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EFFECTS OF EXENDIN-4 AND ANTIOXIDANTS ON ADULT DIABETIC MALE ALBINO RATS

By

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ABSTRACT

Background: Diabetes mellitus is one of the most common endocrine disorders in all populations causing major health problem with long-term complications responsible for its mortality and morbidity. Oxidative stress has been suggested to be one of the factors in the development of diabetes and its chronic complications. **Objective:** Evaluation of the effects of glucagon like peptide-1(GLP-1) analogue (exendin-4) and antioxidants in diabetic male albino rats. **Materials and methods:** Forty adult male albino rats of local strain were chosen to be the model of the present study. They were left for two weeks in the laboratory room before any experimental interference for acclimatization with free access to water and rodent chow diet food. Induction of diabetes was done for all rats except the normal control group by a single subcutaneous injection of alloxan monohydrate 120 mg/kg with glucose by orogastric tube, then they were divided into four equal groups: **group I** (normal control group), **group G II** (diabetic control group), **group G III** (treated by exendin-4 1nm/kg/day given by intraperitoneal injection for 4 weeks and **group G IV** (treated by exendin-4 as above combined with vitamin C 200 mg/kg/day and vitamin E14.4 IU/kg/day by gastric intubation for four weeks). Blood samples were withdrawn for determination of blood glucose and lipid profile. **Results**: Treatment of diabetic rats by exendin-4 and antioxidants (vitamin C and E) caused significant reduction of blood glucose, total cholesterol, LDL and TG, and significant elevation of HDL levels in comparison to diabetic control group. **Conclusion**: Exendin-4 therapy as well as antioxidant, has a marked improvement of blood glucose level and lipid profile in male albino rats

Key Words: Diabetes mellitus, glucagon like peptide-1, antioxidants, exendin-4.

INTRODUCTION

Diabetes mellitus is one of the most common endocrine diseases in all populations and all age groups causing major health problem with long-term complications responsible for its mortality and morbidity **(Kim and Egan, 2008).**

As an incretin hormone, GLP-1 potentiates glucose-induced insulin secretion, avoiding hypoglycemia observed with other pharmaceutical activators of insulin secretion such as sulfonylureas **(Plummer et al., 2015).** GLP-1 has also been shown to reduce excess glucagon secretion, contributing to a reduction in hyperglycemia **(Baggio and Drucker, 2007)**, and has been suggested to reduce inflammation **(Kim et al., 2009).** GLP-1 signaling increases satiety and slows gastric motility and secretion, further contributing to a reduction in food intake **(Wren and Bloom, 2007)**.

The oxidative damage has been suggested to be one of the factors in the development of both types of diabetes and

its disabling chronic complications **(Giacco et al., 2010).**

Antioxidants may improve β-cell function, increase plasma insulin and C-peptide levels, possibly by influencing the antioxidant capacity of the organism and blocking the ability of the immune system to recognize β-cells**.** So, antioxidants therapy could possibly help diabetic patients and prevent diabetic complications **(Song et al., 2005).**

The aim of this study was to determine the effect of glucagon like peptide-1 analogue (exendin-4) and antioxidants on blood glucose level and lipid profile in diabetic male albino rats.

MATERIALS AND METHODS

Animals: This study was performed on 40 adult male albino rats of local strain. These rats weight 120-140 g. They were housed in isolated animal cages (5 rats each) measured 80 X 40 X 20 cm at the animal lab of the Physiology Department, Faculty of Medicine, Al-Azhar University. Animals were treated according to the guidelines for the use and care of laboratory animal in temperature, ventilation, humidity and normal dark/ light cycle with free access to water and fed on rodent chow diet food all over the period of the work (4 weeks). Rats were divided into four equal groups:

Group (I) : Normal control group.

Group (II): Diabetic control group.

Group (III) : Diabetic group receiving exendin-4 (1nm/kg/day I.P) for 4 weeks **(Maduka et al., 2003)**.

Group (IV): Diabetic group receiving exendin-4 (1nm/kg/day I.P), and vitamin C (200 mg/kg/day) as well as vitamin E (14.4 IU/kg/day) by gastric intubation for four weeks (**Gokkusu et al., 2001)**.

Drugs:

Alloxan monohydrate (Nile Pharmaceutical Company Egypt).

Exendin-4 (Sigma Company USA)

Vitamin C: (Memphis Company Egypt).

Vitamin E: (Pharco Pharmaceutical Egypt).

Methods

Induction of Diabetes Mellitus: A single subcutaneous injection (120 mg/ kg body weight) of alloxan accompanied by glucose infusion (3 g/kg body weight) by gastric intubation to diabetic control group (GII), diabetic group received exendin-4 (GIII) and diabetic group received exendin-4 combined with antioxidants (GIV) to overcome fatal hypoglycemia caused be transient hyperinsulinemia after alloxan injection due to destruction of β-cells. The injection was repeated in the 2nd day to obtain response (**Maduka et al., 2003)**.

Collection of blood samples: Blood was collected (3 ml blood from each rat) from the retro-orbital plexus in a dry clean graduated glass centrifuge tube and rapidly set to the centrifugator at 5000 rotations per minute for about 15 minutes. Serum was sucked out into Eppendorf tubes and stored frozen at -20^0C till required and used for the determination of:

1. Blood glucose levels (**Burtis et al., 1986)**.
2. Plasma levels of total cholesterol **(Allain et al., 1974).**

3. Plasma levels of high density lipoproteins (HDL- **Groove, 1979).**
4. Plasma levels of low density lipoproteins **(**LDL-**Friedewald et al., 1972).**
5. Plasma levels of triglycerides (TGs-**Fossati and Prencipe, 1982).**

Statistical Analysis: Data input and analysis were done using SPSS computer program. All results were expressed as the mean ± standard deviation. Mean values of the different groups were compared using a one way analysis of variance (ANOVA). Least significant difference (LSD) post hoc analysis was used to identify significantly different mean values. P value < 0.05 was accepted to denote a significant difference.

RESULTS

Effects of exendin-4 and antioxidants on the measured parameters (Table 1, 2, and 3):

In diabetic control group (G II), there were significant increase in glucose level (384.3±34.31) compared to normal control group (128.2±12.67), and significant increase in TC, LDL-C and TGs levels (131.5±5.54, 74.36±3.52 and 119.3±10.41 respectively) compared to normal control group (99.22±5.32, 56.12±7.49 and 88.73±6.21 respectively). HDL-C significantly decreased in diabetic control group compared to normal control group (33.6±3.06 and 39.44±3.84 respectively).

In diabetic group received Exendin-4, there were significant increase in glucose level (277.2±30.49) compared to normal control group (128.2±12.67), and significant increase in TC, LDL-C and TGs levels (115.7±10.83, 60.61±8.78, and 106.6±9.48 respectively) compared to normal control group. HDL-C significantly decreased (33.5±3.14) compared to normal control group.

In diabetic group received Exendin-4 combined with vitamin C and E, there were significant increase in glucose level, TC and LDL-C (210.7±90.48, 109±6.63, and 61.25±8.53 respectively) compared to normal control group (128.2±12.67, 99.22±5.32, and 56.12±7.49 respectively), non significant decrease in HDL-C (38.42±3.95) and non significant increase in TGs (93.4±5.85) compared to normal control group (39.44±3.84 and 88.73±6.21 respectively).

Intraperitoneal injection of exendin-4 led to significant decrease of blood glucose levels in diabetic group receiving exendin-4 (277.2±30.49 mg/dl), and diabetic group received exendin-4 combined with vitamins C and E (210.7±90.48 mg/dl) compared to diabetic control group (384.30±34.31 mg/dl) with P value <0.05.

Total cholesterol level significantly decreased in diabetic group received exendine-4 (115.7±10.83 mg/dl), and diabetic group received exendin-4 combined with vitamins C and E (109±6.63 mg/dl) compared to diabetic control group (131.50±5.54 mg/dl) with P value <0.05.

LDL level significantly decreased in diabetic group received exendin-4 (60.61± 8.78 mg/dl), and diabetic group received exendin-4 combined with vitamins C and E (61.25± 8.53 mg/dl) compared to diabetic control group (74.36±3.52 mg/dl) with P value <0.05.

Triglycerides (TGs) level significantly decreased in diabetic group received exendin-4 (106.7±9.48 mg/dl), and diabetic group received exendin-4 combined with vitamins C and E (93±5.85 mg/dl), compared to diabetic control group (119.30±10.41 mg/dl) with P value <0.05.

HDL level significantly increased in diabetic group received exendin-4 combined with vitamins C and E (37.0±3.95 mg/dl), compared to diabetic control group (33.60±3.06 mg/dl) with P value <0.05. Non significant decrease in HDL-C level in diabetic group received exendin-4 (33.5±3.14 mg/dl) compared to diabetic control group.

Diabetic group received exendin-4 combined with vitamins C and E, there were significant decrease in glucose and TGs levels (210.7±90.48 and 93.4±5.85 respectively) compared to diabetic group received exendin-4. HDL-C significantly increased (38.42±3.95) in diabetic group received exendin-4 combined with vitamins C and E compared to diabetic group received exendin-4 (33.5±3.14). There were non significant decrease in TC and LDL-C (109±6.63 and 61.25±8.53 respectively) in diabetic group received exendin-4 combined with vitamins C and E compared to diabetic group received exendin-4 (115.7±10.83 and 60.61±8.78 respectively).

Table (1): Effects of exendin-4 and antioxidant supplementation on the measured parameters (mean ± S.D) compared to normal control group.

Groups / Parameters	Group I	G II	G III	G IV
Blood glucose (mg/dl)	128.2±12.67	384.30±34.31 P<0.01	277.2±30.49 P<0.01	210.7±90.48 P<0.05
Total cholesterol (mg/dl)	99.22±5.32	131.50±5.54 P<0.05	115.7±10.83 P < 0.05	109±6.63 P < 0.05
HDL level (mg/dl)	39.44±3.84	33.60±3.06 P<0.05	33.5±3.14 P<0.05	38.42±3.95 P>0.05
LDL level (mg/dl)	56.12±7.49	74.36±3.52 P<0.05	60.61± 8.78 P < 0.05	61.25± 8.53 P < 0.05
TG level (mg/dl)	88.73±6.21	119.30±10.41 P<0.05	106.7±9.48 P<0.05	93.4±5.85 P>0.05

Group I = normal control group, **G II** = diabetic control group, **G III** = group given exendin-4, **G IV** =group given exendin-4 and antioxidant, **HDL**= high-density lipoproteins, **LDL**= low-density lipoproteins, **TG** = triglycerides.

Table (2): Effects of exendin-4 and antioxidant supplementation on the measured parameters (mean ± S.D): compared to diabetic control group

Groups / Parameters	G II	G III	G IV
Blood glucose (mg/dl)	384.30±34.31	277.2±30.49	210.7±90.48
		P<0.05	P<0.05
Total cholesterol (mg/dl)	131.50±5.54	115.7±10.83	109±6.63
		P < 0.05	P < 0.05
HDL level (mg/dl)	33.60±3.06	33.5±3.14	38.42±3.95
		P>0.05	P<0.05
LDL level (mg/dl)	74.36±3.52	60.61± 8.78	61.25± 8.53
		P < 0.05	P < 0.05
TG level (mg/dl)	119.30±10.41	106.7±9.48	93.4±5.85
		P<0.05	P<0.05

G II = diabetic control group, **G III** = group given exendin-4, **G IV** =group given exendin-4 and antioxidant, HDL= high-density lipoproteins, **LDL**= low-density lipoproteins, **TG** = triglycerides.

Table (3): Comparison between diabetic group received Exendin-4 and diabetic group received Exendin-4 combined with vitamins C and E.

Groups / Parameters	G III	G IV	P Value
Blood glucose (mg/dl)	277.2±30.49	210.7±90.48	P<0.01
Total cholesterol (mg/dl)	115.7±10.83	109±6.63	P>0.05
HDL level (mg/dl)	33.5±3.14	38.42±3.95	P<0.05
LDL level (mg/dl)	60.61± 8.78	61.25± 8.53	P>0.05
TG level (mg/dl)	106.7±9.48	93.4±5.85	P<0.05

G III = group given exendin-4, **G IV** =group given exendin-4 and antioxidant, **HDL**= high-density lipoproteins, **LDL**= low-density lipoproteins, **TG** = triglycerides.

DISCUSSION

The prevalence of diabetes continues to increase and globally the World Health Organization (WHO) estimates that 347 million people suffer from diabetes, with approximately 90% having type 2 diabetes **(WHO, 2012)**. Polytherapy is an accepted strategy for improving the treatment of diabetes **(Wright et al., 2010)**. The aim of the present study was to investigate whether exendin-4 alone or combination with vitamins C and E, improved glycemic and hyperlipidemic control in male albino rats.

All groups injected by alloxan (diabetic control group, group received exendin-4 and group received exendin-4 combined with vitamins C and E) showed significant higher levels in the blood glucose in comparison to normal control group. Reactive oxygen species produced by alloxan administration caused breakdown of DNA strands. Such damaged DNA activates nuclear polysynthetase, which depletes the cellular pool of NAD^+, resulting in β-cell damage **(Green et al., 2004)**.

In group received exendin-4 and group received exendine-4 combined with vitamins C and E, the blood glucose level was significantly lower than diabetic control group.

Exendin-4 or incretin mimetic has structural similarity and binds to GLP-1receptors **(Hadjiyanni et al., 2008)**. So, impaired secretion of incretin as well as impaired effect on islet functions could be considered among the factors causing diabetes mellitus **(Vilsboll et al., 2001). Gallwitz (2011)** reported that GLP-1 stimulates glucose-dependent insulin secretion. **Wu et al. (2012) and Koehler et al. (2015)** reported that exendin-4 stimulated insulin secretion and significantly reduced glucose level. **Gonzalez and Gagliardino (2009)** concluded that exogenous administration of incretin which is GLP-1 receptor agonist enhances insulin hormone secretion.

Impaired function of incretin as a transmitter in the enteric axis contributes to the inappropriate metabolism in diabetic patients and this effect might be corrected when exendin-4 was administrated to the diabetics. Consequently exendin-4 might be practically effective in prevention or even cure of diabetes mellitus **(Kim and Egan, 2008).**

Nauk et al. (2002) reported that the inhibition of glucagon secretion is glucose dependant i.e. when glucose is not high enough glucagon is not reduced. Taking in consideration that GLP-1 is the best line of therapy regarding effect on glucose in comparison to other groups. **Dupre (2005)** reported that GLP-1 infusion in diabetic patients without any residual β–cell secretory capacity has glucose-lowering activity due to strong inhibition of glucagon secretion with very high glucose and very low insulin.

In our study, administration of antioxidants in the form of vitamin C and E was significantly associated with lower glucose levels in diabetic group received exendin-4 (210.7±90.48 mg/dl) compared to diabetic control group (384.30±34.31 mg/dl). The results were compatible with **Farvid et al. (2011)** who reported that over 4 months of treatment, vitamins C showed no significant changes in glycemic control. **Ceriello and Motz**

(2004) reported that vitamins C and E produce improvement in insulin-stimulated glucose metabolism and increase insulin-mediated glucose utilization. Therefore, in order to produce glucose lowering effect by vitamins C and E, a proper amount of exendin-4 should be present. Moreover, **Saudek et al. (2006)** reported that vitamins C and E administration reduce blood glucose serum level by lowering glycosylated hemoglobin (HbA1c) level so reduce insulin hormone level.

Ceriello and Motz (2004) reported that vitamins C and E produce improvement in insulin-stimulated glucose metabolism and increase insulin-mediated glucose utilization. GLP-1 improves beta cell function through increased insulin secretory capacity **(Xie et al., 2014).**

The blood glucose level in diabetic group received exendin-4 combined with antioxidants was lower than in diabetic group received exendin-4. Based on the results of this study, the addition of vitamins C and E improves the action of exendin-4.

Our study revealed that alloxan-induced diabetes mellitus in diabetic control group elevated the levels of cholesterol, triglycerides and LDL, while it depressed the level of HDL compared to normal control group. This was compatible with that of **Irshaid (2012)** who revealed that diabetes lead to elevated levels of cholesterol, triglycerides and LDL, and depressing level of HDL. This finding is in consistent with the results of **Rajeswari and Rajagopalan (2013)** who attributed this disturbance in lipid profile to the increased mobilization of free fatty acids (FFA) from adipose tissue in diabetic rats.

Increased cholesterol is attributed to increased intestinal absorption and increased cholesterol biosynthesis **(Subash et al., 2007)**. In the current study, hypertriglyceridemia in diabetic rats could be attributed to increase in the activity of hormone-sensitive lipase, which catalyses the mobilization of fatty acids from triacyl glycerols stored in adipocytes **(Almedia et al., 2012)**. Lipoprotein lipase activity is reduced in diabetes and this reduction promotes diabetic hypertriglycerodemia **(Kondo et al., 2007)**. Increased LDL-C level resulted from glycosylation of lysyl residues of a lipoprotein B, which leads to a decrease in the affinity of LDL-C for its receptors **(Rajeswari and Rajagopalan, 2013)**. Decreased HDL-C is due to diminished lecithin cholesterol transferase activity **(Nwoneri-Chidozie et al., 2014)**.

In diabetic group received exendin-4 and diabetic group received exendin-4 combined with antioxidants, the total plasma cholesterol, LDL and TG level were significantly lower than diabetic control group, while plasma HDL level was significantly higher. Similar results were also obtained by **Buse et al. (2004) and Viswanathan et al. (2007)**.

According to study of **Khoo et al. (2009),** chronic administration of exendin–4 caused significant reduction in triglycerides and free fatty acid levels, and it caused a significant change in total cholesterol. They also reported that exendin-4 possibly produces its lipid lowering effect through reduced production of intestinal triglycerides rich particle after fat rich meal and/or

augmentation of lipid mobilization and oxidation. It may occur also through inhibition of its absorption from the gut, either by producing deceleration of gastric emptying with delay of nutrients reaching the duodenum and preventing the increase in cholesterol and triglycerides (**Schirra et al., 2005)**, or due to inhibition of gastric lipase and inhibition of lymph flow **(Qin et al., 2005).**

One of the most effective mechanisms for the lipid lowering effect of exendin-4 on cholesterol in diabetics is through increased insulin secretion which suppresses lipolysis with decreased triglycerides **(Meier et al., 2006).** In addition, depressed glucagon may contribute to the significant reduction of free fatty acid **(Franklin et al., 2005). Meier et al. (2006)** observed that glucagon concentration during infusion of exendin-4 closely seems as a mirror for the free fatty acid.

Nakamura et al. (2015) stated that elevated serum cholesterol levels occur in both types I and II diabetes, and tend to fall toward the normal level with the control of hyperglycemia. **Vega et al. (2015)** found that hyperglycemia was accompanied by an elevation in plasma cholesterol and triglyceride levels.

Armstrong et al. (2006) stated that the reduced lipid peroxidation and improved antioxidant status may be one mechanism by which treatment with vitamins C and E contributes to the prevention of diabetic complications.

In our study there were a significant decrease in glucose and triglycerides levels, significant increase in HDL level, and non significant changes in TC and LDL levels, in diabetic group received exendin-4 combined with antioxidants compared to diabetic group received exendin-4 alone, these improvement of the results may be attributed to the hypoglycemic and hypolipedimic effect of vitamins C and E in addition to action of exendin-4. **Masuoka et al. (2014)** reported that antioxidants can prevent decrease of insulin concentration in the blood. **Kathore and Bansode (2015)** found that supplementation with vitamins C and E caused improvement in blood glucose and lipid levels in patients with type 2 diabetes, also a study by **Vaksh et al. (2013)** concluded that vitamin C was effective in improving hyperglycemia and hyperlipidemia in type 2 diabetes.

In the current study, treatment of diabetic rats by exendin-4 alone or combined with antioxidant reduced glucose level and improved lipid profile but the level not returned to normal levels in comparison to normal control rats. These results explained by the possibility of action of alloxan experimentally in rats which is selectively toxic to pancreatic beta cells, leading to induction of cell massive destruction and necrosis **(Sulaiman et al., 2012)**. The results of lipid profile support this possibility where the antioxidant effect of vitamins C and E caused return lipid profile to near normal level, moreover a study by **Mangmool et al. (2013)** reported that GLP-1 receptor agonist provides protective effect of oxidative stress.

CONCLUSION

Exendin-4 therapy as well as antioxidants have marked improvements of blood glucose level and lipid profile in male albino rats. This was most probably due to increasing insulin sensitivity and decreasing hepatic fat biosynthesis.

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تأثير عقار إكزندين-4 ومضادات الأكسدة علي ذكور الجرذان البيضاء المصابة بالداء السكرى

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خلفية البحث: مرض البوال السكرى من أكثر أمراض الغدد الصماء إنتشارا في العالم ويسبب مشاكل ومضاعفات صحية على المدى البعيد والتي تؤدى إلى إنتشار الأمراض والوفاة، ويعتبر إختلال الأكسدة من أهم العوامل التي تؤدى إلى حدوث المضاعفات المزمنة المصاحبة لمرض البوال السكرى. **الهدف من البحث:** التعرف على تأثير عقار إكزندين -4 (شبيه الببتيد-1) ومضادات الأكسدة على ذكور الجرذان البيضاء المصابة بمرض البوال السكري.

مواد وطرق البحث: تمت هذه الدراسة علي أربعين جرذا أبيضا من السلالات المحلية تتراوح أوزانهم ما بين 120-140 جراما، تم إستحداث مرض البوال السكري لكل الجرذان عدا المجموعة الضابطة الطبيعية عن طريق عقار الألوكسان بالحقن تحت الجلد بجرعة 120 ملجم / كجم من وزن الجرذ مع الجلوكوز لتفادى حدوث نقص السكر المميت للحيوانات، وتم تقسيم الجرذان إلي أربع مجموعات متساوية كما يلي : المجموعة الضابطة الطبيعية، المجموعة الضابطة المصابة بمرض البوال السكرى، والمجموعة المعالجة بعقار إكزندين -4 بجرعة 1 نانومول / كجم / يوم عن طريق الحقن داخل الغشاء البريتوني لمدة أربعة أسابيع، والمجموعة المعالجة بعقار إكزندين -4 بالإضافة إلي فيتامين ج بجرعة 200 ملجم / كجم / يوم وفيتامين هـ بجرعة 14.4 وحده دولية / كجم / يوم في مياه الشرب لمدة 4 أسابيع . وفي نهاية فترة التجربة (4 أسابيع) تم قياس مستوي الجلوكوز في الدم ومستوي الكولسترول الكلي في البلازما ومستوي الدهون عالية الكثافة في البلازما ومستوي الدهون منخفضة الكثافة في البلازما و مستوي الدهون الثلاثية في البلازما.

النتائج: أظهرت النتائج أن الجرذان المعالجة بعقار إكزندين -4 وكذلك المعالجة بمضادات الأكسدة تدني مستوي السكر في الدم وإنخفاض الكولسترول والدهون منخفضة الكثافة والدهون الثلاثية في البلازما وإرتفاع مستوى الدهون عالية الكثافة مقارنة بالمجموعة الضابطة المصابة بالبوال السكرى.

الإستنتاج: العلاج بعقار الإكزندين-4 ومضادات الأكسدة موصي به لمرضي داء البوال السكري حيث أدى إلى تحسن فى مستوى سكر الدم والدهون.