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HAMSTER AS A MODEL FOR DIABETIC STUDY

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ABSTRACT

Diabetes is a non communicable, life style disorder and is one of the most significant global health issues. Theoretically, high metabolism (weight reduction and exercise) could improve Type 2 Diabetes Mellitus (T2D), but in reality human life style does not permit the above remedy to succeed. Hence, the search for new therapies for diabetes is always in demand. Symptoms of diabetes in the hamsters are very similar to those in humans; therefore, hamsters were used in the present study instead of earlier models like rat and mice. Hamsters having high fat diet (HFD) and were given a single dose of streptozotocin (STZ) (60mg/kg) to induce T2D. After confirming diabetes in the hamsters after 72 hrs, the damages caused by HFD+STZ induced diabetes were observed. The diabetic animals exhibited significant increase in serum glucose level and reduction in serum insulin level. HFD+STZ induced diabetes also led to disruption in the pancreatic histoarchitecture as noted in our animal model golden hamsters. The induction of T2D in the hamsters significantly reduced the glycogen content of both liver and muscle tissues. The impaired glucose homeostasis caused derangements in the lipid profile as evidenced by increased total cholesterol (TC), LDL cholesterol (LDL-C) and decreased HDL cholesterol (HDL-C) in the hamsters. Our data clearly suggest that hamsters, a long photoperiodic rodent, having close similarity with humans may prove to be an excellent model for diabetology.

Keywords: Diabetes, Hypoinsulinemia, Streptozotocin (STZ), High Fat Diet (HFD)

1. INTRODUCTION

Sedentary lifestyle, obesity, stress, reduced sleep, geriatric problems, alcoholism, etc., are the major causes of diabetes that is spreading like an epidemic and hence it is referred to as a life style disorder. It not only affects a person's physiological wellbeing but also influences the financial welfare. According to World Health Organization (WHO) the number of persons suffering from diabetes would reach to 36 million by 2030 globally [1]. Diabetes is a metabolic disorder where environmental factors combined with multiple stressors induce loss of pancreatic β-cell function, along with impairment in insulin action and secretion resulting in hyperglycemia. The prevailing hyperglycemic condition leads to perturbation in the metabolism of fat, protein and carbohydrate [1 ,2, 3]. There are two main types of diabetes are type 1 (T1D) and type 2 (T2D). 90-95% of patients are diagnosed with T2D and it has become common worldwide. T2D in later stages leads to various metabolic syndromes like neuropathy, retinopathy, cardiac disease and nephropathy. Theoretically, high metabolism (weight reduction and exercise) could improve Type 2 Diabetes (T2D), but

in reality human life style does not permit the above remedy to succeed [1]. Therefore search for new remedies for this dreaded disease is always in progress. Rodents have always been a preferred model for study of diabetic pathophysiology because of their similarities to those in humans [4]. The purpose of the present study was to use one of the rodents *Mesocricetus auratus* (Golden hamster) for the induction of diabetes by using high fat diet (HFD) followed by a single injection of streptozotocin (STZ) and observing the diabetes led damages in the hamsters.

2. MATERIALS AND METHODS

2.1. ETHICAL CONSIDERATIONS

All the experiments on the animals were conducted in accordance with institutional practice and within the framework of CPCSEA (Committee for the purpose of control and supervision of experimental animals) and the rule of Government of India (2001) for animal welfare.

2.2. ANIMALS

The animal model for the study, *Mesocricetus auratus* (Golden hamster) were procured from CDRI, Lucknow for the establishment of the colony. The animals from the inbred colony were used for this study. The hamsters were kept in polypropylene cages during the experiments and maintained in a well ventilated room exposed to ambient conditions ($27+2^{o}$C, with gentle ventilation), fed with commercial animal feed and water *ad libitum*.

2.3.INDUCTION OF DIABETES

For induction of T2D, hamsters weighing 100±10 gm were divided into two groups consisting of six animals each. Group first was control group which was given normal diet while group second, was fed with high fat diet (HFD) for 10 weeks. At the end of 10^{th} week the animals of second group were fasted overnight and received a single dose of intra-peritoneal injection of streptozotocin (STZ) dissolved in a citrate buffer (pH=4) of 60 mg/kg [5] while the control group received only citrate buffer. The animals received water and food *ad libitum.* To avoid initial STZ-induced mortality, the animals were given 20% glucose solution for 24h. 72 hours after injection fasting blood glucose (FBG) was checked (AccuChek, USA). The animals having FBG greater than 200 mg/dl were considered diabetic type 2. The observation was extended for two more weeks. During the whole experiment the body weight and food/water consumption was monitored daily.

2.4.SAMPLE COLLECTION

At the end of 12^{th} week, the animals were fasted overnight and next day they were weighed and sacrificed by total body anesthesia. Blood was collected directly from the heart. Serum was separated, and frozen at -80^{o}C till ELISA for insulin (DIAMETRA, Lot no. DKO076), and biochemical estimations for serum glucose, total cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL) was carried out. Pancreas, liver and muscle were dissected out on ice, blotted free from blood, cleaned from extra tissue. Pancreas was fixed in Bouin's

fluid for histology while liver and muscle were kept for biochemical estimations of glycogen.

2.5. HISTOLOGY

After fixation in Bouin's fluid pancreas was processed for routine histological procedure. Some 6-µm sections were deparaffinised and stained using Ehrlich's hematoxylin and eosin. The stained sections of the tissues were observed in a microscope (Nikon, USA) and documented.

2.6.BIOCHEMICAL ESTIMATIONS

Concentration of serum glucose, total cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL), glycogen level in liver and muscle was estimated according to manufacturer's protocol (Bio Lab Diagnostics, India). Hormone insulin was measured in serum following the details from the kit (Diametra, DKO076).

3. STATISTICAL ANALYSIS:

The data was analyzed using the Student's t-test. All the data are presented as the mean $\pm$ standard error of mean (SEM). Values of $p \leq 0.05$ were considered as statistically significant.*=$p \leq 0.05$; **=≤ 0.01.

4. RESULTS:

4.1. BIOCHEMICAL PARAMETERS

In the present study it was found that the HFD+STZ led to significant increase in plasma glucose level (Fig.1). The induction of T2D in the hamsters significantly reduced the glycogen level in both liver and muscle tissues (Fig.2 & 3).There was a marked increased total cholesterol (TC), LDL cholesterol (LDL-C) and decreased HDL cholesterol (HDL-C) in the diabetic animals as compared to the control group (Fig. 4, 5, 6).

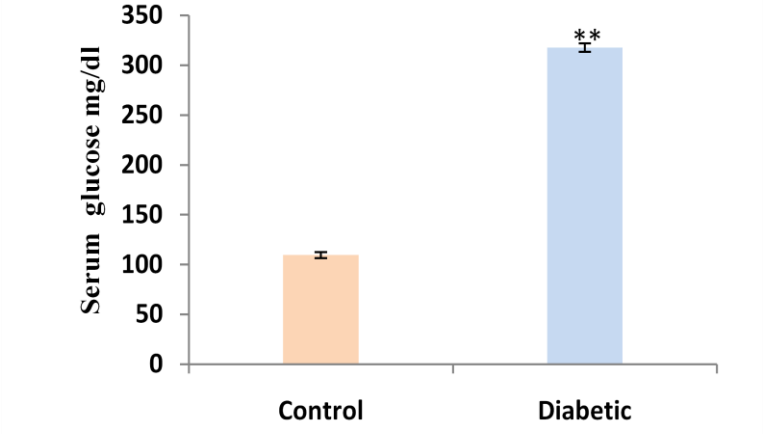

Fig.1 Serum glucose concentration

Fig. Bar graphs depicting significant elevation in serum glucose concentration leading to hyperglycemia after HFD+STZ induced T2D

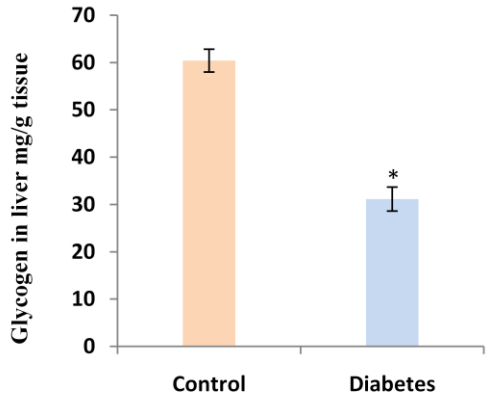

Fig.2 Glycogen concentration in liver

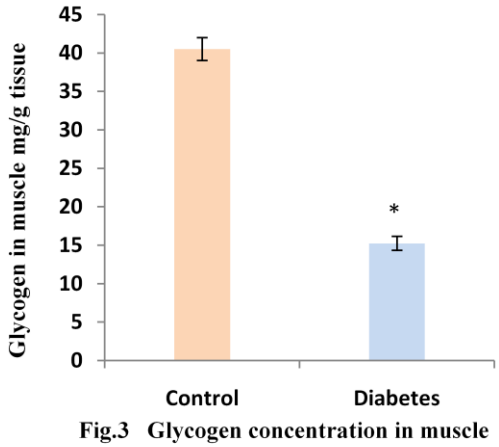

Fig.3 Glycogen concentration in muscle

Fig: The bar graphs depicting significant reduction in liver (Fig.2) & muscle (Fig.3) glycogen following T2D induction

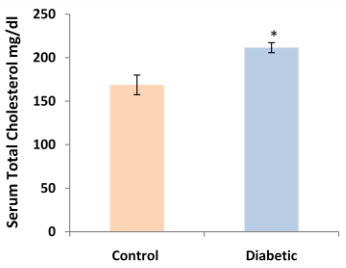

Fig.4 Serum total cholesterol (TC)

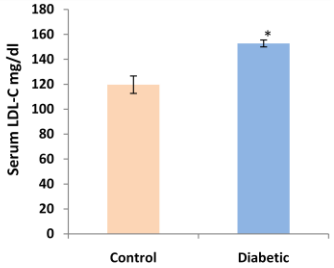

Fig.5 Serum low density lipoprotein cholesterol (LDL-C)

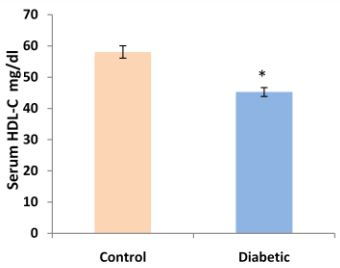

Fig.6 Serum High density lipoprotein cholesterol (HDL-C)

Fig: Bar graphs showing significant changes in TC (Fig.4), LDL-C (Fig.5) & HDL-C (Fig. 6) after T2D induction

4.2.HORMONAL ANALYSIS

A significant reduction was observed in serum insulin level following HFD+STZ (Fig. 7).

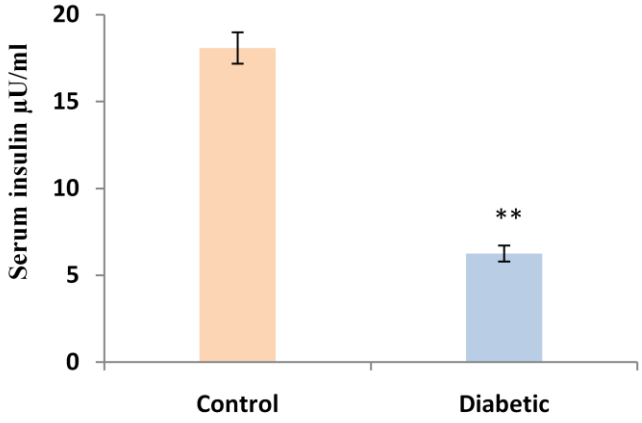

Fig.7 Serum insulin concentration

Fig. Bar graphs depicting significant reduction in serum insulin concentration leading to hypoinsulinemia after HFD+STZ induced T2D

4.3.HISTOLOGY

HFD+STZ induced diabetes also led to disruption in the pancreatic histoarchitecture as noted in our animal model golden hamsters (Fig. 8).

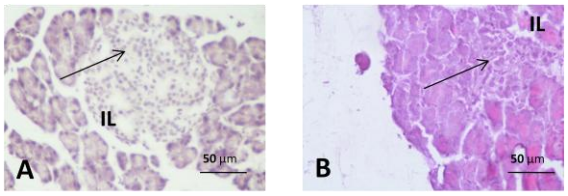

Fig. 8 Photomicrograph of hematoxylin and eosin stained pancreas sections from control hamsters(A) and HFD+STZ treated hamsters(B). IL: Islet of Langerhans. The pancreas cells of control animals showed their normal proportions. The islet cells (IL) are seen embedded within the acinar cells and surrounded by a fine capsule. The pancreas of the HFD+STZ treated hamsters demonstrated damage to the tissue. The islet is showing shrinkage and is not well covered with a fine capsule.

5. DISCUSSION

Numerous studies have shown that high fat diet and obesity are the main risk factors for theT2D. The aim of the present study was to induce T2DM in the animal model, *Mesocricetus auratus*. It has been reported in many studies that feeding high fat diet (HFD) induces tissue insulin resistance. This insulin resistance is caused due to accumulation of lipids in the skeletal muscles, adipose tissue and liver. Along with this insulin resistance a dose of STZ leads to partial destruction of β cells which closely mimics the T2D in humans and is responsible for long term glucose [2, 3].

It has been suggested in some earlier studies [1, 3], that HFD leads to insulin resistance while STZ causes dysfunction of β-cells that in a combined way lead to hyperglycemia. In response to insulin resistant state, the secretory capacity of the pancreatic β cells decreases to compensate the existing insulin resistance, thereby leading to hypoinsulinemia (which is achieved practically by injection with STZ) [3].The significant increase in plasma glucose level and reduction in insulin level was noted in the golden hamsters in the present experiment as well and that gets support from the above references. HFD+STZ induced diabetes also led to disruption in the pancreatic histology as noted in our animal model golden hamsters.

Insulin is the most important factor in lowering blood glucose level by enhancing glycogenesis in liver and muscle. Hence, glycogen level in these tissues is considered to be an important marker for the study of insulin activity [6]. The induction of T2D in the hamsters significantly reduced the glycogen level in both liver and muscle tissues of the diabetic hamsters.

Relating to other previous studies [7, 8] the disrupted glucose homeostasis caused disturbance in the lipid profile of the experimental hamsters as manifested by increased total cholesterol (TC), LDL cholesterol (LDL-C) and decreased HDL cholesterol (HDL-C) in the present study. This pronounced hyperlipidemia characterizes the diabetic state and the reduced insulin can be related to the enhanced lipolysis, increased influx of free fatty acids to the liver and disturbed lipoprotein metabolism during diabetes [9].The main objective of the present study was to induce the HFD+STZ led type 2 diabetes in hamsters and to study the effects of induced diabetes on general physiology such as carbohydrate metabolism and hormonal changes, It was found that the induced diabetes caused marked changes in the biochemical, hormonal along with the histological parameters of the pancreas of hamsters.

Our data clearly suggest that hamsters, a long photoperiodic rodent, having close similarity with humans may prove to be an excellent model for diabetology.

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