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COMPARATIVE STUDY OF ERYTHROPOIETIN AND EXTENDIN-4 ON ADULT MALE DIABETIC ALBINO RATS

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ABSTRACT

Background: Erythropoietin (EPO) and exendin-4 are widely used in treatment of type 2 diabetes and enhance the general and metabolic conditions in diabetic patients.

Objective: Assessing the effect of erythropoietin and exendin-4 administration on experimental diabetic adult male albino rats.

Design: experimental design.

Materials and Methods: Forty adult male albino rats of local strain were housed in 8 suitable metal cages (20 ×32× 20 cm for every 5 rats). They were divided into five equal groups: Group I served as a control group, group II was diabetic control, group III was diabetic group-treated with erythropoietin subcutaneously in a dose of 300 uint/kg 3 times a week for 4 weeks, group IV was diabetic group received exendin-4 intraperitonealy in a dose of 1 microgram /kg once daily for one week period, and group V was diabetic-treated with both drugs. Blood samples were collected for measuring fasting glucose, fasting insulin , cholesterol(CHO), triglycerides (TG), low density lipoprotein cholesterol (LDL-c), high density lipoproteins cholesterol (HDL-c), and hematological parametres: hematocrite value , hemoglobin content, red blood cells (RBCs) and white blood cells (WBCs) .

After induction of diabetes by alloxan, the first diabetic group was kept diabetic without any treatment (diabetic control G II) , the second diabetic group was treated with erythropoietin subcutaneously in a dose of 300 uint/kg 3 times a week for 4 weeks (G III), the third diabetic group was treated with exendin-4 intraperitonealy in a dose of 1 microgram /kg once daily for one week (G IV), and the fourth diabetic group of rats was treated with both drugs (G V).

Results: Alloxan-induced diabetes mellitus was associated with significant higher levels of blood glucose, total cholesterol, triglycerides and LDL, and significantly lower levels of, insulin, , HDL and hematological parameters (HV,HB%,RBCs,WBCs) as compared with normal control group. Erythropoietin injection in diabetic rats produced significant lower levels of blood glucose, total cholesterol, triglycerides and LDL, with significantly higher levels of insulin, HDL and hematological parameters as compared with control diabetic group. Exendin-4 showed significant lower levels of blood glucose, total cholesterol and TG, and significant higher levels of HDL, and insignificant results on insulin and hematological parameters as compared with the control diabetic rats. Treatment of rats with erythropoeitin and exendin-4 resulted in significant lower levels of blood glucose, total cholesterol and LDL, and significant high levels of insulin, HDL and hematological parameters as compared with control and other groups .

Conclusion: Erythropoietin and exendin-4 were more potent in reducing hyperglycemia than the effect of each one separately. Erythropoietin improved the general condition of diabetic rats due to its hematopoitic effect.

Key words: EPO, exendin-4, alloxan, experimental diabetes.

INTRODUCTION

EPO is produced primarily in the peritubular fibroblasts in the kidney with a small contribution from the liver in adults (**Chateauvieux et al., 2011 and Choi et al., 2011**). Its principal function is to regulate red blood cell production by binding to the EPO receptor (EPOR) on erythroid progenitor cells. The expression of EPO is not confined to the kidney and liver, and EPO mRNA has also been detected in the lungs, testis, uterus and brain in rodents, and skeletal muscles in humans (**Lamon et al., 2014).** The expression of EPOR has been detected in non-erythroid cells including endothelial cells, epicardium and brain neuro-epithelium **(Choi et al., 2011).** Treatment with EPO can exert several extra-hemato-poietic effects. Previous studies have revealed that EPO exerts multiple protective effects including anti-oxidative (**Zhang et al., 2011 and Dimitrijevic et al., 2012)**, anti-inflammatory (**Nairz et al., 2012),** and anti-apoptotic effects **(Stoyanoff et al., 2014)**

It has been reported that 90% of DM cases are type 2 diabetes mellitus, the pathogenesis of which involves abnormalities in glucose metabolism including inadequate insulin secretion from pancreatic β-cells and insulin resistance (**Ohshima et al., 2012**). In 2003, **Fenjves *et al.*** demonstrated that pancreatic islets express EPOR protein. EPO exerts cytoprotective effects on non-erythroid tissues by modulating a variety of signaling pathways, which involve mitogen-activated protein kinase, nuclear factor (NF)-κB and phosphatidyl inositol 3-kinase(PI3K)/Akt (**Kwon et al., 2014**). It is well known that activation**.** of the PI3K/Akt signaling pathway has protective effects on DM. Therefore, several previous studies have focused on investigating the effects of EPO on islet cells and, in particularly, the effect of EPO in the type 1 and 2 diabetes (**Zhang et al., 2011).**

Exendin-4 is a glucagon-like peptide-1 (GLP-1) agonist, and 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 **(Chen et al., 2017).** It is insulinotropic and plays a role in the incretin effect, i.e. augments insulin response observed when glucose is absorbed through the gut **(Eunhui Seo et al., 2017).** Exendin-4 has structural similarity and binds to GLP-1 receptors (**Gupta, 2013)**. GLP-1 and its long acting agonist exendin-4 stimulates the proliferation and differentiation of stem cells in the pancreas into β cells **(Zaccardi et al., 2016).** This study was carried out to compare the effects of erythropoitine and exendine 4 on adult male diabetic albino rats.

MATERIAL AND METHODS

This work was done at the laboratory of Physiology Department, Faculty of Medicine, Al- Azhar University (Assiut).

Chemicals: EPO (Shenyang sunshine pharmaceutical co, Ltd, Shenyang, china).

Exendin 4 (Baxter Pharmaceutical Solutions LLC Bloomington, USA).

Animals: A total number of 40 adult male albino rats of a local strain weighing 160 -180 g were used in this study. The animals were obtained from the animal farm, Faculty of Medicine, Assiut University. Rats were housed in normal

environmental conditions of temperature and humidity. Animals were kept under normal day / dark cycle with free access to food and water in metal cages (35x30x35 per 5 rats)

After two weeks of acclimatization, rats were divided into two groups, control group (8 rats), and diabetic groups (32 rats).

Induction of diabetes: Alloxan mono-hydrate was administered in a dose of 150 mg /kg body weight intra-peritoneally to the overnight fasted rats. The animals were kept for the next 24 hours on 10% glucose to prevent hypoglycemia. After 48- 72 hours, fasting blood sugar was determined by using Accuchek gluco-meter strips (Roche Diagnostics). Animals with fasting blood sugar (FBG) more than 200 mg /dl were considered diabetic **(Jain and Arya, 2011).**

Group I: Control group was given an amount of citric acid buffer equal to the amount of injected alloxan.

The diabetic rats were divided into 4 equal groups:

Group II: Diabetic control group.

Group III: Diabetic rats treated with EPO subcutaneously in a dose of 300 unit/kg 3 times a week for 4 weeks.

Group IV: Diabetic rats treated with exendin 4 intraperitonealy in a dose of 1 microgram/kg body weight once daily for 7 days.

Group V: Diabetic rats treated with both EPO and exendine in the same doses.

At the end of the experimental period (30 days), blood samples were collected into two tubes:

1. One collected with EDTA-normal saline solution for hematological analysis: hemoglobin (Hb), erythrocytic count (RBCs), leucocytic count (WBCs), and hematocrit value.
2. The second blood sample was left for a short time to allow clotting, then serum sample obtained by centrifugation at 3000 rpm for 20 min was kept at -20°C until used for estimation of lipid profile, insulin, and blood glucose using commercial kits purchased from Biodiagnostics co, Dokky, Giza, Egypt.

Statistical analysis of the results was carried out using one way classification ANOVA test. The statistical significance was referred to $P<0.05$.

RESULTS

Effect of injection of alloxan, erythropoeitin and exendin-4 administration on measured parameters (Table 1): Injection of alloxan into rats (group II) showed significant higher level of blood glucose from 99.25±4.5 to 310.43±3.91 as compared with control group, and significant lower level of insulin from 1.32±0.0 to 0.61±0.08 as compared with control group. Administration of erythropoeitin into rats showed significant lower level of blood glucose when compared with diabetic control group from 310.43±3 to 231.28±2.11 91, and significant higher level of insulin from 0.61±0.08 to 1.49±0.08 as compared with diabetic control group. Exendin-4 administration into rats showed significant lower level of blood glucose when compared with diabetic control group from 310.43±3.91 to 238.28±5.76, and insignificant change in insulin level from 0.61±0.08 to 0.65±0.07 as compared with diabetic

control group . Injection of both drugs into rats showed signficant lower level of blood glucose when compared with diabetic control group from 310.43±3.91 to 210.38±2.5, and significant increase in insulin level from 0.61±0.08 to 1.65±0.23. Also, there was a significant decrease in blood glucose level as compared with other treated groups (group III) and (group IV), and also

a significant increase in insulin level than the other individually drug treated groups (1.65±0.23, 1.49±0.08 and 0.65±0.07 respectively).

Table (1): Changes in blood glucose and insulin level in different groups.

Parameters / Groups	FBS (mg/dl	Fasting insulin Mu/L
Group I	99.25±4.5	1.32±0.0
Group II	310.43±3.91*	0.61±0.08*
Group III	230.28±2.11*#	1.49±0.08*#
Group IV	238.28±5.76*#	0.65±0.07*
Group V	210.38±2.5*#+³	1.65±0.23*#+³

Significant results as compared with group (I)*.
Significant results as compared with group (II)#.
Significant results as compared with group (III)+ and group (IV)³.

Injection of alloxan into rats showed significant lower levels of hematological parameters as compared with control group as shown in table (2) Hemoglobin (HGB) from 14.39 ± 0.38 to 11.5 ± 0.21, (RBC) count from 7.14±0.34 to 3.63 ± 0.53, (WBC) count from 12.42±0.41 to 8.91 ± 0.54 and (PCV) from 44.23±0.53 to 30.84 ± 0.61 as compared with control group. Erythropoeitin injection in rats showed higher significant levels of hematological parameters, as compared with diabetic control group (HGB) 13.83 ± 0.25, 11.5 ± 0.2I,(RBC) count 5.95±0.2 to 3.63 ± 0.53 (WBC) count 10.31 ± 0.31 to 8.91 ± 0.54 and (PCV) 46.16±0.32 to 30.84 ± 0.61 respectively. as shown in table (2) exendin-4 injection in rats (group IV) showed insignificant results in (HGB) 12.3±0.1I to 11.5±0.2I, (PCV) 30.79±0.35 to 30.84±0.61 and (RBC) 3.49±0.22 to 3.63±0.53 and (WBC) 9.12±0.35 to 8.91±0.54 when compared with diabetic control group administration of both drugs in rats showed the highest significant result of hematological parameters when compared with diabetic group, (HB%) from15.25 ± 0.12c to 11.5±0.2Ia,(RBCs) from 7.35 ± 0.15a to 3.63 ± 0.53b, (WBCs) from 14.68 ± 0.32 to 8.91 ± 0.54 and (PCV) from 46.85 ± 0.35b to 44.23 ± 0.53.

Table (2): Changes in hematological parameters in different groups.

Parameter / Groups	Hb (g/dl)	RBCs (m/µL)	WBCs (mm)³	PCVs %
Group I	14.39±0.38	7.14±0.34	12.42±0.41	44.23±0.53
Group II	11.5±±0.2I*	3.63±0.53*	8.91±0.54 *	30.84±0.61*
Group III	13.83±0.25#	5.95±0.2 I#	10.31± 0.31*#	46.16±0.32#
Group IV	12.3±0.1I*#	3.49±0.22*	9.12±0.21+	30.79±0.35*
Group Vs	15.25 ±0.12*#+	7.35±0.15#+	14.68±0.32#+	46.85±0.35#

Significant results as compared with group 1*.
Significant results as compared with group II #.
Significant results as compared with group (III)+.

Injection of alloxan into rats resulted in significant higher levels of cholesterol from 70.5 ± 3.4 to 210.87 ± 2.81 , TG from 95.85 ± 4.48 to 109.48 ± 3.11, LDL from 18.37 ± 3.13 to 28.52 ± 2.16 and decrease HDL from 32.99 ± 2.4 to 24.54 ± 1.35 as compared with normal control group. Injection of erythropoietin into diabetic rats resulted in significant lower levels of cholesterol from 210.87 ± 2.81b to 179.08 ± 4.9, TG from 109.48 ± 3.11b to 80.02 ± 3.16a LDL from 28.52±2.16 to 20.1 ± 23I and significant elevation of HDL from 24.54 ± 1.35b to 29.98 ± 2.55 rats treated with exendine-4 significant decrease in levels of cholesterol from 210.87 ± 2.81 to 173.08 ± 2.95, TG from 109.48 ± 3.11 to 82.03±3.52, LDL from 28.52 ± 2.16 to19.9 ± 1.5 and significant increase of HDL from 24.54 ± 1.35 to 28.88 ± 2.55 as compared with control diabetic group.

The effect of both drugs resulted in significant decrease in the levels of cholesterol from 210.87 ± 2.81b to 172 ± 2.99b, TG from 109.48 ± 3.11 to 81.59 ± 2.53, LDL from 28.52 ± 2.16 to 17.98 ± 1.65 and significant increase in HDL level from 24.54 ± 1.35 to 30.21 ± 3.5 as compared with diabetic control group.

Table (3): Changes in lipid profile in different groups.

Parameters / Groups	Cholesterol Mg/dl)	TG (mg/dl)	LDL(mg/dl)	HDL (mg/dl)
Group I	70.5±3.4	95.85±4.48	18.37±3.13	32.99±2.4
Group II	210.87±2.81*	109.48±3.11*	28.52±2.16*	24.54±1.35*
Group III	179.08±4.9*	80.02±3.16#	20.1±23I#	29.98±2.55#
Group IV	173.08±2.95*#	82.03±3.52#	19.9±1.5#	28.88±2.55#
Group V	172±2.99*#	81.59±2.53#	17.98±1.65#	30.21±3.5#

Significant with group 1*.
Significant with group II #**.**

DISCUSSION

The aim of the present study was to compare between the effect of erythropoeitn and exendine 4 on adult male diabetic albino rats

Previous studies have reported that there may be an association between EPO levels and hypoglycemia, which suggests a potential protective effect of EPO in the treatment of diabetes (**Chateauvieux et al., 2011, Choi et al., 2011 and Stoyanoff et al., 2014).** All groups injected by alloxan showed significant higher levels in the blood glucose and significant lower level of serum insulin level in comparison to normal 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^{2+} homeostasis and DNA damage **(Rohilla and Ali, 2012).**

Induction of diabetes led also to disturbed lipid profile in the form of higher levels of cholesterol, triglycerides and LDL-c, and lower levels of HDL-c. 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). Irshaid et al. (2012)** 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., 2014).** 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., 2013).**

In our study, induction of diabetes led to significant decrease in hematological parameters ,HB, RBC,WBC and PCV. In diabetes, reduced haemoglobin has been reported which may be accompanied by a fall in the red blood cell count and packed cell volume (**Muhammad and Oloyede, 2009**). In the present study, diabetic group received erythropoietin showed significant decrease in blood glucose level and significant increase in insulin level and in comparison to diabetic control. **Niu et al.** (**2016**) found that the EPO decreases FBS in diabetic rats which is decreased from the first week of treatment with EPO, and also found that EPO attenuated hyperglycemia dose dependently in type one diabetic rats lacking insulin .

Animals treated with exendin-4 (group IV) showed decrease FBG with no change in insulin level. This result agreed with the results reported by **Gulati et al. (2012**) who found that, exendin-4 significantly decreased blood glucose level without enhancing serum insulin concentration. **Fan et al. (2011)** reported that after 10

days exendin-4 administration showed significant improvement in glucose control.

Increased insulin secreting might not be involved in the glucose regulating effect of exendin-4 in our normal non diabetic models as insulin secretion level did not significantly increased. This suggested that the non-insulin effect of exendin-4 may also play a major glucose modulating role. Also beta cell proliferation rate was slightly but not significantly reduced after exendin-4 treatment **(Kim et al., 2016).**

Rats treated with both drugs (group V) showed a significant decrease in FBG and increase insulin levels comparing with other groups, so; the effect of either drug must be augmented with the use of another one or another hypoglycemic element.

The current study induced the ameliorative effect of EPO on lipid profile of diabetic rats as significant decrease in cholesterol, TG, LDL levels, and increase HDL. Our results are in concordance with what reported by **Hashim et al. (2013)** who found that, EPO therapy is associated with improvement of blood lipid profile especially cholesterol, LDL. Another study reported by **Ponnudhali and Nagarajan (2011)** reported that EPO therapy is associated with an improvement of blood lipid profile especially LDL in diabetic patients.

In our study, animals treated with exendin-4 (group IV) induced a significant decrease in levels of cholesterol, LDL, TG and increase HDL. Our results were in concordance with the results reported by **Shiwei et al. (2015)** who found that exendin-4 markedly reduces the accumulation of fat droplets, as well as level of cholesterol, and LDL in a dose-dependant manner.

Group of animals treated with both drugs resulted in a significant decrease in cholesterol ,TG,and LDLand significant increase in insulin and HDL levels as compared with the diabetic groups. The current study resulted in significant improvement in hemopoietic parameters after EPO administration as increases levels of HB, MCV, RBCs, and WBCs in the diabetic group. These results were in concordance with the results reported by **Xian et al. (2015)** who found that EPO regulates hemopoeitic function in diabetic rats.

CONCLUSION

Erythropoietin and exendin-4 have beneficial effects on control of blood glucose level and lipid profile on treatment of diabetic rats ,EPO administration improve the general condition of diabetic rats owing to its heamopoetic effect.

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دراسة لمقارنة تأثير الإرثروبويتين وإكسيندين-٤ على ذكور الجرذان البيضاء البالغين المصابين بمرض البوال السكري

سامح سلطان

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خلفية البحث : يستخدم إريثروبويتين وإكسندين-٤ على نطاق واسع في علاج مرض **البوال** السكري من النوع الثانى وذلك لتعزيز الحالة العامة والتمثيل الغذائي في مرضى **البوال** السكري.

الهدف من البحث: تقييم تأثير الإرثروبويتين وإكسندين-٤ على ذكور الجرذان البيضاء المصابة بمرض **البوال** السكرى.

مواد وطرق البحث: تم تقسيم الجرذان إلى ٥ مجموعات: المجموعة الضابطة الطبيعية و٤ مجموعات مصابة بداء السكري.وقد تم إحداث مرض البوال السكرى بحقن الجرذان بآلألوكسان حيث تركت المجموعة الأولى المصابة بداء البول السكري دون أي علاج، وتم علاج المجموعة الثانية بالحقن بالإرثروبويتين بجرعة ٣٠٠ وحدة / كجم ٣ مرات في الأسبوع لمدة ٤ أسابيع، وتم علاج المجموعة الثالثة المصابة بمرض البوال السكري بالإكسندين ٤ لمدة بجرعة ١ ميكروجرام/ كجم مرة واحدة يوميا لمدة أسبوع واحد، والمجموعة الرابعة لمرضى البوال السكري من الجرذان تم التعامل معها بالعقارين سويا. وقد أظهرت النتائج أن الإرثروبويتين احدث انخفاضا ذا دلالة إحصائية فى مستوى السكر ومستوى الدهون في الدم، وارتفاعا فى مستوى الإنسولين، والهيموجلوبين، وكرات الدم الحمراء. أما في الجرذان المصابة بداء البوال السكري التى حقنت بالإكسندين ٤ فقد ظهر إنخفاضا إحصائيا لمستوى السكر في الدم والدهون،وعدم تغير فى مستوى الإنسولين مع ارتفاع غير إحصائى فى مستوى القياسات البيولوجية التى ذكرت من قبل، وأظهرت الجرذان مع العقارين سويا أيضا إنخفاضا ذو دلالة إحصائية فى نسبة السكر والدهون في الدم ، وارتفاعا إحصائيا فى نسبه الإنسولين والقياسات البيولوجية الأخرى مقارنه بباقى المجموعات .

الخلاصة: إريثروبويتين وإكسندين-٤ لهما سيطرة جيدة على مستوى السكر والدهون في الدم بالإضافة إلى قيمة إرثروبويتين في تحسين الحالة العامة في الجرذان المصابة بداء السكري.