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Biochemical Profiles of Different Approaches Applied to Induction of Diabetes in Rats

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BACKGROUND: Diabetes mellitus, as a chronic metabolic disease, is characterized mainly by hyperglycemia due to insulin deficiency. The cornerstone of diabetes research is the experimental induction of diabetes in laboratory animals, thus various approaches were applied for induction. **Objective:** The aim of this study was the evaluation of different methods applied to the induction of diabetes in experimental animals. **Methods:** Alloxan (200 mg/kg of body weight), streptozotocin (50mg/kg body weight) and a high carbohydrate diet were applied in rats, for one month. 45 male albino rats at age 2-4 months and weight (220-260g) were gathered into 5 groups (9 rats for each group). Body physiological parameters and serum glucose, insulin, insulin resistance, and serum lipid profile were estimated. **Results:** Outcomes reveal that the body weight and body mass index were increased in treated groups, as well as, the greatest serum glucose, minimum serum insulin, and insulin resistance were in the group of the streptozotocin+diet. Whereas the maximum lipid profile fluctuation was in the group of the Alloxan+diet. **Conclusion:** It could be concluded that the different approaches of experimentally induction of diabetes in rats have a diverse degree of impact on the physiological and biochemical profiles.

Keywords: Alloxan, Diabetes mellitus, Diet, Rats, Streptozotocin.

Introduction

Diabetes Mellitus (DM), characterized by hyperglycemia, is a chronic metabolic disorder due to absolute or relative insulin deficiency leading to the default metabolism of carbohydrates, lipids, and proteins [1]. DM consider the leading metabolic disease of humans and animals [2]. abnormalities of lipids in diabetes called diabetic dyslipidemia, are classically characterized by increased serum total cholesterol, triacylglycerol, and low-density lipoproteins (LDL), and a decline of serum high-density lipoprotein cholesterol [3]. Therefore, sustained attention was assumed to it for many decades due to the wide prevalence (especially in dogs and cats) of DM, as well as, it affects nearly most body systems, and it has a divergence of signs [4]. The original and public diagnostic guides of DM are hyperglycemia and (in severe cases) glycosuria. In that concern, the irregular metabolism of carbohydrates in DM, and related thoughtful modifications of glycolytic pathways [5,6] provoke the stimulation of substitute polyol metabolic pathways with a subsequent intracellular gathering of sorbitol [7] and glucose auto-oxidation [8]. These unbalanced metabolic events have been concerned in the pathogenesis of diabetic peripheral retinopathy,

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and neuropathy, as well as, in the fluctuations in the body weight, and body mass index [9, 10]. Configurations of dyslipidemia in DM and involving principal threat factors have been defined in many reports [11-13]. Atherosclerosis-provoked heart disease, stroke, and hypertension are the chief causes of the growing rate of mortalities among DM patients [14,15]. Although relative or absolute insulin deficiency is prevailing, there is a wide range of variations in etiology and pathophysiology of DM. Thus a long journey of DM research began many decades ago and is still continuous [16]. On the other hand, the milestone of DM research is the experimental induction of DM in lab animals; by streptozotocin, alloxan, and other specific substance, and other methods (such as pancreatectomy) [17]. So we conduct this project to evaluate a common induction method of DM by using, steroptosotozien, alloxan and specific diet approaches in rats.

Experimental

Experimental Animals

Forty-five male albino rats at age 2-4 months and weight (220-260g) were used in this project, all experimental animals appear healthy and manipulated under suitable and ethical properties in a laboratory animals house, College of Veterinary Medicine, University of Mosul. Rats were set in special breeding cages for rat (dimensions of 17X20X50cm) and environmental conditions were identical for rats, the temperature of 22±2 ºC, dark/light cycle 12/12 hours, stander diet (except for candidate diet group) for rats and water *ad libitum* [18,19]. Rats were divided into the following groups:

1- Control group:

Nine rats were considered a control group and not treated with any chemicals or foods.

2-Alloxan group:

Nine rats were injected subcutaneously (one time) with alloxan (Ayonchen, UK) 200 mg/kg of body weight [20]. The level of glucose was measured frequently by using Accu-Chek® device (Roche, Germany).

3- Streptozotocin (STZ) group:

Nine rats were injected subcutaneously with STZ (Direvo industrial biotechnology, Germany) 50mg/kg body weight [20], weekly for one month.

4- Alloxan+diet group:

Nine rats were injected subcutaneously (one time) with alloxan 200 mg/kg and given white bread only as a food with saturated fructose solution 40% W/V as a drinking water for one month.

5- STZ+diet group:

Nine rats were injected subcutaneously with STZ 50 mg/kg body weight weekly and given white bread with saturated fructose solution 40% W/V as a drinking water, for one month.

Body physiological parameters:

An electronic weighing scale with a 0.01 g accuracy has been utilized, whereas abdominal circumference, and body length have been determined by scale tape at the start and end of each experiment. From the nose to the origin of the tail was considered the body length [21]. Abdominal circumference was measured around the anterior region of the abdomen. Anyway, the body mass index (BMI) was calculated as BMI=body weight(g)/ body length^2 (cm^2) [22].

Biochemical tests:

In all groups, blood was collected by a heparinized capillary tube from the retro-ocular vein of the eye [23], and then serum was separated by centrifugation (3000xg) for 15 min. The serum was kept at -20 ºC for biochemical analysis. Serum insulin level was determined by using a sandwich-ELISA kit (Elabscience, USA) specific for rats, and a microtiter reader (Biotek, USA) was used at 450 nm. Serum glucose level was determined by enzymatic (oxidase-peroxidase) method, by using a kit (Biolab, France) and the concentration was determined at 505 nm by spectrophotometer (Vispectrophotometer, China). From the data of insulin and glucose levels (as mentioned above), insulin resistance was estimated mathematically as follows [24]:

HOMA-IR* = Serum glucose X Serum insulin / 22.5

*HOMA-IR (Homeostatic Model Assessment for Insulin Resistance)

Serum lipid profile:

Serum total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein (HDL), low-density lipoprotein–cholesterol (LDL-C), and

serum very low-density lipoprotein-cholesterol (VLDL-C) were measured by using an enzymatic colorimetric method, (Biolabe, France) and the concentration determined at 500 nm by using the spectrophotometer (Vispectrophotometer, China) (24). While atherogenic index (AI) was determined as follows [25]:

AI = TC –HDL/HDL

Statistical analysis

All experimental data were analyzed statistically by applying SPSS (ver.25) to determine mean ± S.D, and for measuring significance ANOVA tests were used and the results were considered significant when p≤0.05 [26].

Results and Discussion

Successfully, diabetes mellitus was induced in albino rats by alloxan, STZ, and a special diet. Induction of diabetes conducted by the direct impact of the beta cell of the islet of Langerhans [13]. The precise mechanism of diabetogenic action of alloxan consider mainly on selective attack of beta cell by oxidation of –SH groups, glucokinase inhibition, intracellular calcium imbalance, and free radical formation [14]. The selectivity of alloxan to the beta cells may be due to particularly to their analogue similarity with glucose, so glucose transporter (GLUT) perform an uptake mechanism, in addition to significant affinity and preference of beta cell for uptake of alloxan [15]. Table 1 shows that the body weight was greatest in the group of STZ+diet, followed by the group of alloxan+diet, and this may be due to a high carbohydrate in food and drinking water which contributed to the high body weight gain [27]. Also remarkably, the rats which have injected with alloxan and STZ have a low body weight when compared with the control group (Table 1). This result may be due to that diabetes causes a deterioration in most body systems leading to body weight loss because of the inability of most body cells to utilize glucose (although it is at a higher level in the serum) with default insulin [27,28]. Accordingly, the body mass index was greater significantly (p ≤0.05) in STZ+diet and alloxan+diet groups, and lesser in alloxan and STZ groups, when compared with the control group.

On the other hand, the greatest serum glucose level was in the group of STZ+diet (244.79 mg/dl ±9.7) (Table 2), and there was a significant difference (p ≤ 0.05) between all treated groups when compared with the control group. In the same table 2, the greater level of serum Insulin was in the same group (STZ+diet). In the same manner, HOMA-IR and HOMA-B index was lowest in group STZ+diet. So our results agree with many authors [16] who induced diabetes in rats by injection of alloxan. Also, our findings may be due to the synergistic effect of both approaches in which diabetes status (induced by alloxan) was exacerbated by a diabetogenic diet [17, 29]. As well as, the level of serum insulin (Table 2) confirms the above hypothesis.

However, lipid profiles (Table 3) reveal a greater elevation of cholesterol in the group alloxan+diet (240.75 ± 15.89), also all treated groups have a significantly (p ≤0.05) higher

TABLE 1. Body physiological parameters.

Groups	Body weight (g)	Length (cm)	BMI	Abdominal circumference (cm)
Control	276±19^{c}	22.2±1.1^{a}	0.56±0.12^{b}	18.6±1.4^{b}
Alloxan	251±17^{d}	22.6±1.3^{a}	0.49±0.14^{c}	17.8±1.4^{b}
STZ	248±17^{d}	22.4±1.0^{a}	0.49±0.12^{c}	17.0±1.7^{b}
Alloxan+diet	362±20^{b}	22.9±1.1^{a}	0.69±0.10^{a}	21.7±1.2^{a}
STZ+diet	422±21^{a}	23.5±1.6^{a}	0.76±0.15^{a}	22.9±1.3^{a}

-All rats in this group have an initial weight of 220±10 g.
-Each value represents mean±S.D
-Different letters within each column means a significant difference (p≤0.05) between groups.

cholesterol level when compared with the control group. In the same manner, serum triacylglycerol and LDL are greater in a group of alloxan+diet. (Table 3). Consequently, serum HDL level was the lowest in the group of alloxan among all groups, while the greatest serum VLDL was in the group of STZ (59.48 ± 5.3). All treated groups have a significant difference ($p \leq 0.05$) when compared with the control group. The strong association between diabetes and dyslipidemia is confirmed by many authors [30-34]. Thus, hypertriglyceridemia may be considered the principal irregularity of fat metabolism in diabetes, and this may be due to a rise of the triglyceride-carrying lipoproteins, VLDL, and chylomicrons [35]. The crucial pathogenesis for hypertriglyceridemia is the diminished deprivation of VLDL and the chylomicron-clearance, which is caused by reduced activity of the enzyme lipoprotein lipase. Therefore, serum total cholesterol level is significantly raised when there is poor metabolic control, LDL level can be increased and HDL decreased in reliance on the metabolic control [36,37]. Other authors suggested that hypertriglyceridemia is amplified VLDL and triacylglycerol formation in the liver particularly due to improved free fatty acids (FFA) flux. Furthermore, the activity of the enzyme lipoprotein lipase can be declined [38].

Conclusion

From this study, it could be concluded that the different approaches for experimental induction of diabetes in rats have a diverse degree of impact, according to the method, on the physiological parameters, biochemical and lipid profiles. It seems that STZ+diet method of the induction of diabetes be more elevating the body weight and serum glucose, while the induction of diabetes by alloxan+diet could be more compelling in causing dyslipidemia. As well as, depending on the results of the lipid profile, especially in the group of alloxan+diet, this model can be applied in the research of cholesterol-lowering drugs in diabetes.

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Conflicts of Interest

The authors declare that they have no competing interests.

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TABLE 2. Biochemical Parameters of control and treated groups.

Groups	Serum glucose mg/dl	Insulin mg/dl	HOMA-IR
Control	75.66±6.2^{e}	20.22±2.0^{b}	67.99±0.55^{c}
Alloxan	166.87±12.4^{d}	10.1±1.1^{c}	74.90±0.606^{b}
STZ	184.32±5.5^{c}	12.4±1.8^{c}	101.58±0.44^{a}
Alloxan+diet	204.80±11.2^{b}	8.75±1.0^{d}	79.58±.54^{b}
STZ+diet	244.79±9.7^{a}	33.92 ±2.7^{a}	36.9±1.8^{e}

-Each value represents mean±S.D

-Different letters within each column means a significant difference ($p \leq 0.05$) between groups.

TABLE 3. Lipid profile of control and treated groups.

Groups	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	AI
Control	71.48 ±9.7^{e}	66.90±3.9^{a}	45.53±1.9^{e}	34.45±6.1^{a}	18.20±1.6^{a}	0.57±0.1^{e}
Alloxan	144.82±12.3^{d}	120.23±4.4^{c}	17.77±4.8^{a}	96.90±5.7^{c}	48.38±3.4^{d}	7.14±1.1^{a}
STZ	180.50±14.7^{c}	92.88±4.4^{b}	23.24±1.3^{b}	91.88±3.5^{c}	59.48±5.3^{d}	6.76±1.2^{a}
Alloxan+diet	240.75±18.8^{a}	117.60±6.2^{c}	30.50±1.7^{b}	135.95±11.9^{d}	37.44±4.2^{c}	6.89±1.1^{a}
STZ+diet	172.40±13.6^{c}	107.40±4.1^{b}	29.44±1.8^{b}	123.70±10.7^{d}	29.34±2.4^{b}	4.85±0/9^{b}

-Each value represents mean±S.D

-Different letters within each column means a significant difference ($p \leq 0.05$) between groups.

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المعايير الكيميائية الحيوية للطرق المختلفة لاستحداث داء السكري في الجرذان

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يتميز داء السكري، باعتباره مرض ايضي مزمن، بارتفاع كلوكوز الدم بسبب نقص الأنسولين. يعد استحداث داء السكري أهم جزء عند اجراء البحوث التجريبية لداء السكري، لذلك استخدمت طرق مختلفة لاستحداث داء السكري في الحيوانات المختبرية. كان الهدف من الدراسة الحالية هو تقييم الطرق المختلفة لاستحداث داء السكري في حيوانات التجارب. تم استعمال كل من الالوكسان والستربتوزوتوسين وغذاء عالي الكربوهيدرات في ذكور الجرذان البالغة. وأظهرت نتائج الدراسة وجود زيادة في وزن الجسم ومعامل كتلة الجسم، كما أن أعلى مستوى من الكلوكوز في الدم، وأقل مستوى من الأنسولين، ومقاومة الأنسولين كانت في مجموعة الستربتوزوتوسين+ الغذاء الخاص. بينما التذبذب في مستوى شحوم الدم كان في مجموعة الالوكسان + الغذاء الخاص. ويمكن الاستنتاج من هذه الدراسة أن الطرق المختلفة لاحداث داء السكري تجريبياً في الجرذان لها درجات متنوعة من التأثير على القيم الكيميائية الحيوية.

الكلمات الدالة: داء السكري، الالوكسان، الستربتوزوتوسين، الغذاء، الجرذان.