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EFFECT OF EXENDINE-4 WITH OR WITHOUT MUSCULAR EXERCISE ON DIABETES MELLITUS IN MALE ALBINO RATS

By

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ABSTRACT

Background: Exendin-4 (glucagon like peptide-1 agonist) is an insulinotropic gut peptide and is being evaluated for the regulation of blood glucose in diabetes mellitus. **Objective:** Evaluating the possible effects of exendin-4 administration with or without muscular exercise on diabetic male albino rats. **Materials and Methods**: Forty adult male albino rats were divided into four equal groups: Group I served as a normal control group, group II was diabetic control, group III was diabetic group treated with exendin-4, and group IV was diabetic group subjected to swimming exercise and receiving exendin-4. At the end of the experimental period, blood samples were collected for measuring of blood glucose, total cholesterol, triglycerides (TG), low density lipoproteins **(**LDL), high density lipoproteins (HDL) and C-peptide. **Results**: Alloxan-induced diabetes mellitus was associated with significant higher levels of serum blood glucose, total cholesterol, TG and LDL-C with significant lower levels of HDL-C and C-peptide as compared with the control normal group. Exendin-4 with or without muscular exercise showed significant lower levels of blood glucose, total cholesterol, TG and LDL-C levels, and significant higher levels of HDL-C and C-peptide as compared with the control diabetic rats. **Conclusion**: Exendin-4 therapy has a marked effect on improvement of blood glucose, C-peptide level and lipid profile. This was most probably due to increasing insulin sensitivity and decreasing hepatic fat biosynthesis. As regards the differences between the muscular exercise with exendine-4 group (group 4) and exendine-4 treated group (group 3), the obtained data showed a significant lower value of serum triglyceride in the muscular exercise with exendine-4 group compared with the exendine-4 treated group.

Key words: Alloxan, Exendin-4, Exercise, Diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a common metabolic disease characterized by increased circulating glucose concentrations associated with abnormalities in carbohydrate, fat and protein metabolism **(Alejandro et al., 2011)**. Lipid abnormalities occur in diabetes, even in those who have reasonable glycemic control (**Mooradian, 2009)**. Increased lipid peroxidation and reduced antioxidant status may contribute to the development of complications in diabetes **(Giacco & Brownlee, 2010 and Matough et al., 2012).** C-peptide is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion in patients with diabetes **(Jones and Hattersley, 2013)**. C-peptide is considered a reliable marker of residual β-cell function in patients with type I diabetes during the

long-lasting process of immune destruction of β-cells which may assist in differentiating type I from type II diabetes **(Almeida et al., 2013).**

Exendin-4 which is glucagon like peptide-1 (GLP-1) agonist is one of new lines of treatment of diabetes. Glucagon-like-peptide is the product of post-translational processing of proglucagon in the gut and the brain **(Cabou and Burcelin, 2011)**. It is insulinotropic and plays a role in the incretin effect, i.e. augmented insulin response observed when glucose is absorbed through the gut **(Arnes et al., 2009).** Exendin-4 or incretin mimetic has structural similarity and binds to GLP-1 receptors (**Gupta, 2013)**. GLP-1 and its long acting agonist exendin-4 stimulate the proliferation and differentiation of stem cells in the pancreas into β cells **(Kim et al., 2013-a).**

Exercise is extremely important in the management of diabetes because of its effect on blood glucose and free fatty acids. Exercise burns calories and helps to control weight, eases stress and tension, and maintains a feeling of well-being. In addition, regular exercise improves the response to insulin and may make oral anti-diabetic drugs and insulin more effective **(Nelson et al., 2013).** It also promotes circulation, and lowers cholesterol and triglyceride levels, thus reducing the risk of cardiovascular diseases **(Buse et al., 2007).** Diabetic patients should not be excluded from the physical activities or games, unless there are complications and on the advice of a physician **(Knowler et al., 2002)**.

The present work was a trial to evaluate the effects of exendin-4 with and without muscular exercise against alloxan-induced diabetes mellitus.

MATERIALS AND METHODS

Chemicals: Alloxan monohydrate (2, 4, 5, 6-tetra-oxy pyraminndin, 5,6 dioxyuracil) was used in a commercial form as powder provided by Nile pharmaceutical company, Egypt while exendin-4 was obtained from SIGMA Chemical Company, U.S.A.

Animals and experimental design: Forty adult male albino rats of local strain, weighing 130 – 150 g were brought from Nile Pharmaceuticals Company and were kept in cages (20 × 32 × 20 cm for every 5 rats) at room temperature with the natural 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). They were kept for 2 weeks for the adaptation to the new environment before the start of the experiment.

The rats were randomly divided into four equal groups: The first group (normal control group; C) received normal saline (i.p.) for 8 weeks, the second group (diabetic control group; D1) received single dose of alloxan, the third group (diabetic group; D2) received the same dose of alloxan and exendin-4 (1nmol/kg/day, i.p.) for 8 weeks **(Park et al., 2007)**, and the fourth group (diabetic group; D3) received the same dose of alloxan and exendin-4 and underwent to swimming exercise (5 days/week) for 8 weeks.

Induction of Diabetes Mellitus: A single intraperitoneal dose of 120 mg/ kg body weight of alloxan dissolved in 0.2 ml cold saline was used immediately after solubility **(Kumawat et al., 2010).** 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 destruction of beta cells. The injection was repeated in the 2nd day to obtain response as reported by **Wang et al. (2010)**. The rats with a plasma glucose level above 250 mg/dl were selected for the experiment and considered as diabetics **(Zhang et al., 2006)**.

Swimming exercise training program: Rats in exercising group were subjected to swimming in groups of four in a swimming plastic barrel 50 cm diameter with a depth of 50 cm, filled with tap water at 32 ± 2°C. Rats were given the chance to stay in water on the first day for 10 min/day till reaching 60 min/day on the sixth day to be familiar and adapted with water. The exercise protocol was continued for 5d/wk for 8 weeks **(Estadella et al., 2004)**.

Blood Sampling: At the end of experiment, fasting rats were lightly anesthetized by ether 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 °C till used for determination of blood glucose **(Braham and Trinder, 1972)**, total cholesterol **(Allain et al., 1974)**, triglycerides **(Fossati and Prencipe**, **1982**), low-density lipoproteins **(Friedewald et al., 1972),** high-density lipoproteins **(Groove, 1979),** and C-peptide levels **(Ashby and Frier, 1981).**

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 $P<0.05$.

RESULTS

Effects of injection of alloxan on the measured parameters (Figure 1-6): i.p. injection of alloxan into rats (group II) showed a significant higher levels of blood glucose from 78.7 ± 8.8 mg/dl to 352.3 ± 32.1 mg/dl, total cholesterol from 95.7 ± 7.05 mg/dl to 145.5 ± 6.84 mg/dl, triglycerides from 86.7 ± 9.2 mg/dl to 121.27±11.7 mg/dl and LDL from 38.95 ± 9.7 mg/dl to 78.36 ± 4.2 mg/dl, with a significantly lower levels of HDL from 38.7 ± 3.12 mg/dl to 31.12 ± 3.6 mg/dl and C-peptide from 32.75 ± 4.7 ng/dl to 9.8 ± 2.1 ng/dl as compared with normal control group (group I).

Effects of exendin-4 administration without muscular exercise on the measured parameters (Figure 1-6): Injection of exendin-4 in diabetic rats (group III) produced significant lower levels of blood glucose from 352.3 ± 32.1 mg/dl to 208.7 ± 60.0 mg/dl, total cholesterol from 145.5 ± 6.84 mg/dl to 114.6 ± 13.7 mg/dl, triglycerides from 121.27 ± 11.7 mg/dl to 103.7 ± 9.4 mg/dl and LDL from 78.36 ± 4.2 mg/dl to 60.64 ± 6.83 mg/dl with a significant higher levels of HDL from 31.12 ± 3.6 mg/dl to 35.4 ± 2.05 mg/dl and C-peptide from 9.8

± 2.1 ng/dl to 17.26 ± 3.2 ng/dl as compared with control diabetic group (group II).

Effects of exendin-4 administration with muscular exercise on the measured parameters (Figure 1-6): Administration of exendin-4 with exercise in diabetic rats (group IV) produced significant lower levels of blood glucose level from 352.3 ± 32.1 mg/dl to 188.8 ± 50.0 mg/dl, total cholesterol from 145.5 ± 6.84 mg/dl to 101.85 ± 6 mg/dl, triglycerides from 121.27 ± 11.7 mg/dl to 94.8 ± 8.6 mg/dl and LDL from 78.36 ± 4.2 mg/dl to 57.03 ± 5.2 mg/dl with a significant higher levels of HDL from 31.12 ± 3.6 mg/dl to 36.8 ± 2.4 mg/dl and C-peptide from 9.8 ± 2.1 ng/dl to 19.45 ± 4.3 ng/dl as compared with control diabetic group (group II).

Results of the present study showed that the effects of exendin-4 with muscular exercise produced insignificant changes of blood glucose, total cholesterol, LDL, HDL and C-peptide. On the other hand, the effects of exendin-4 with muscular exercise produced significant lower levels of triglycerides in respect to exendin-4 without exercise.

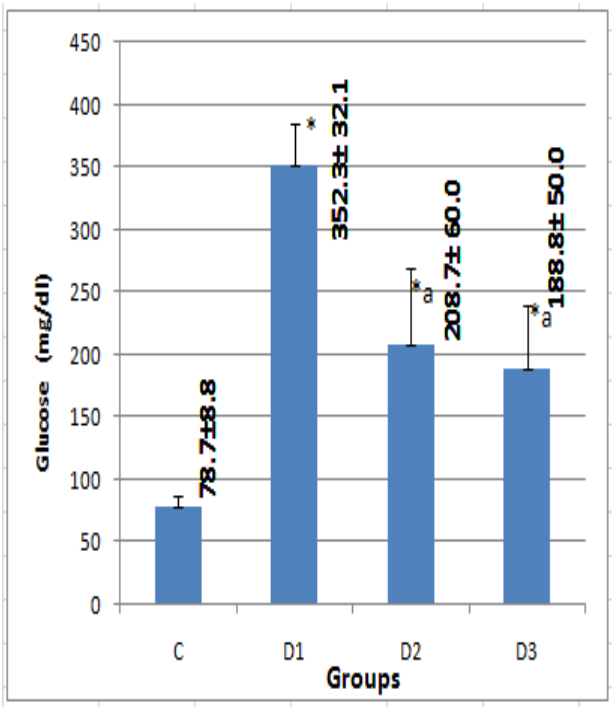

Figure (1): Mean ± SD of blood glucose level in different studied groups. C: normal control, D1: diabetic control, D2: diabetic control receiving exendin-4, D3: diabetic control receiving exendin-4 with exercise. *, Significantly different with control group. [a], Significantly different with diabetic group D1.

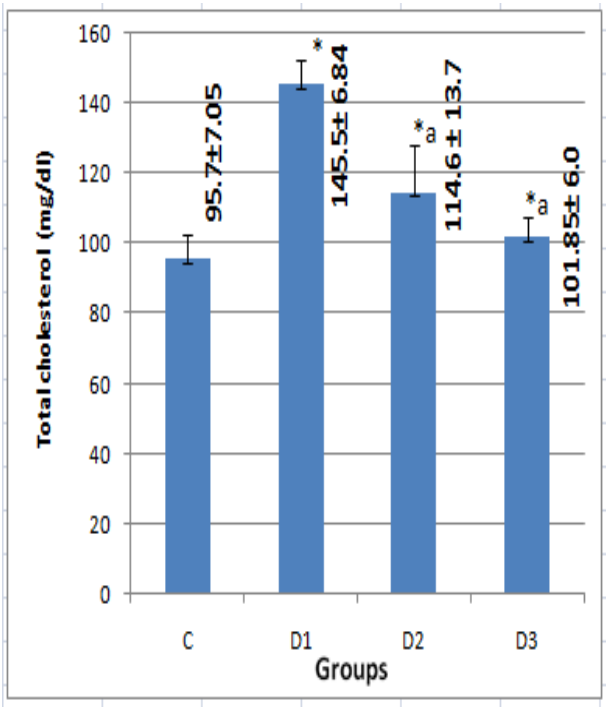

Figure (2): Mean ± SD of cholesterol level in different studied group. C: normal control, D1: diabetic control, D2: diabetic control receiving exendin-4, D3: diabetic control receiving exendin-4 with exercise. *, Significantly different with control group. [a], Significantly different with diabetic group D1.

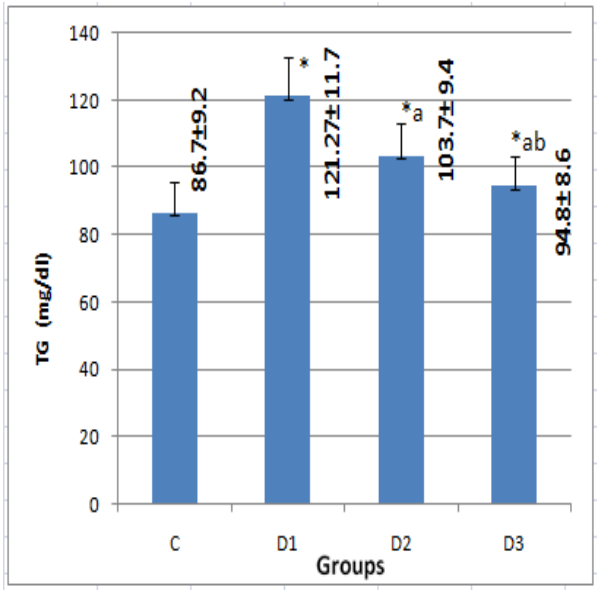

Figure (3): Mean ± SD of triglycerides level in different studied groups. C: normal control, D1: diabetic control, D2: diabetic control receiving exendin-4, D3: diabetic control receiving exendin-4 with exercise. *, Significantly different with control group. [a], Significantly different with diabetic group D1, [b], Significantly different with diabetic group D2.

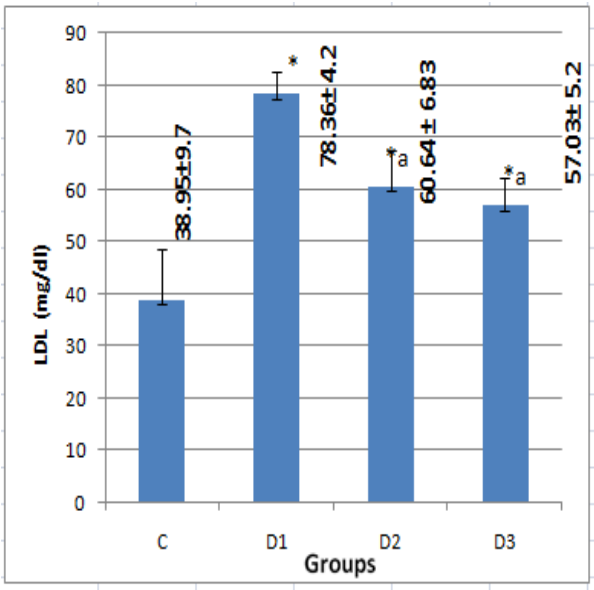

Figure (4): Mean ± SD of LDL level in different studied groups. C: normal control, D1: diabetic control, D2: diabetic control receiving exendin-4, D3: diabetic control receiving exendin-4 with exercise. *, Significantly different with control group. [a], Significantly different with diabetic group D1.

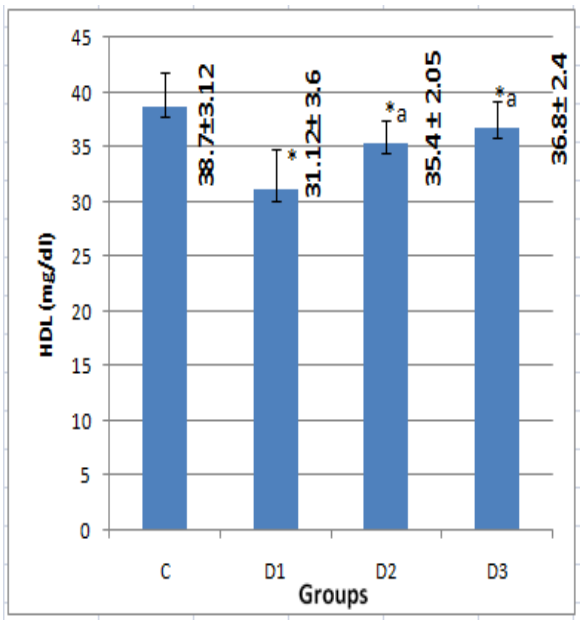

Figure (5): Mean ± SD of HDL level in different studied groups. C: normal control, D1: diabetic control, D2: diabetic control receiving exendin-4, D3: diabetic control receiving exendin-4 with exercise. *, Significantly different with control group. [a], Significantly different with diabetic group D1.

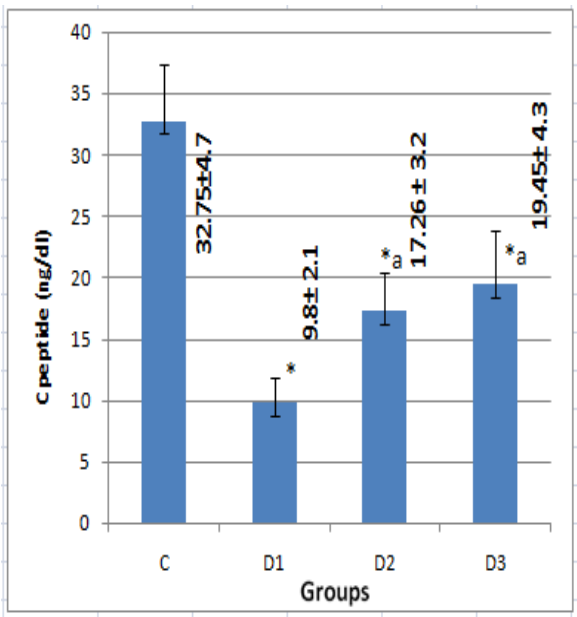

Figure (6): Mean ± SD of C-peptide level in different studied groups. C: normal control, D1: diabetic control, D2: diabetic control receiving exendin-4, D3: diabetic control receiving exendin-4 with exercise. *, Significantly different with control group. [a], Significantly different with diabetic group D1.

DISCUSSION

Several drugs such as biguanid, sulfonylurea and insulin are available to control diabetes mellitus (DM). However, these medications have many side effects. So, 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 future complications and decreasing side effects of ordinary drugs **(Nicholson & Hall, 2011 and Shawer et al., 2014).** Much attention has focused on exendine-4 (glucagon like peptide-1 agonist) which has incretin effects **(Weiss et al., 2014).**

Results of the present work showed that alloxan injection showed a significant higher level of blood glucose and lower level of C-peptide 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, disturbances in intracellular Ca^{++} homeostasis and DNA damage **(Rohilla and Ali, 2012)**. Such damaged DNA activates nuclear poly-synthetase, which depletes the cellular pool of oxidized nicotinamide adenine dinucleotide (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 diabetes may be attributed to the initiation of reverse cholesterol transport from cells to the liver for excretion **(Annema and Tietge, 2012).** In addition, the plasma LDL-cholesterol levels increase in diabetes mellitus possibly because insulin stimulates LDL receptors **(Gossain et al., 2010).**

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. Also, cholesterol synthesis is found to be greater in the gut of diabetic animals than in controls. This enhancement of sterol synthesis occurs soon after the onset of the disease and causes elevation in plasma cholesterol concentrations **(Lee et al., 2004).** Cholesterol acyltransferase activity in intestinal mucosa is increased in diabetic rats. Therefore, an enhancement of cholesterol acyltransferase-dependent cholesterol esterification in the intestine might be one of the major factors that are responsible for hypercholesterolemia in diabetes **(Jiao et al., 2003).**

The treatment of the diabetic rats with exendin-4 significantly lowered blood glucose levels, while C-peptide levels were significantly higher than that of diabetic group. Exendin-4 caused significant increase in insulin and C-peptide level when it was given in chronic dose to diabetic rate **(Lotfy et al., 2014)**.

Campbell (2009) and **Kim et al. (2013-b)** concluded that the exendin-4 can protect β cells by reducing its apoptosis, promoting its proliferation and neogenesis. This finding can be explained by **Liu et al. (2013)** who found that

Exendin-4 can activate phospho-insitide-3 kinase signaling pathway which has proliferative and anti-apoptotic effect on β cells.

Exendin-4 increased insulin secretion through calcium/calmodulin-dependent serine protein kinase **(Zhu et al., 2014),** and promoted hepatic insulin signaling by potentiating tyrosine phosphorylation of insulin receptor substrate-2 **(Park et al., 2010)**. Exendin-4 enhances glucose utilization by different tissues, and inhibits gluconeogenesis and glycogenolysis by hepatocyte **(Parlevliet et al., 2012)**. Insulin stimulates glycogenesis in liver and skeletal muscle **(Parlevliet et al., 2012).**

Exendin-4 has extra pancreatic effect. It increased glucose uptake by muscle and adipocyte through its direct stimulating effect on glucose transporter-4 (GLUT-4) expression mRNA or protein (**Wu et al., 2012)**. The hypoglycemic effect of exendin-4 could be related to delay gastric emptying and inhibition of glucagon secretion **(Marathe et al., 2013)**. On the other hand, **Nachnani et al. (2010)** reported that chronic use of exendin-4 in rats lead to pancreatitis with associated beta cells dysfunction.

The treatment of the diabetic rats with exendin-4 significantly lowered blood cholesterol, triglyceride and LDL levels, while HDL levels were significantly higher than that of diabetic group. The lipid lowering effect of exendin-4 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. Both effects lead to inhibition of lipolysis, reduction of free fatty acids as well as lipogenesis in adipose tissue. The non-hormonal mechanisms of exendin-4 augment lipid lowering effects through reduced 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).**

The results of our work showed that administration of exendin-4 with exercise significantly lowered blood glucose level while C-peptide level was significantly higher than that of diabetic group. These results were in agreement with **Olson (2012)** and **Liu et al. (2015)** who reported that aerobic exercise can increase insulin content of beta cell of pancreas and improve glucose tolerance through increased protein expression of GLUT-4 and insulin receptor substrate-1**.** Exercise minimizes the insulin resistance that develops with a sedentary life, improves and increases the insulin receptor sensitivity **(Heo and kim, 2013).**

Also, our results were compatible with **Park et al. (2010)** who found that exendin-4 with exercise reduces hepatic glucose output by decreasing the expression of phosphoenol pyruvate carboxykinase. Exercise improves both hepatic and hypothalamic insulin signaling by activating the phosphory-lation of cyclic adenosine non-phosphate-responding element binding proteins to induce insulin receptor substrate-2 expression.

The obtained data of this work revealed that administration of exendin-4

with exercise significantly lower total cholesterol, triglycerides and LDL levels, while the plasma HDL level was significantly higher than that of diabetic group. These results were in agreement with **Hung et al. (2015)** who reported that endurance exercise can decrease lipogenesis, promote fatty acid oxidation, and increase mitochondrial biosynthesis in adipose tissue, muscle and liver.

Alam et al. (2004) confirmed that short or long term exercise have a major reduction on hepatic LDL-C synthesis rate due to increased clearance and/or reduced hepatic production of lipoproteins in patients with type II diabetes.

Our data showed also that muscular exercise with exendine-4 was more effective on the metabolic disorders of lipid compared with that of the exendine-4-treated group. This gives out our attention to the value of taking exendine-4 with muscular exercise as a line of treatment for diabetic patients.

It could be concluded that exendin-4 could be used as a supportive therapeutic line as it showed the best results of lowering blood glucose and elevating C-peptide level. The remarkable therapeutic effect of exendin-4 consequently is that it improves hyperlipidemia. So, the use of exendin-4 might help to avoid or reverse diabetic complications as hyperlipidemia. Also, the effectiveness of muscular exercise with exendine-4 in lipid metabolism is higher than that of exendine-4 alone.

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[illegible]

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خلفية البحث: يجري تقييم إكزندين-4 (ناهض بيبتيد-1مثيل الجلوكاجون) لتنظيم الجلوكوز في المرضى المصابين بالداء السكري. بالإضافة إلى الإنسولين وأدوية السكر التى تعطى للمرضى عن طريق الفم مع أو بدون ممارسة التمرينات الرياضية.

الهدف من البحث: صمم هذا العمل لبيان مدى تأثير مادة إكزندين-4 مع أو بدون التمرينات الرياضية على ذكور الجرذان البيضاء المصابة بالداء السكرى.

مواد وطرق البحث: إشتملت عينة البحث على أربعين جرذاً من الذكور وقد قسمت الجرذان إلى أربعة مجموعات متساوية وتم معالجتها كما يلى:

- **المجموعة الأولى**: مجموعة ضابطة غير مصابة بالداء السكرى أعطيت محلولاً ملحياً طبيعياً يومياً لمدة 8 أسابيع.
- **المجموعة الثانية**: مجموعة ضابطة مصابة بالداء السكرى خضعت للحقن بجرعة واحدة من الألوكزان في التجويف البريتوني تعادل 120 مجم / كجم لإحداث الإصابة بالداء السكرى.
- **المجموعة الثالثة**: مجموعة مصابة بالداء السكرى أعطيت إكزندين-4 بجرعة (1 نانومول/ كجم) داخل التجويف البريتونى يومياً لمدة 8 أسابيع.
- **المجموعة الرابعة**: مجموعة مصابة بالداء السكرى وخضعت للتمرينات الرياضية عن طريق برنامج تدريبي فى السباحة لمدة 5 أيام من كل أسبوع لمدة 8 أسابيع مع إكزندين-4 بجرعة (1 نانومول/كجم) يومياً لمدة 8 أسابيع.

وقد تم سحب عينات دم وريدية في نهاية التجربة وذلك لقياس: مستوى الجلوكوز بالدم والكوليستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة والبروتين الدهني عالي الكثافة ومستوى السي بيبتايد.

النتائج: أظهرت نتائج البحث أن الحقن بالألوكزان يحدث إرتفاعا ذو دلالة إحصائية فى مستوى الجلوكوز والكولستيرول والدهون الثلاثية وإنخفاض ذو دلالة إحصائية فى مستوى البروتين الدهني عالي الكثافة والسي بيبتايد مقارنة بالمجموعة الضابطة الغير مصابة بالداء السكرى. ومن ناحية أخرى فقد أثبتت النتائج أن إعطاء مادة إكزندين-4 مع وبدون التمرينات الرياضية للجرذان المصابة بالداء السكرى أدى إلى إنخفاض مستويات الجلوكوز والكولستيرول والدهون الثلاثية وإرتفاع مستوى البروتين الدهني عالي الكثافة والسي بيبتايد بنسب دالة إحصائياً مقارنة بالمجموعة الثانية. فى حين لم تحمل هذه النتائج دلالات إحصائية للمجموعة الرابعة عند مقارنتها بالمجموعة الثالثة.

الإستنتاج: إكزندين-4 له تأثير إيجابى فى تحسين مستويات الجلوكوز ودهنيات الدم فى الجرذان المصابة بالداء السكرى مما يجعل منه عقار المستقبل الذى يمكن إستخدامه فى علاج مرضى الداء السكرى. كما يتضح دور التمرينات الرياضية فى خفض مستوى الجلوكوز والدهون بالدم مما يساعد فى علاج مرضى الداء السكرى ويقلل من خطر المضاعفات المصحوبة بإرتفاع نسبة الدهون في الدم.

ونتائج هذه الدراسة تلفت النظر إلى أهمية التمرينات الرياضية مع إستخدام الإكسندين-4 فى علاج الداء السكرى ويتطلب الأمر مزيداً من الدراسة لإستخدام التمرينات الرياضية مع الإكسندين كأسلوب جديد لعلاج الداء السكرى.