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ROLE OF THIAZOLIDINEDIONES (TZDs) AND GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AGONISTS AND ANTAGONOSTS IN TYPE-II DIABETES MELLITUS ON ADULT MALE ALBINO RATS

By

Nageh Mabrouk Gabr and Albayoumi Ali Fouda

Department of Medical Physiology, Faculty of Medicine, Al-Azhar University

ABSTRACT

Background: The rising incidence of insulin resistance to epidemic proportions has closely paralleled the surge in the prevalence of diabetes and outpaced therapeutic advances in diabetes prevention and treatment. Thiazolidinediones and glucagon-like peptide-1 agonists are insulinotropic peptides and are being evaluated for the regulation of lipid profile in diabetes mellitus (DM). Thiazolidinedione and glucagon-like peptide-1 antagonists have anti- insulinotropic effects.

Objectives: Evaluating the possible effects of thiazolidinediones and glucagon-like peptide-1 agonists, and their antagonists in lipoststic function in diabetic male albino rats.

Materials and Methods: Seventy adult male albino rats were divided into seven equal groups: Group I served as a normal control group, group II was diabetic control, group III was diabetic group treated with thiazolidinedione agonist (pioglitazone), group IV was diabetic group treated with glucagon-like peptide-1 agonists (exendin-4), and group V was diabetic group treated with both pioglitazone and exendin-4, group VI was diabetic group treated with thiazolidinedione antagonist [Bisphenol A diglycidyl Ether (BADGE)], and group VII was diabetic group treated with glucagon-like peptide-1 antagonist (Exendin- 9-39). At the end of the experimental period, blood samples were collected for measuring of fasting blood glucose, insulin level, total cholesterol, triglycerides (TG), low density lipoproteins (LDL), high density lipoproteins (HDL), aspartate transaminase (AST), and alanine transaminase (ALT). Body weights at the beginning and at the end of the study were determined.

Results: Alloxan-induced diabetes mellitus was associated with significant higher levels of serum blood glucose, total cholesterol, TG and LDL-C, AST, and ALT, with significant lower levels of insulin, and HDL-C as compared to the control normal group. Pioglitazone, exendin-4 or both showed significant lower levels of blood glucose, total cholesterol, TG, LDL-C, AST, and ALT, and significant higher levels of insulin and HDL-C as compared with the control diabetic rats. BADGE and exendin-9-39 revealed significant higher levels of serum blood glucose, total cholesterol, TG, LDL-C, AST, and ALT, and significant lower levels of insulin and HDL-C as compared with the control normal group. As regards the differences between pioglitazone (group III) with exendine-4 group (group IV), the obtained data showed insignificant changes in all parameters. There were insignificant changes also between groups VI and VII in all parameters.

Conclusion: Thiazolidinediones and glucagon- like peptide-1 agonists therapy has a marked effect on improvement of blood glucose, lipid profile and liver enzymes, while their antagonists blocked insulin secretion and impaired liver enzymes.

Key words: Pioglitazone, BADGE, Exendin, Thiazolidinediones, Oxidative stress.

INTRODUCTION

Diabetes is a lifestyle non-communicable disease of mankind considered as one of the most significant global health problems that affect both young and old in all parts of the world irrespective of their gender. The increasing prevalence of type-II diabetes mellitus together with its burden of patient suffering and social costs underscores the importance of finding effective strategies for both prevention and treatment *(Stanley et al., 2017)*.

Most patients eventually require therapy intensification with multiple antidiabetic drugs to achieve glycemic control *(Olga et al., 2018)*. For second-line treatment intensification, the American Diabetes Association recommends thiazolidinediones, glucagon-like peptide-1 receptor agonists, sulphonylureas, dipeptidyl peptidase inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors or insulin *(American Diabetes Association, 2017)*.

Thiazolidinediones (TZDs) are synthetic antidiabetic compounds that have been shown to bind and activate peroxisome proliferator-activated receptor-gamma (PPAR-γ) *(Stevens et al., 2018)*. PPAR-γ is a nuclear hormone receptor that is expressed at highest levels in adipose tissue and lower levels in other tissues to enhance insulin sensitivity and reduce serum glucose in diabetic patients *(Marchesini et al., 2016)*.

TZDs can ameliorate glucose metabolism and improve whole body insulin sensitivity in many animal models of obesity and diabetes *(Jeong et al., 2018)*. Pioglitazone (Actos), troglitazone (RezulinTM) and rosiglitazone (Avandia) are thiazolidinediones that currently used in the treatment of type-II diabetes mellitus without signs of signi?cant toxicity *(Chunmei et al., 2018)*.

Bisphenol A diglycidyl ether (BADGE) is a synthetic ligand for PPAR-γ. This compound has no apparent ability to activate the transcriptional activity of PPAR-γ and antagonize the ability of agonist ligands such as rosiglitazone to activate the transcriptional and adipogenic action of this receptor *(Yuan et al., 2018)*. These results provide the first pharmacological evidence that PPAR-γ activity is required for the hormonally-induced differentiation of adipogenic cells *(Yu et al., 2015)*.

GLP-1 is synthesized from post-translational processing of proglucagon in L-cells of the duodenum, distal ileum, and colon. It is responsible for nearly 50% to 70% of insulin secreted in response to ingested carbohydrates in healthy individuals *(Elisabet, 2018)*. Furthermore, L-cells are located in close proximity to both neurons and the microvasculature of the intestine, which allows the L-cells to be affected by both neural and hormonal signals *(Nauck, 2016)*.

GLP-1 is an insulinotropic and plays a role in the incretin effect, i.e. augmented insulin response observed when glucose is absorbed through the gut *(Chris et al., 2016)*. Exendin-4 has structural similarity and binds to GLP-1 receptors, and stimulates the proliferation and differentiation of stem cells in the pancreas into β-cell *(Jukka et al., 2018)*.

Exendin-9-39 is a GLP-1 receptor antagonist that can be used in humans to block effects of endogenously secreted GLP-1. It is a classic and essential

requirement in endocrinology to use specific inhibition of the putative endogenous hormone by receptor blockade to evaluate physiological relevance. Exendin (9-39) is a competitive strong antagonist of glucagon-like peptide-1 receptors (GLP-1R) blocking the cellular and metabolic effects of GLP-1*(Jorg et al., 2015)*.

The present study was a trial to assess the effects of thiazolidinediones and glucagon- like peptide-1 agonists and their antagonists against alloxan-induced diabetes mellitus.

MATERIALS AND METHODS

Chemicals: Alloxan monohydrate (2, 4, 5, 6-tetra-oxy pyraminndin and 5, 6 dioxyuracil) was used in a commercial form as powder provided by Nile Pharmaceutical Company, Egypt. Exendin-4, exendin-9-39, pioglitazone, and Bisphenol A Diglycidyl Ether were obtained from SIGMA Chemical Company, U.S.A.

Animals and experimental design: This experimental study was performed at Medical Physiology Department, Al-Azhar Faculty of Medicine, Cairo. A total of seventy adult male albino rats of a local strain were used in this study ranging in weight from 150 -175 grams at the time of the research. The animals were housed under similar standard environmental conditions in suitable cages (30 x 42 x 30 cm for every 5 rats) with wide meshed raised floors to prevent coprophagia. They were kept ten days on basal diet before starting experimental diet for adaptation. They were also kept at room temperature and normal light/dark cycle. Rats had free access to water and fed on rodent chow diet food all over the period of the work (8 weeks). Animals were divided randomly and equally into 7 groups as follows:

Group I (normal control group): Rats received normal saline I.P. daily for 8 weeks.

Group II (Alloxan-treated diabetic control group): The overnight fasted rats were subjected to induction of diabetes by a single intraperitoneal injection of alloxan (140 mg/kg body weight) in normal saline *(Kumawat et al., 2010)*.

Group III (diabetic group + pioglitazone): Received the same dose of alloxan and pioglitazone (45 mg/kg/day, orally) for 8 weeks *(Swetha et al., 2016)*.

Group IV (diabetic group + exendin-4): Received the same dose of alloxan and exendin-4 (1 nmol/kg/day, i.p.) for 8 weeks *(Park et al., 2010)*.

Group V (diabetic group + pioglitazone and exendin-4): Received the same doses of alloxan, pioglitazone and exendin-4 for 8 weeks.

Group VI (diabetic group + Bisphenol A diglycidyl ether): Received the same dose of alloxan and Bisphenol A diglycidyl ether (30 mg/kg in 10 % dimethyl sulfoxide solution (DMSO) for 8 weeks *(Yuan et al., 2018)*.

Group VII (diabetic group + exendin-9-39): Received the same dose of alloxan and exendin-9-39 (25 nmol/kg in 0.9% saline, i.p.) for 8 weeks *(Park et al., 2010)*.

Induction of Diabetes Mellitus: A single intraperitoneal dose of 140 mg/ kg body weight of alloxan dissolved in 0.2 ml saline was used immediately after solubility *(Ezazul et al., 2012)*.

After the injection, the rats were given glucose infusion (3 g/kg body weight) by gastric intubation to all diabetic rats to overcome fatal hypoglycemia caused by transient hyperinsulinemia due to partial destruction of beta cells. The injection was repeated in the 2nd day to obtain response as reported by *Wang et al. (2016)*. The rats with a plasma glucose level above 250 mg/dl were selected for the experiment and considered as diabetics *(Zhang et al., 2010)*.

Determination of body weight gain percentage (BWG %): The biological values of diets were assessed by the determination of body weight gain percent (BWG %) which was calculated at the end of the experimental period. It was calculated using the equation of *(Lei et al., 2007)*:

$$\frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}} \times 100.$$

Blood Sampling: At the end of experiment, fasting rats were lightly anesthetized by isoflurine and venous blood samples were withdrawn from the retro-orbital plexus by heparinized capillary tubes, and rapidly set to the centrifugator at 5000 rotations per minute for 15 minutes. Serum was separated and stored at -20 oC till used for determination of blood glucose and insulin *(Vardarli et al., 2014)*, total cholesterol, triglycerides, low-density lipoproteins, and high-density lipoproteins *(Sloan et al., 2012)*.

Statistical analysis:

Data input and analysis were done using SPSS version 16 computer program. All results were expressed as the mean ± SD. Statistical comparisons between different groups were done using one-way analysis of variance (ANOVA) followed by the Tukey-Kramer multiple comparison test to judge the difference between various groups. Significance was considered at $P \leq 0.05$.

RESULTS

In this study, body weight gain percentage (BWG %) was 13.29 ± 1.15, 28.16 ± 1.30, 18.01 ± 3.05, 17.76 ± 2.99, 17.01 ± 1.19, 20.11 ± 4.02 and 20.71 ± 3.15 in groups I, II, III, IV, V, VI and VII respectively. Diabetes resulted in a significant elevation in the BWG % in group II (diabetic group) in respect to control group I. Treatment with pioglitazone, exendin-4 and combined treatment significantly decreased BWG % when compared to group II. Groups VI and VII that were treated with BADGE and exendin-9-39 respectively showed significant changes BWG % in respect to the normal control group I and to diabetic group II (Table 1).

The mean ± standard deviation of blood glucose was 76.4 ± 9.42, 384.30 ± 34.31, 277.2 ± 90.49, 210.7 ± 90.98, 189 ± 73.27, 385.20 ± 9.32 and 384.30 ± 30.21 mg/dl in in groups I, II, III, IV, V, VI and VII respectively. Diabetes induced by alloxan resulted in a significant elevation in the levels of fasting blood glucose (FBG) in group II (diabetic group) in respect to control group I. while the treatment with pioglitazone, exendin-4 and combined treatment reduced the elevated fasting blood glucose significantly in groups III, IV and V

respectively in respect to untreated alloxan-induced diabetic group. Also, Groups VI and VII that are treated with BADGE and exendin-9-39 respectively showed insignificant difference in fasting blood glucose levels changes in respect to each other and to diabetic group II (Table 2).

The mean ± standard deviation of serum insulin was 30.18 ± 4.77, 7.28 ± 2.37, 14.94 ± 0.78, 16.83 ± 1.82, 14.97 ± 1.09, 7.33 ± 3.35 and 7.01 ± 7.32 ?IU/ml in groups I, II, III, IV, V, VI and VII respectively. Diabetes induced by alloxan resulted in a significant reduction in the levels of insulin in group II (diabetic group) in respect to control group I. while the treatment with pioglitazone, exendin-4 and combined treatment elevated the reduced insulin significantly in groups III, IV and V respectively in respect to diabetic group. Groups VI and VII that are treated with BADGE and exendin-9-39 respectively showed insignificant difference in insulin levels in respect to each other and in relation to group II (Table 2).

The mean ± standard deviation of serum total cholesterol was 96.5 ± 7.01, 131.50 ± 5.54, 115.7 ± 10.83, 114.6 ± 15.65, 109 ± 6.63, 131.01 ± 5.05 and 132.02 ± 0.1 mg/dl in groups I, II, III, IV, V, VI and VII respectively. The mean ± standard deviation of triglycerides (TG) was 98.9 ± 7.01, 119.30 ± 10.41, 106.7 ± 9.48, 117.7 ± 11.83, 932 ± 5.85, 118.20 ± 9.14 and 120.01 ± 1.03 mg/dl in groups I, II, III, IV, V, VI and VII respectively. While the mean ± standard deviation of LDL cholesterol was 37.95 ± 9.99, 74.36 ± 3.52, 60.61 ± 8.78, 65.64 ± 9.83, 61.25 ± 8.53, 75 ± 0.01 and 74.55 ± 4.01 mg/dl in groups I, II, III, IV, V, VI and VII respectively. Diabetes resulted in a significant elevation in the levels of total serum cholesterol, triglycerides and LDL in group II (diabetic group) in respect to control group I. Treatment with pioglitazone, exendin-4 and combined treatment significantly decreased the total serum cholesterol, triglycerides and LDL levels when compared to group II. Groups VI and VII showed insignificant changes in total cholesterol, triglycerides and LDL in respect in respect to each other and in relation to diabetic group II (Table 2).

The mean ± standard deviation of HDL was 93.7 ± 9.4, 39.9 ± 2.38, 74.01 ± 6.2, 75.3 ± 9.3, 76.9 ± 7.2, 89.0 ± 3.95, and 90.62 ± 2.05 mg/dl in groups I, II, III, IV, V, VI and VII respectively. Diabetes resulted in a significant reduction in the levels of HDL in group II (diabetic group) in respect to control group I. Treatment with pioglitazone, exendin-4 and combined treatment significantly elevated HDL levels when compared to group II. Groups VI and VII that are treated with BADGE and exendin- 9-39 showed insignificant changes in HDL in respect to each other and in relation to diabetic group II (Table 2).

The mean ± standard deviation of AST was 55.24 ± 2.31, 106.38 ± 4.33, 90.02 ± 0.22, 92.72 ± 2.59, 89.11 ± 0.23, 97.02 ± 1.59, and 99.94 ± 3.03U/L in groups I, II, III, IV, V, VI and VII respectively. The mean ± standard deviation of ALT was 26.74 ± 0.88, 50.00±3.01, 38.30 ± 1.10, 40.50 ± 4.10, 29.33 ± 0.55, 47.05 ± 1.19 and 45.24 ± 0.55 U/L in groups I, II, III, IV, V, VI and VII respectively. Diabetes resulted in a significant elevation in the levels of AST and ALT in group II

(diabetic group) in respect to control group I. Treatment with pioglitazone, exendin-4 and combined treatment significantly decreased the AST and ALT levels when compared to group II. Groups VI and VII that were treated with BADGE and exendin-9-39 respectively showed insignificant changes in AST and ALT in respect in respect to each other and in relation to diabetic group II (Table 2).

It was noted that these results were more prominent in treatment with combined pioglitazone and exendin-4 than treatment with pioglitazone alone or exendin-4 alone especially in blood glucose and HDL levels (Table 1 and 2).

Table (1): Effects of diabetes, TZDs and GLP-1 agonists and antagonists on body weight gain %(BWG %) in different groups

Parameter / Groups	Body weight gain (%)	P value
Group I (normal control group)	13.29 ± 1.15	
Group II (Alloxan-treated diabetic control group)	28.16 ± 1.30	P < 0.05*****
Group III (diabetic pioglitazone-treated group)	18.01 ± 3.05	P < 0.05***** P < 0.05®
Group IV (diabeticexendin-4-treated group)	17.76 ± ٢.99	P < 0.05***** P > 0.05≠
Group V (diabeticpioglitazone-exendin-4-treated group)	17.01 ± 1.19	P < 0.05***** P > 0.05**@** P < 0.05**Ω**
Group VI (diabetic BADGE-treated group)	20.11 ± ٤.0٢	P < 0.05* P < 0.05**?**
Group VII (diabetic exendin 9-39-treated group)	20.71 ± 3.١5	P < 0.05* P > 0.05¶ P < 0.05**?**

Number of rats in each group = 10.
*All groups were compared to control group I.
≠ Groups IV was compared to group III.
® Groups III was compared to group II.
? Groups VII was compared to group II.
@ Groups V were compared to group IV.
Ω Groups V was compared to group II .
¶ Groups VII was compared to group VI.
? Groups VI was compared to group II.

Table (2): Effects of diabetes, TZDs and GLP-1 agonists and their antagonists in different groups (Mean ± SD)

Groups / Para-meters	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII
Fasting blood glucose (mg/dl)	76.4 ± 9.42	384.30 ± 34.31 P < 0.05*	277.2 ± 90.49 P < 0.05* P < 0.05 ®	210.7± 90.98 P < 0.05* P > 0.05≠	189 ± 73.27 P < 0.05* P < 0.05@ P < 0.05Ω	385.20 ± 9.32 P < 0.05* P > 0.05 ?	384.30 ± 30.21 P < 0.05* P > 0.05¶ P > 0.05?
Insulin (?IU / ml	30.18 ± 4.77	7.28 ± 2.37 P < 0.05*	14.94 ± 0.78 P < 0.05* P < 0.05 ®	16.83±1.82 P < 0.05* P > 0.05≠	14.97 ± 1.09 P < 0.05* P > 0.05@ P > 0.05Ω	7.33 ± 3.35 P < 0.05* P > 0.05 ?	7.01±7.32 P < 0.05* P > 0.05¶ P > 0.05?
Total cholesterol (mg/dl)	96.5 ± 7.01	131.50 ± 5.54 P < 0.05*	115.7 ± 10.83 P > 0.05* P < 0.05 ®	114.6 ± 15.65 P < 0.05* P > 0.05≠	109 ± 6.63 P < 0.05* P > 0.05@ P > 0.05Ω	131.01 ± 5.05 P < 0.05* P > 0.05 ?	132.02 ± 0.1 P < 0.05* P > 0.05¶ P > 0.05?
TG (mg/dl)	98.9 ± 9.53	119.30 ± 10.41 P < 0.05*	106.7 ± 9.48 P > 0.05* P < 0.05 ®	117.7 ± 11.83 P < 0.05* P < 0.05≠	93 ± 5.85 P < 0.05* P < 0.05@ P > 0.05Ω	118.20 ± 9.14 P < 0.05* P > 0.05 ?	120.01 ± 1.03 P < 0.05* P > 0.05¶ P > 0.05?
LDL (mg/dl)	37.95 ± 9.99	74.36 ± 3.52 P < 0.05*	60.61± 8.78 P > 0.05* P < 0.05 ®	65.64 ± 9.83 P < 0.05* P < 0.05≠	61.25 ± 8.53 P < 0.05* P >0.05@ P > 0.05Ω	75 ± 0.01 P < 0.05* P > 0.05 ?	74.55 ± 4.01 P > 0.05¶ P > 0.05?
HDL (mg/dl)	93.7 ± 9.4	39.9 ± 2.38 P < 0.05*	74.01± 6.2 P > 0.05* P < 0.05 ®	75.3 ± 9.3 P < 0.05* P < 0.05≠	76.9 ± 7.2 P < 0.05* P < 0.05@ P > 0.05Ω	89.0 ± 3.95 P < 0.05* P < 0.05# P > 0.05 ?	90.62 ± 2 .05 P < 0.05* P > 0.05¶ P > 0.05?
AST(U/L)	55.24 ± 2.31	106.38 ± 4.33 P < 0.05*	90.02 ± 0.22 P > 0.05* P < 0.05 ®	92.72 ± 2.09 P < 0.05* P > 0.05≠	89.11 ± 0.23 P < 0.05* P > 0.05@ P > 0.05Ω	97.02 ± 1.59 P < 0.05* P < 0.05# P > 0.05 ?	99.94 ± 3.03 P < 0.05* P > 0.05¶ P > 0.05?
ALT(U/L)	26.74 ± 0.88	50.00 ± 3.01 P < 0.05*	38.30 ± 1.10 P > 0.05* P < 0.05 ®	40.50 ± 4.10 P < 0.05* P > 0.05≠	29.33 ± 0.55 P < 0.05* P > 0.05@ P > 0.05Ω	47.05 ± 1.19 P < 0.05* P < 0.05# P > 0.05 ?	45.24 ± 0.55 P < 0.05* P > 0.05¶ P > 0.05?

Number of rats in each group = 10.
*All groups were compared to control group I.
≠ Groups IV was compared to group III.
® Groups III was compared to group II.
? Groups VII was compared to group II.
@ Groups V were compared to group IV.
Ω Groups V was compared to group II .
¶ Groups VII was compared to group VI.
? Groups VI was compared to group II.

DISCUSSION

Several drugs such as thiazolidinediones, analogues of GLP-1, sulfonylurea and insulin are available to control diabetes mellitus *(Jeong et al., 2018)*. It is mandatory to deal with DM by polytherapy regimens which include diet control, regular physical activity and new line of drugs to improve symptoms, reduce complications and decrease side effects of ordinary drugs *(Pearson, 2016)*. Much attention has focused on thiazolidinediones and glucagon-like peptide-1 agonists *(Weiss et al., 2014)*.

Achieving good weight control is a critical component of managing diabetes, especially because some antidiabetic agents as insulin and sulfonylureas have the unwanted side effect of promoting weight gain *(Wang et al., 2016)*.

Results of the present study revealed incidence of significant increases in BWG % of diabetic rats when compared to the control rats. These findings were in agreement with those obtained by *Nwozo et al. (2016)* who confirmed our results. The increase in body weight of diabetic rats might be due to the increase of feed and caloric intake by rats *(Amin et al., 2015)*.

Results of the present study showed that alloxan injection showed a significant higher level of blood glucose and lower level of insulin compared to control group. The toxic action of alloxan on pancreatic β-cells is the summation of several processes such as generation of free radicals, inhibition of glucokinase, and DNA damage *(Michael, 2017)*. Such damaged DNA activates nuclear poly-synthetase which depletes the cellular pool of oxidized NAD+ resulting in β-cells damage *(Hina et al., 2014)*.

Results of the present work showed that induction of diabetes led also to disturbed lipid profile in the form of higher levels of cholesterol, triglycerides and LDL, but lower levels of HDL. These effects of hyperglycemia may be attributed to the initiation of reverse cholesterol transport from cells to the liver for excretion *(Seyedeh et al., 2017)*. The present findings were in the same line as with those reported by *Menezes et al. (2015)* who demonstrated that lipid metabolic disorders and levels of serum TC and TG increased significantly when compared to control group.

The present study showed that serum HDL-c level decreased significantly in diabetic group in respect to the control group. These results were well documented by the study of *Farideh et al. (2017)* It has been reported that cholesterol transport to extra-hepatic tissues is primarily ensured by LDL-c (bad cholesterol), while HDL-c (good cholesterol) has an important role in reversing the cholesterol transport process *(Faghihimani et al., 2017)*.

These results were in agreement with the finding of *Irshaid (2012)* who stated that insulin promotes the esterification of fatty acids in adipose tissue. When triglycerides in adipose tissue are hydrolyzed, fatty acids are released and can be oxidized, re-esterified, or they can enter the circulation. So, the net result of insulin lack on adipose tissue is enhancement of mobilization of fatty acids out of the tissue .

Plasma AST and/or ALT, are primarily recommended for the assessment of hepatocellular injury. They are sensitive markers for liver damage, and the elevated activities of these marker enzymes in plasma are indicative of cellular leakage and loss of the functional integrity of cell membranes in the liver *(Gurbet et al., 2013)*.

The untreated diabetic group exhibited a statistically signi?cant rise in liver enzymes indicating the relation between diabetes and the incidence of hepatotoxicity. These results agreed with *Vagula et al. (2014)* who emphasized that diabetic patients are suffering from hepatic failure compared to patients who do not have diabetes. Some potential explanations for elevated transaminases in diabetic states include oxidant stress from reactive lipid peroxidation.

Our findings have shown that pioglitazone promoted weight loss, but did

not fully restore body weight to normal level. This result was in agreement with *Akiyama et al. (2016)* who mentioned that pioglitazone is associated with weight loss in diabetic patients due to enhancement of satiety centers .

In the present study, treatment by pioglitazone resulted in a highly signi?cant reduction in FBG, and significant elevation of insulin level in comparison with diabetic untreated group. These ?ndings could be attributed to pioglitazone PPAR-γ activation effect that lead to improved hepatic insulin sensitivity resulting in decreased hepatic glucose production *(Elizabeth et al., 2017)*. Pioglitazone also improved muscle insulin sensitivity resulting in increased tissue glucose uptake. That is why insulin sensitizer drugs as TZDs and GLP-1 can be regarded as beneficial treatment for liver injury *(Jeong et al., 2018)*.

The treatment of the diabetic rats with pioglitazone significantly lowered blood total cholesterol, triglyceride and LDL levels, while HDL levels were significantly higher than that of diabetic group. Pioglitazone inhibits gastric lipase and inhibits lymph flow *(Campbell and Drucker, 2013)*.

Our results indicated that the levels of AST and ALT significantly reduced in the patients treated with pioglitazone. The hepato-protective effects of pioglitazone could be due to amelioration of insulin resistance and reduction of the TNF-α production. The ability of pioglitazone to improve liver enzymes could be explained by activation of PPAR-γ that caused down regulation of inflammation and fibrosis through its effect on Kupffer and hepatic stellate cells *(El-Gawly et al., 2016)*.

There is no evidence that pioglitazone administration has a harmful effect on the liver. Conversely, it has potential bene?cial effects on the liver during treatment of diabetic rats *(Xu et al., 2014)*.

Administration of GLP-1 agonist (exendin-4) decreased the body weight gain percent significantly in respect to control group I. It inhibited gut mobility and gastric emptying, allowing nutrients in the ileum to reduce food intake *Emil et al., 2017)*. *Elizabeth et al. (2017)* mentioned that infusion of GLP-1 into normal human subject's significantly enhanced satiety and decreased food intake.

Consistent findings have shown that GLP-1R agonism promoted weight loss, but did not fully restore body weight and improved glucose homeostasis *(Hilda et al., 2018)*. Such weight-reducing properties have also been well-documented for GLP-1 mimetics as exendin-4 *(Lean et al., 2014)*. *Wang et al. (2016)* who mentioned that GLP-1 agonists are associated with weight loss in diabetic patients.

Our data revealed that treatment of the diabetic rats with exendin-4 significantly lowered blood glucose level and significantly increased insulin level .

Chris and his Coworkers (2016) mentioned that GLP-1R agonist (Exendin-4) is signaling in ?-cells, where it mediates increased insulin synthesis, storage and secretion. *Heppner et al. (2015)* mentioned that GLP-1R agonists have an insulin releasing function. Exendin-4 increases ?-cell mass, and promotes the proliferation and survival of pancreatic β-cells *(Murad et al., 2017)*.

The treatment of the diabetic rats with exendin-4 significantly lowered blood total cholesterol, triglyceride and LDL levels, while HDL levels were significantly higher than that of diabetic group. The lipid lowering effect could be due to hormonal and non-hormonal mechanisms. The hormonal mechanisms are the most effective mechanism. Exendin-4 stimulates insulin secretion and inhibits glucagon secretion *(Lingvay, 2016)*. Both effects lead to inhibition of lipolysis, reduction of free fatty acids as well as lipogenesis in adipose tissue *(Chen et al., 2017)*. The non-hormonal mechanisms of exendin-4 augment lipid lowering effects through reducing the production of chylomicrons after fat rich meal. Also, it inhibits fat absorption from the gut, either by producing deceleration of gastric emptying or preventing the production of cholesterol and triglycerides. Exendin-4 inhibits gastric lipase and inhibits lymph flow *(Campbell and Drucker, 2013)*.

There were statistically significant decreases of AST and ALT levels between the exendin 4-treated groups in respect to control group. This result was in agreement with *Armstrong et al. (2016)* who mentioned that GLP-1 agonists improve transaminase levels, reduce oxidative stress and reduce hepatic steatosis. *Li et al. (2018)* mentioned that exendin-4 significantly decreased AST and ALT levels in diabetic rats. This could be explained by weight loss which decreases hepatic steatosis or by reduced leakage of AST and ALT into the circulation, due to its protective effect of hepatocyte by decreasing hepatic oxidative stress *(Wang et al., 2017)*.

Administration of exendin-9-39 for 8 weeks to diabetic rats had an increasing effect on body weight in respect to control, diabetic exendin4-treated and diabetic pioglitazone-treated groups. GLP-1 is believed to exert satiety effects which can be reversed by exendin-9-39. This result was in agreement with Einhorn et al. (2016) who mentioned that exogenous exendin-9-39 significantly accelerated gastric emptying and increased body wight.

This study has shown that administration of GLP-1 antagonist (Exendi-9-39) in diabetic rats caused a slight impairment of glucose homeostasis. Exendin-9-39 infusion leads to a minimal decrease in insulin. This could result in a slight increase in glucose concentrations *(Murad et al., 2017)*. *Jorg et al. (2015)* mentioned that the increase of glucagon plasma levels in response to the GLP-1 antagonist was maintained even during hyperglycemia.

Nance et al. (2017) mentioned that human GLP-1 agonist (exendin-4) stimulation increased insulin secretion that could be partially inhibited by exendin (9-39), a potent and selective GLP-1receptor antagonist .

This result was in agreement with *Matheni et al. (2013)* who mentioned that no effect of exendin (9-39) on absolute β-cell responsivity was observed by chronic exendin (9-39) treatment.

Exendin (9-39) in this study showed higher levels of cholesterol, triglycerides and LDL, but lower levels of HDL. These effects of hyperglycemia may be attributed to cholesterol transport from

cells to the liver for excretion *(Jorge et al., 2015)*.

This result was in agreement with *(Goke et al., 2015)* who mentioned that GLP-1 antagonist inhibits lipogenic enzymes increasing lipid aspects and decreasing HDL cholesterol Level.

There was an insignificant increase of AST and ALT levels in exendin 9-39-treated group when compared to the diabetic exendin 4-treated and pioglitazone-treated groups, while there was a significant increase when compared to control group. Exendin-9-39 increases leakage of AST and ALT into the circulation by its steastic effect on hepatocytes *(Wettergren et al., 2014)*.

In this study, administration of BADGE for 8 weeks to diabetic rats had minimal increasing effect on body weight in respect to control, diabetic exendin-4-terated and diabetic-pioglitazone-treated groups. BADGE affects the regulation of gastrointestinal functions such as gastrointestinal motility and gastric emptying *(Jorg et al., 2015)*.

BADGE showed that blood glucose levels significantly increased and insulin levels decreased. Improvement of glucose metabolism by TZDs prevented by PPAR-γ antagonists (BADGE). This suggested that PPARs play more important roles in glucose metabolism *(Wakutsu et al., 2015)*.

In this study, BADGE treatment showed disturbed lipid profile in the form of higher level of cholesterol, triglycerides and LDL, but lower levels of HDL. These effects of hyperglycemia may be attributed to cholesterol transport from cells to the liver for excretion *(Dallongeville et al., 2014)*. *Toshimasa et al. (2001)* mentioned that PPAR-γ antagonist inhibits lipogenic enzymes increasing lipid aspects and decreasing HDL cholesterol Level.

PPAR-γ antagonist inhibits the function pioglitazone a strong PPAR-γ stimulator, increases lipid levels, and induces insulin resistance *(Spiegeleman, 2012)*.

There was an insignificant increase in AST and ALT levels in BADGE-treated group when compared to the diabetic exendin 4-treated and pioglitazone-treated groups, while there was a and significant increase when compared to control group. Disturbed lipid profile caused by impaired diabetes mellitus may be the cause of elevated liver enzymes *(Shih and Chou, 2016)*.

CONCLUSION

Exendin-4 and TZDs (pioglitazone) could be used as a supportive therapeutic line because both showed the best results of lowering blood glucose and increasing insulin levels. There were remarkable therapeutic effects of these drugs consequently improving hyperlipidemia. Also, there was mild effectiveness of TZDs or GLP-1 antagonists on diabetes and lipid metabolism in this study. In addition, the effectiveness of combined exendin-4 and pioglitazone was higher than that of each drug alone especially for blood glucose and HDL levels.

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دور ناهِضَىْ البيبتيد-١ مثيل الجلوكاجون) إكزندين-٤) والثيازوليدين ديون (بيوجليتازون) ومضاداتهما على تنظيم الجلوكوز والإنسولين ودلالات الدهون في الجرذان المصابة بالداء السكري

ناجح مبروك جبر – البيومى على فوده

قسم الفسيولوجيا الطبية - كلية الطب - جامعة الأزهر

خلفية البحث : إن زيادة حدوث مقاومة الإنسولين لدرجة تصل للوباء يتوازى بدرجة مضطردة مع حدوث مرض الداء السكرى ومدى التقدم العلاجى فى منع المرض وفاعلية علاجه. وناهِضَىْ البيبتيد-١مثيل الجلوكاجون (إكزندين-٤) والثيازوليدين ديون (بيوجليتازون) محفزات للإنسولين ويعملان على تنظيم الجلوكوز والانسولين ودلالات الدهون في الجرذان المصابة بالداء السكري. بينما مضادات الثيازوليدين ديون و البيبتيد-١مثيل الجلوكاجون لهما تأثيرا مضادا للإنسولين.

الهدف من البحث: صمم هذا العمل لبيان مدى تأثير ناهِضَىْ البيبتيد-١مثيل الجلوكاجون (إكزندين-٤) والثيازوليدين ديون (بيوجليتازون) ومضاداتهما على تنظيم الجلوكوز والإنسولين ودلالات الدهون في الجرذان المصابة بالداء السكري.

مواد وطرق البحث: إشتملت عينة البحث على سبعين جرذاً ذكراً، وقد قسمت الجرذان إلى سبع مجموعات متساوية وتم معالجتها كما يلى:

• **المجموعة الأولى:** مجموعة ضابطة غير مصابة بالداء السكرى أعطيت محلولاً ملحياً طبيعياً داخل التجويف البريتونى يومياً لمدة ٨ أسابيع.

• **المجموعة الثانية:** مجموعة ضابطة مصابة بالداء السكرى خضعت للحقن بجرعة واحدة من الألوكزان في التجويف البريتوني تعادل ١٤٠ مجم / كجم لإحداث الإصابة بالداء السكرى.

• **المجموعة الثالثة:** مجموعة مصابة بالداء السكرى أعطيت بيوجليتازون (٤٥ مليجرام/ كجم) داخل التجويف البريتونى يومياً لمدة ٨ أسابيع.

• **المجموعة الرابعة:** مجموعة مصابة بالداء السكرى أعطيت إكزندين-٤ بجرعة (١ نانومول/ كجم) داخل التجويف البريتونى يومياً لمدة ٨ أسابيع.

• **المجموعة الخامسة:** مجموعة مصابة بالداء السكرى أعطيت بيوجليتازون (٤٥ مليجرامم/ كجم) وإكزندين-٤ بجرعة (١ نانومول/ كجم) داخل التجويف البريتونى يومياً لمدة ٨ أسابيع.

• **المجموعة السادسة:** مجموعة مصابة بالداء السكرى أعطيت مضادا للثيازوليدين ديون (بيسفينول أ داى جليسدايل إثير) بجرعة (٣٠ مليجرام/ كجم) داخل التجويف البريتونى يومياً لمدة ٨ أسابيع.

• **المجموعة السابعة:** مجموعة مصابة بالداء السكرى أعطيت إكزندين٩ --٣٩ بجرعة (٢٥ نانومول/ كجم) داخل التجويف البريتونى يومياً لمدة ٨ أسابيع.

وقد تم سحب عينات دم وريدية في نهاية التجربة لكل المجموعات، وذلك لقياس: مستويات الجلوكوز والإنسولين بالدم والكوليستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة والبروتين الدهني عالي الكثافة. كما تم متابعة وزن الجسم لكل جرذ فى بداية ونهاية التجربة ومعرفة نسبة زيادة وزن الجسم.

النتائج: أظهرت نتائج البحث أن الألوكزان أدى إلى إرتفاعات ذات دلالات إحصائية فى مستويات الجلوكوز والكولستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة وكذلك نسبة زياذة وزن الجسم، كما أدى إلى إنخفاضات ذات دلالات إحصائية فى مستويات البروتين الدهني عالي الكثافة ومستوى الانسولين مقارنة بالمجموعة الضابطة الغير مصابة بالداء السكرى. ومن ناحية أخرى، أثبتت النتائج أن إعطاء مادة البيوجليتازون وكذلك إكزندين-٤ منفردين أو مجتمعين للجرذان المصابة بالداء السكرى أديا إلى إنخفاض مستويات الجلوكوز والكولستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة وكذلك نسبة زياذة وزن الجسم، كما أدى إلى إرتفاع مستويات البروتين الدهني عالي الكثافة والإنسولين إرتفاعات ذات دلالات إحصائية مقارنة بالمجموعة الثانية. وقد أدى إزدواج العقارين إلى إنخفاض أكثر مما ذكر فى المجموعة الخامسة. ولم تحمل هذه النتائج دلالات إحصائية للمجموعة الثالثة و الرابعة والخامسة عند مقارنتهم ببعض، بينما لم يؤثر عقارى البيسفينول أ داي جليسيدايل إثير والإكزندين -٩-٣٩ تأثيرات ذات دلالات إحصائية على مستوي الجلوكوز والإنسولين والكوليستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة والبروتين الدهني عالي الكثافة ونسبة زيادة وزن الجسم مقارنة بالمجموعات المصابة بمرض الداء السكرى المعالجة بالبيوجليتازون أو الإكزندين-٤.

الاستنتاج: لإزدواج عقارى البيوجليتازون والإكزندين-٤ تأثيرات إيجابية فى تحسين مستويات الجلوكوز والدهون بالدم فى الجرذان المصابة بالداء السكرى عن استخدام كل منهما على حدة، مما يجعل منهما عقاراً المستقبل الذى يمكن إستخدامه فى علاج مرضى الداء السكرى لتنظيم دلالات الدهون فى الدم الأمر الذى ساعد فى علاج مرضى الداء السكرى ويقلل من خطر المضاعفات المصحوبة بإرتفاع نسبة الدهون بالدم. ولم يتضح فى هذا البحث دوراً واضحاً لعقارى البيسفينول أ داي جليسيدايل إثير والإكزندين -٩-٣٩ فى تنظيم مستوى الجلوكوزوالإنسولين والدهون بالدم.