check for the intestinal absorption of glucose. Insulin secretory capacity and resistance were measured using the Homeostasis Model Assessment (HOMA) and Insulin Sensitivity Index (ISI) methods. **Results:** Type 2 diabetic rats showed significantly higher blood glucose levels at fasting ( $p < 0.001$ ) and at 90 min ( $p < 0.001$ ). Significantly high levels of total cholesterol ( $p = 0.002$ ), triglycerides ( $p = 0.04$ ), and low levels of HDL cholesterol ( $p = 0.04$ ) were observed in diabetic rats compared to control. Glucose absorption in the intestine was found to be significantly higher in almost all the perfusate samples. The diabetic rats had significantly lower serum insulin levels as compared to the control at fasting and at the 90 min period ( $p < 0.001$ ) after oral glucose load. In diabetic rats, insulin secretory capacity (HOMA%B) and ISI composite were notably lower ( $p < 0.001$ ) and insulin sensitivity (HOMA%S) was significantly higher ( $p < 0.001$ ) compared to control. **Conclusion:** n-2 STZ *Long Evans* rats showed glycemetic and lipidemic abnormalities due to insulin secretory dysfunction which could not be balanced by inadequate compensatory decrease in insulin resistance. Experimental scientists are required to be aware of this basic defect when interpreting their data on such animals.

**Keywords:** *Long Evans* rats, Streptozotocin, Insulin secretory dysfunction, Insulin resistance, Lipids.

## Correspondence:

**Dr. Ramendu Parial**

PhD, Associate Professor, Department of Biochemistry and Molecular Biology, University of Chittagong, Chattogram-4331, BANGLADESH.  
Email: parialbmb@cu.ac.bd

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## INTRODUCTION

Type 2 Diabetes (T2D) is a complex and heterogeneous disorder with insulin resistance and insulin secretion defects.<sup>1</sup> It is worth mentioning that the number of diabetic patients as well as the prevalence of diabetes have been increasing steadily every year.<sup>2</sup> The main cause of T2D is the malfunction of pancreatic  $\beta$  cells to payoff for insulin resistance.<sup>1</sup> However, research on this chronic disease and its associated disorder is ongoing both *in vitro* and in animal model of T2D to study this disease more effectively.<sup>3</sup>

For this, it is important to select and/or produce efficient animal models of T2D to identify the cause and therapeutic outcome of this life threatening disease. To be an appropriate animal model of T2D, it is important to confirm the appropriateness of model regarding their sign and symptoms reflect the human disease or not.<sup>4</sup> Although, it is impossible to accommodate all the symptoms/conditions of diabetes in one single model, many animal models have very similar characteristics of T2D such as chronic hyperglycemia, hyper or hypoinsulinemia, and altered plasma lipid levels.<sup>5</sup> STZ-induced diabetic model is commonly used in the laboratory to study on diabetes, its complications, and remedy. However, no information regarding the insulin secretory and sensitivity status of this model was found. Hence, we focused on evaluating the basic pathophysiology of diabetes in neonatal-STZ *Long Evans* diabetic model rats; particularly



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to explore the association of glycemic and lipidemic status with insulin secretory defect and insulin resistance.

## MATERIALS AND METHODS

### Experimental animal models

*Long Evans* male rats of 180-220 g were used for this study. These rats were bred at the BIRDEM animal house. A total of 38 rats (20 diabetic and 18 controls) were used in this study. The control and diabetic rats were matched regarding age (months,  $M \pm SD$ ,  $3.0 \pm 0.6$  vs  $3.2 \pm 0.7$ ,  $p=0.349$ ) and body weight (g,  $M \pm SD$ ,  $201.6 \pm 8.76$  vs  $198 \pm 9.56$ ). Appropriate conditions like a room temperature of  $22 \pm 5^\circ\text{C}$ , a humidity of 40-70%, and 12 hr day-night cycle for rats, a standard pellet diet, and water were provided routinely to both control and diabetic rats. All the experimentation was done following the institutional ethics committee's animal handling guidelines [Ref No: PIHS/IIRB/ 2021/12(3)].

### Induction of type 2 diabetes

The T2D model was produced by inducing a single injection of STZ in citrate buffer, at a dose of 90 mg/kg body weight, to the 48-hr-old pups intraperitoneally.<sup>6</sup> After three months of injection, when the pups became adults, they were used for experimentation.

### Collection of blood sample

Blood was collected from tail tip of the rat by amputation under mild anesthesia induced by diethyl ether. Just before cutting, the tail was immersed into warm water ( $40^\circ\text{C}$ ) for 30 sec to dilate the vessels. About 0.5 mL blood was collected carefully in small test tubes avoiding haemolysis. After that, serum was collected by centrifuging the collected blood samples for 15 min at 2500 rpm.

### Screening for type 2 diabetes

Blood glucose level of fasting (12 hr), 45 min and 90 min after an oral glucose load was measured and rats with fasting value more than 8.5 and after glucose load 10 mmol/L and above was taken as diabetic model rats for experiments.

### Analytical methods

Glucose was measured following the Glucose Oxidase (GOD-PAP) method. Enzymatic colorimetric (GPO-PAP) and (CHOD-PAP) methods were used to measure the serum triglyceride and HDL cholesterol, respectively. Total cholesterol was measured following the cholesterol oxidase/ peroxidase method. All the reagents were purchased from Randox Laboratories Ltd., UK. ELISA was used to estimate the insulin (Linco Research Inc., USA). Insulin secretion and insulin sensitivity were calculated using HOMA-CIGMA software. The Insulin Sensitivity Index (ISI) was calculated by the ISI composite Index.<sup>7</sup>

### Gut perfusion to determine intestinal glucose absorption

To check the intestinal absorption of glucose in control and diabetic rats, an intestinal perfusion technique was applied. After 36 hr of fasting and anesthetizing with sodium pentobarbital, glucose (Kreb's solution supplemented with glucose) solution of 65.0 gm/l was passed through the upper part of the duodenum of rat and the solution was collected at the end of the ileum. The perfusate was collected once every 5 min for 35 min (in total 07 samples were collected). The absorption of glucose is expressed as a percentage, measuring the amount of glucose in the solution before and after the perfusion.

### Statistical analysis

Data was analyzed using SPSS software (SPSS Inc., Chicago, Illinois, USA). Results are expressed as mean  $\pm$  SD/SEM and percentage (%) as appropriate. An unpaired *t*-test was done to check for differences between the groups. A *p*-value of  $<0.05$  was considered statistically significant.

## RESULTS

### Age and body weight

Thirty-eight male rats were included in this study; of which twenty were diabetic and eighteen were control. Age and body weight were matched between control and diabetic rats (control vs diabetic rat, age  $3.0 \pm 0.6$  vs  $3.2 \pm 0.7$  month; body weight  $201.6 \pm 8.76$  vs  $198 \pm 9.56$  g).

### Glycemic status of control and diabetic *Long Evans* rats

A significant difference between diabetic and control rats was found in the case of fasting glucose ( $p < 0.001$ ). Glucose levels of 45 min and 90 min after an oral glucose load were also significantly higher in diabetic rats compared to control ( $p < 0.001$  and  $p < 0.001$  respectively). Percent increase of glucose in diabetic rats was also significant at 45 min ( $p = 0.001$ ) and at 90 min ( $p = 0.001$ ) in comparison to control rats (Figure 1).

### Lipid status of control and diabetic rats

Table 1 shows significantly high cholesterol ( $p = 0.002$ ), TG ( $p = 0.04$ ), and significantly low HDL-cholesterol ( $p = 0.04$ ) in diabetic rats compared to controls.

### Intestinal glucose absorption of diabetic and control rats

Amount of glucose absorbed by gut were measured in normal and diabetic rats at 6 different times point (every 5 min after treatment) for 30 min. Absorption of glucose was calculated considering the amount of glucose in solution before and after administration of glucose in the gut region. Results showed that

the intestinal glucose absorption of normal rats is significantly lower than diabetic rats (Table 2).

**Insulinemic status of control and diabetic Long Evans rats**

The diabetic rat had significantly lower serum insulin value as compared to control both at fasting ( $p=0.001$ ) and 90 min ( $p=0.001$ ). The fasting insulin-glucose ratio was significantly low ( $p=0.001$ ) in diabetic rats compared to the control. In the case of insulin secretory function of  $\beta$  cells and insulin sensitivity, diabetic rats had significantly lower HOMA % B value ( $p=0.001$ ) and significantly higher HOMA% S ( $p=0.001$ ) value as compared to the control. ISI composite index was significantly higher in diabetic rats compared to the control ( $p=0.001$ , Table 3).

**Association between fasting glucose and HOMA% B, HOMA% S, and ISI composite index in control and diabetic model rats**

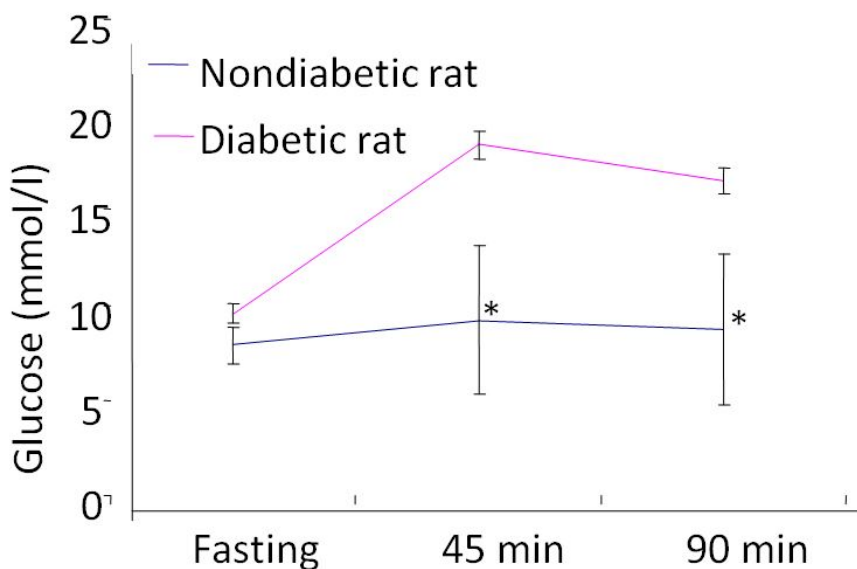
A significant negative correlation was observed with HOMA%B and fasting glucose both in diabetic ( $r =0.628, p=0.029$ ) and control rats ( $r=-0.679, p<0.011$ ) A negative correlation was also found between ISI composite index and fasting glucose in

diabetic rats ( $r=-0.725, p<0.008$ ), but no correlation was found in control rats.

In the case of fasting glucose and HOMA %S, no significant correlation was found ( $r=0.463, p<0.130$ ) in the diabetic model (Tables 4 and 5).

**DISCUSSION**

Animal models are essential tools for proper understanding of the cause, pathogenesis, complications, and genetic or environmental influences that increase the risk of diseases. Various types of animal models are now available to study diabetes, and these models can be obtained spontaneously, chemically, through dietary or surgical manipulation, and/or by a combination of a few of them.<sup>7</sup> For the chemical-induced model for T2D, STZ is one of the preferred agents to induce diabetes. Because of a relatively longer half-life (15 min), constant hyperglycemia for a longer duration and well characterized diabetic complications development with insignificant incidences of ketosis and mortality, STZ is used to create n-2 STZ neonatal model for T2D. As STZ destroy pancreatic beta cells at neonate, the n- STZ model are considered to be better tools for the understanding of the mechanisms associated with regeneration, the functional



**Figure 1:** Glycemic status of nondiabetic and diabetic Long Evans rats. Data are presented as Mean±SD. An unpaired t-test was used as the test of significance. \* $p<0.001$ .

**Table 1: Lipid status of non-diabetic and diabetic Long Evans rats.**

Group	TG (mg/dl)	Cholesterol (mg/dl)	HDL (mg/dl)
Non-diabetic (control) (n=18)	92.98±30.29	53.93±7.58	38.70±6.80
Diabetic (n=20)	115.97±29.06*	67.22±14.019**	33.84±7.039*

Data are presented as mean±SD; n=Number of rats. An unpaired t-test was used as the test of significance. \* $p<0.05$ , \*\* $p<0.001$ .

**Table 2: Percentage (%) of glucose absorbed from the gut in normal and diabetic rats.**

Time of experiment (Min after treatment)	Normal rats (n=10, Mean±SEM)	Diabetic rats (n=10, Mean±SEM)	t/p value*
5 min	18.59±1.78	26.00±2.26	-2.57/0.028
10 min	19.87±1.42	26.85±1.30	-3.61/0.005
15 min	18.70±2.91	25.52±0.94	-2.22/0.05
20 min	20.84±2.65	28.80±1.74	-2.50/0.031
25 min	18.29±1.35	23.61±3.09	-1.57/0.146
30 min	12.25±2.63	22.32±2.62	-2.70/0.022

Data are expressed as Mean±SEM. Unpaired *t* test was used as the test of significance. \**p*< 0.05 was considered as test of significance. SEM, Standard error of mean, *n*=Number of rats.

**Table 3: Insulinemic status of nondiabetic and diabetic Long Evans rats.**

Group	Fasting insulin (pmol/L)	Insulin at 90 min (pmol/L)	Fasting insulin glucose ratio	HOMA% B	HOMA% S	ISI Composite Index
Control (n=13)	196±36.88	402±102.54	24.87±50	114±20.73	22.30±3.75	1.65± 0.148
Diabetic (n=13)	121± 19.93*	213±39.60*	12.52±1.87*	54.02±12.82*	33.11±4.71*	1.90±0.18*

Data are presented as Mean±SD; *n*=Number of rats. Unpaired *t* test was used as the test of significance \**p*<0.001.

abnormalities of the beta cells, and the emergence of defects in insulin action.<sup>7</sup> STZ-induced T2D mellitus has been fairly well characterized in Sprague-Dawley and Wistar rats,<sup>8</sup> but it has not been studied in detail in *Long Evans* rats. Hence, the present study focused on exploring the basic defects associated with T2D mellitus in neonatal-STZ *Long Evans* rats.

To do this, we first checked the glucose status among diabetic rats. As expected, the n-2 STZ showed a fairly good simulation with human T2D mellitus. The fasting blood glucose was only moderately higher in diabetic rats compared to control but on oral glucose challenge, the blood glucose of diabetic rats nearly doubled. The finding is almost similar to that found in Wistar and Sprague-Dawley rat<sup>9</sup> and it reflects the substantial regain in insulin secretory capacity through regeneration of pancreatic  $\beta$  cells. Next, we checked for intestinal glucose absorption in the diabetic model. Metabolic abnormalities in diabetes include a disruption of normal absorption of glucose from the small intestine. Convincing results on this matter were obtained from human experiments, which supported earlier animal experiments too, showing that intestinal absorption of glucose is twice as high in diabetics as in normal people.<sup>10</sup> In our gut perfusion study, glucose absorption was found significantly higher in diabetic rats than in normal rats in different timed collections of perfusate (Table 2). Atherogenic dyslipidemia (raised total cholesterol, raised TG, raised LDL, and decreased HDL) is another feature of human T2D.<sup>11</sup> Hypercholesterolemia and hypertriglyceridemia have been reported to occur in STZ-induced diabetic rats.<sup>12</sup> So, we also checked for lipid status alteration in diabetic model rats compared to the control. In our study, serum cholesterol and serum TG of diabetic rats were also significantly high (*p*<0.002 and *p*<0.04 respectively) in comparison to control. Serum HDL was significantly lower (*p*<0.04) in diabetic rats compared to

control rats. HDL levels in animal models have not been reported before. The major focus of the present study was to explore the basic defects of diabetes (insulin secretory dysfunction and insulin resistance in the n-STZ *Long Evans* rat models). Absolute values of insulin were significantly lower in diabetic rats compared to control rats both in the basal and glucose-stimulated conditions. In parallel to the blood glucose responses, the insulin response at 90 min after oral glucose load was only about 50% of the control value. The same compromise was found when insulin secretion was considered in relation to glucose by the insulin-glucose ratio (Table 3). Further exploration was continued by homeostasis model assessment where HOMA%B showed similar defect (*p*<0.001) in insulin secretion in the diabetic rats. Insulin resistance is another major defect in T2D mellitus, but the emergence of this defect in n-2-STZ rats is still an unclear issue. There is evidence that severe reduction in the  $\beta$  cells obtained from subjects with Type 2 DM or animals after STZ injection is associated with no severe insulin resistance.<sup>13</sup> On the other hand some authors claim that insulin resistance can develop secondarily in these models<sup>14,15</sup> and a certain degree of insulin deficiency is necessary to induce insulin resistance.<sup>16-18</sup> It is interesting to note that in the present study insulin sensitivity did not deteriorate in the diabetic rats; rather there was a moderate but significant increase in insulin sensitivity in the n-2 STZ animals. The conclusion on insulin sensitivity was supported both by Homeostasis Model Assessment (HOMA%S) as well as ISI values. Our model, induced by STZ, lacks severe obesity, which is a major driver of insulin resistance in the traditional fat-based nutritional and genetic models.<sup>19</sup> The observed increase in insulin sensitivity seems to suggest a compensatory mechanism in peripheral tissues, potentially involving enhanced glucose uptake in skeletal muscle or reduced hepatic gluconeogenesis

**Table 4: Correlation between fasting glucose and HOMA% B, HOMA% S and ISI composite index in control rats.**

		HOMA% B	HOMA% S	ISI composite index
Fasting glucose (mmol/L)	r value	-0.679(*)	0.060	-0.433
	p value	0.011	0.846	0.160

\*Correlation is significant at the 0.05 level (2-tailed).

**Table 5: Correlation between fasting glucose and HOMA% B, HOMA %S and ISI composite index in type 2 diabetic rat.**

		HOMA% B	HOMA% S	ISI composite index
Fasting glucose (mmol/l)	r value	-0.628(*)	-0.463	-0.725(**)
	p value	0.029	0.130	0.008

\*Correlation is significant at the 0.05 level (2-tailed).\*\*Correlation is significant at the 0.01 level (2-tailed).

in the liver. The compensatory response, however, is inadequate to balance the diabetogenic effects of the secretory defect and this is supported by the fact that the mean HOMA%B is more than 2-times (2.11) lower in the diabetic as compared to control rats whereas the corresponding increase in HOMA%S is much less (1.48) than 2-times (Table 3). This phenomenon reflects a lean type 2 diabetes phenotype, where  $\beta$ -cell dysfunction dominates over insulin resistance,<sup>20</sup> which seems to be a unique phenomenon for n-STZ *Long Evans* rats. Further validation in additional rodent models, such as appropriate diet-induced diabetes in non-genetic rat strains, could help elucidate the broader applicability of our findings. While better markers for insulin sensitivity (like clamp techniques) should be used to investigate this phenomenon, the present data is an important step to understanding the predominant defects in this model. A good number of experiments have been conducted in Bangladesh with STZ-induced diabetic rats, particularly involving medicinal plants. The evidence from the present study indicates that the n-2 STZ *Long Evans* rat mimics the insulin secretory dysfunction arm of the two-pronged defect in T2D mellitus. Thus experimental data with these animals must be interpreted keeping this abnormality in mind. It is highly interesting to note that the predominant defect in Bangladeshi T2D mellitus subjects is the insulin secretory defect.<sup>21</sup> Thus the n-STZ *Long Evans* model may better reflect the basic abnormality in the diabetic population of this region.

## CONCLUSION

In conclusion, n-2 STZ *Long Evans* rats mimic the glycemic and lipidemic abnormalities of human diabetes with fair parallelism; however, these abnormalities are manifestations of insulin secretory dysfunction rather than insulin resistance.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**STZ:** Streptozotocin; **T2D:** Type 2 diabetes; **n-2 STZ model:** neonatal day 2 streptozotocin induced model; **HOMA:** Homeostatic model assessment; **ISI:** Insulin sensitivity index; **TG:** Triglycerides; **HDL:** High-density lipoprotein; **LDL:** Low-density lipoprotein.

## ETHICAL APPROVAL

Ethical permission was obtained from the institutional ethical review committee (Ref No: PIHS/IIRB/ 2021/12(3)).

## SUMMARY

The objective of the present study was to characterize the basic defects (insulin secretory and sensitivity) along with the glycemic and lipidemic status of neonatal Streptozotocin (n-2 STZ) induced diabetic model of *Long Evans* rats. Blood glucose, lipid, and insulin status were measured following standard procedure. The glycemic and lipidemic status were similar in other diabetic rat models, however, insulin sensitivity was found to increase in this model. The conclusion on insulin sensitivity was supported both by Homeostasis Model Assessment (HOMA%S) as well as ISI values. The modest lowering of insulin resistance, probably due to a compensatory mechanism for preserving glucose homeostasis seems to be a unique phenomenon for n-STZ *Long Evans* rats which needs further investigation.

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