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EFFECTS OF C -PEPTIDE AND GLUCAGON-LIKE PEPTIDE-1 ON DIABETIC MALE ALBINO RATS WITH AND WITHOUT ANTIOXIDANTS

By

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ABSTRACT

Background: Diabetes mellitus is a major health problem with long-term complications responsible for its mortality and morbidity. Administration of C-peptide improves nervous and renal functions in diabetic patients and animals. Glucagon like peptide-1 is secreted in response to meal. It is able to increase the disposal of glucose under hyperglycemic conditions independent of its effect on insulin or glucagon. An interesting analog is exendin-4.

Objective: Determination of the effects of C-peptide and glucagon-like peptide-1 analogue exendin-4 with and without antioxidants on blood and plasma levels of glucose, insulin, glucagon, lipid profile and malondialdehyde (MDA) in diabetic model of adult male albino rats.

Material and Methods: Seventy adult male albino rats of local strain weighed 150-180 g were used in this study. They were divided into seven equal groups: **Control group (C): R**ats received saline i.p. daily for 4 weeks, **Diabetes group (D_1):** After overnight fasting, rats received a single subcutaneous injection of alloxan monohydrate with glucose by gastric intubation to avoid fatal hypoglycemia, **Diabetes with C-peptide (D_2)** were given alloxan and C-peptide by intraperitoneal injection for 4 weeks, **Diabetes with exendin-4 (**D_3**)** were given alloxan and glucagon-like peptide -1 (GLP-1) analog exendin-4 i.p. for 4 weeks, **Diabetes with C–peptide and exendin-4 (D_4)** were given combined intraperitoneal injection of C-peptide and exendin-4 with alloxan for 4 weeks, **Diabetes with antioxidants (vitamins C & E) (D_5)** received alloxan, vitamin C and vitamin E by gastric intubation for 4 weeks, **Diabetes with C–peptide, exendin-4 and antioxidants (vitamins C & E) (D_6)** received combined C-peptide, exendin-4 and vitamins C and E in by gastric intubation with alloxan for 4 weeks. Blood samples were taken from all groups. Blood glucose, plasma insulin, plasma glucagon, plasma lipid profile, and plasma level of malondialdehyde (MDA) with their relationships to C–peptide and exendin-4 (D_4) treatment with and without antioxidants (vitamins C & E) supplementation were investigated.

Results: Treatment of diabetic rats by C-peptide and exendin-4 caused significant reduction in total cholesterol, triglycerides, LDL, MDA and glucose with elevated insulin and HDL. Treatment of diabetic rats by C-peptide and exendin-4 with antioxidants (vitamins C & E) showed reduction of glucose, cholesterol, LDL and triglycerides with significantly elevated insulin in comparison to diabetic group.

Conclusion: Adding C–peptide to exendin-4 caused significant reduction in total triglycerides, cholesterol, and more reduction of LDL than exendin-4 group. Vitamins C & E improved serum lipid profile and level of MDA as an oxidative stress indicator.

Key words: Diabetes mellitus, alloxan, C–peptide, glucagon-like peptide-1 (GLP-1), exendin-4 and antioxidants.

INTRODUCTION

In addition to insulin and oral hypoglycemics, it is necessary to treat diabetes mellitus with poly therapy including drugs, diet, exercise and other new lines of treatment which are required to cover the variety of symptoms and to prevent future complications ***(Pradhan et al., 2007 and Vaxillaire et al., 2008).***

Cotter et al. (2003) reported that administration of C-peptide improves nervous and renal functions in diabetic patients and animals. These beneficial physiological effects might occur by the action of C-peptide on both Na^+/K^+ ATPase and NO synthase enzymes ***(Wahren et al., 2012)***.

Glucagon like peptide-1 (GLP-1) is usually secreted in response to meal absorption ***(Punjabi et al., 2011). Nishizawa et al. (2003)*** reported that GLP-1 is able to increase the disposal of glucose under hyperglycemic conditions independent of its effect on insulin or glucagon. The physiological dose of GLP-1 might increase the net hepatic glucose uptake ***(Pala et al., 2010).*** It also regulates the β-cell proliferation and cytoprotection ***(Buteau, 2008).***

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).*** So, antioxidants therapy could possibly help diabetic patients and prevent diabetic complications ***(Ziegler et al., 2011).***

The present work was a trial to detect the effect of C-peptide and glucagon-like peptide-1 analogue exendin-4 with and without antioxidants in diabetic male albino rat.

MATERIALS AND METHODS

This study was performed on seventy adult male albino rats of local strain weighing 150-180 g. Rats were housed in isolated animal cages (every 4 rats in a cage 80x40x40 cm). Rats had free access to water and fed on rodent chow diet food all over the period of the work (4 weeks). The rats were kept at room temperature. The rats were divided into seven equal groups:

1. **Control group (C):** Rats received saline i.p. daily for 4 weeks.
2. **Diabetes group (D_1):** After overnight fasting, rats received a single subcutaneous injection of alloxan monohydrate 120 mg/kg of the rat body weight with glucose by gastric intubation to avoid fatal hypoglycemia ***(Maduka et al., 2003).***
3. **Diabetes with C-peptide (D_2)**: Rats were given alloxan and C-peptide 50 nmol/kg/day i.p. for 4 weeks ***(Rebsomen et al., 2006)***.
4. **Diabetes with exendin-4 (D_3):** Rats were given alloxan and GLP-1 analog exendin-4 1 nmol /kg/day i.p. for 4 weeks ***(Park et al., 2007)***.
5. **Diabetes with C–peptide and exendin-4 (D_4):** Rats were given combined i.p. injection of C-peptide and exendin-4 with alloxan.
6. **Diabetes with antioxidants (vitamins C & E) (D_5):** Rats received alloxan, vitamin C (200 mg/kg/day) and 14.4 IU/kg/day of vitamin E by gastric intubation for 4 weeks ***(Paget &***

Barnes, 1964 and Gokkusu et al., 2001).

7. **Diabetes with C–peptide, exendin-4 and antioxidants (vitamins C & E) (D_6):** Rats received alloxan and combined C-peptide, exendin-4, and vitamins C and E by gastric intubation with alloxan for 4 weeks.

Blood samples were taken from all groups and sera were separated for the determination of the fasting levels of:

1. Blood glucose level (mg/dl) by enzymatic calorimetric determination (***Tietz, 1986)***.
2. Plasma level of insulin (?I U / ml) by radioimmunoassay ***(Burrin, 1994)***.
3. Plasma level of glucagon (pg/ ml) by radioimmunoassay (RIA) ***(Saito et al., 1979).***
4. Plasma level of total cholesterol (mg/dl) ***(Allain et al., 1974).***
5. Plasma level of high density lipoproteins (HDL-mg/dl) ***(Groove, 1979).***
6. Plasma level of low density lipoproteins **(**LDL-mg/dl) ***(Friedewald et al., 1972).***
7. Plasma level of triglycerides (mg/dl) ***(Fossati and Prencipe, 1982).***
8. Plasma level of malondialdehyde (MDA- nmol/m) ***(Erdelmeier, 1997).***

Statistical Analysis: All statistical analyses were computed by SPSS version 14. The values obtained were revealed as mean ± S.D. Data were analyzed using student's t-test and results were considered significant at $P < 0.05$. Comparison between groups was done using analysis of variance (1-way ANOVA) followed by Post-HOC test to find inter-group significance.

RESULTS

The blood glucose level (mg/dl) in groups D_2: (277.2± 90.49), D_3 (210.7± 90.98), D_4 (331± 73.27) and D_6 (265.20± 16.63) was significantly higher than that of the control group (C) (76.4± 9.42), while significantly lower than that of the diabetic group D_1 (384.30± 34.31) except diabetic with antioxidants vitamins C & E (D_5) group (356.5± 36.12), which was insignificantly lower than D_1.

The plasma insulin level (?I U / ml) in groups D_2 (14.94± 0.78), D_3 (16.83± 1.82), D_4 (14.97± 1.09), D_5 (11.23± 0.72) and D_6 (15.42± 0.99) was significantly lower than that of C (30.18± 4.77), while that of the D_1 (7.28± 2.37) was significantly lower than that of all other groups.

The plasma glucagon level (pg/ ml) groups D_3 (74.57± 3.84) and D_6 (75.24± 7.56) was insignificantly lower than that of the C (76.92±4.16), and significantly higher than D_1 (70.65± 6.18). In the group D_2 (66.77± 2.370), it was significantly lower than that of D_1. Groups D_4 (72.2± 3.19) and D_5 (71.94± 3.32) showed insignificant differences compared to D_1.

The plasma cholesterol level (mg/dl) in groups D_2 (115.7± 10.83), D_3 (114.6± 15.65), D_4 (109± 6.63), D_5 (122.1± 9.49) and D_6 (115.30± 5.12) was significantly higher than that of C (96.5± 7.01), while significantly lower than D_1 (131.50± 5.54) which was significantly higher than that of all other groups.

The plasma HDL level (mg/dl) in groups D_3 (37.1± 2.02), D_4 (37.0± 3.95), D_5 (36.9± 2.38) and D_6 (37.20± 1.55) was

significantly lower than that of C (39.9± 2.38), while HDL level of D_1 (33.60± 3.06) was significantly lower than that of other groups except D_2 (33.5± 3.14) where it showed insignificant difference when compared to D_1.

The plasma LDL level (mg/dl) in all groups was significantly higher than that of C (37.95± 9.99), while LDL level of D_1 (74.36± 3.52) was significantly higher than that of groups D_2 (60.61± 8.78), D_3 (65.64± 9.83), D_4 (61.25± 8.53) and D_6 (66.12± 4.77), while D_5 (72.05± 11.25) showed insignificant difference when compared to D_1.

The plasma triglyceride level (mg/dl) in groups D_2 (106.7± 9.48), D_4 (93± 5.85), D_5 (100± 7.16) and D_6 (97.90± 7.02) was significantly higher than that of C (98.9± 9.53), while that of the D_1 (119.30± 10.41) was significantly higher than that of other groups except D_3 (117.7± 11.83) where it showed insignificant difference when compared to D_1.

The plasma MDA level (nmol/m) in groups D_2 (12.7± 1.83), D_3 (12.5± 0.85), D_4 (12.6± 1.35), D_5 (12.9± 1.45) and D_6 (12.90± 1.52) was significantly higher than that of C (6.5± 0.85), while that of D_1 (19.40± 1.51) was significantly higher than that of all other groups.

Table (1): ANOVA changes of each parameter for different groups (Mean ± SD).

Groups / Parameters	Control (C)	(D1)	(D2)	(D3)	(D4)	(D5)	(D6)	ANOVA	
								F	P Value
Glucose (mg/dl)	**76.4± 9.42**	**384.30± 34.31**	**277.2± 90.49**	**210.7± 90.98**	**331± 73.27**	**356.5± 36.12**	**265.20± 16.63**	**30.87**	P<0.05.
Insulin (?IU / ml)	**30.18± 4.77**	**7.28± 2.37**	**14.94± 0.78**	**16.83± 1.82**	**14.97± 1.09**	**11.23± 0.72**	**15.42± 0.99**	**13.58**	P<0.05.
Glucagon (pg/ ml)	**76.92± 4.16**	**70.65± 6.18**	**66.77± 2.37**	**74.57± 3.84**	**72.2± 3.19**	**71.94± 3.32**	**75.24± 7.56**	**12.93**	P<0.05.
Cholesterol (mg/dl)	**96.5± 7.01**	**131.50± 5.54**	**115.7± 10.83**	**114.6± 15.65**	**109± 6.63**	**122.1± 9.49**	**115.30± 5.12**	**17.30**	P<0.05.
HDL (mg/dl)	**39.9± 2.38**	**33.60± 3.06**	**33.5± 3.14**	**37.1± 2.02**	**37.0± 3.95**	**36.9± 2.38**	**37.20± 1.55**	**95.98**	P<0.05.
LDL (mg/dl)	**37.95± 9.99**	**74.36± 3.52**	**60.61± 8.78**	**65.64± 9.83**	**61.25± 8.53**	**72.05± 11.25**	**66.12± 4.77**	**5.10**	P<0.05.
Triglycerides (mg/dl)	**98.9± 9.53**	**119.30± 10.41**	**106.7± 9.48**	**117.7± 11.83**	**93± 5.85**	**100± 7.16**	**97.90± 7.02**	**19.81**	P<0.05.
MDA (nmol/m)	**6.5± 0.85**	**19.40± 1.51**	**12.7± 1.83**	**12.5± 0.85**	**12.6± 1.35**	**12.9± 1.45**	**12.90± 1.52**	**73.16**	P<0.05.

DISCUSSION

The present study demonstrated the protective effects of C-peptide with exendin-4 and antioxidants against the risks of diabetes and its complications in male rats.

All groups injected by alloxan showed significant higher level in the blood glucose in comparison to control group (C). These results were in agreement with ***Green and his Co-workers (2004)*** who mentioned that reactive oxygen species produced by alloxan administration causes breakdown of DNA strands, resulting in β-cell damage.

The results of glucose with C-peptide were in agreement with ***Nordquist et al. (2007)*** who reported that C-peptide given to diabetic rats resulted in reduced blood glucose levels. This effect of C-peptide on blood glucose has previously been described by ***Sato et al. (2004)*** as they referred this action to improved glucose utilization, renal function and capillary diffusion capacity in type I diabetic patients. ***Meyer et al. (2008)*** reported that C-peptide facilitates glucose clearance and the release of a nitric oxide stimulus via the GLUT1 transporter. The results of this work were compatible with those of ***Chailurkit et al. (2007)*** who stated that C-peptide could enhance the function of β-cell to secrete insulin. ***Shafqat et al. (2006),*** after studying the rat pancreas, reported that C-peptide effects seem to mimic some of insulin–stimulating effects on glycogen synthesis and amino acid uptake. Therefore, it might play a role in insulin secretion through auto–feedback mechanism activating the insulin-signaling pathway.

Insulin and/or C-peptide and glucagon dominance over each other might be due to feedback mechanism, i.e. when insulin and/or C-peptide increase, glucagon decreases and vice versa ***(Ciell 2008).*** The results of this work were compatible with those of ***XU et al. (2006)*** who reported that insulin, and hence C-peptide, suppresses glucagon release. The results of this work were also compatible with those of ***Sima et al. (2004)*** who reported that C-peptide circulates at plasma concentrations five times higher than that of insulin. Therefore, by feedback inhibition, C– peptide depresses the plasma glucagon level.

The results of glucose, insulin and glucagon with exendin-4 were in agreement with ***DeFronzo et al. (2005)*** who correlated that the chronic administration of exendin-4 in diabetic animals, with significant lowering of the blood glucose, similarly to that observed in diabetics with other lines of therapy. ***Gonzalez and Gagliardino (2009)*** concluded that exogenous administration of incretin which is GLP-1 receptor agonist enhances insulin hormone secretion. The results of this work were also compatible with those of ***Holst and Orsokov (2004)*** who reported that 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 adminis-trated to the diabetics. Consequently, exendin-4 might be practically effective in prevention or even cure of diabetes mellitus ***(Kim and Egan, 2008).*** Many studies indicate that GLP-1 and its long-acting agonist exendin-4 stimulate the proliferation and differentiation of stem

cells into pancreatic β-cell ***(Buteau, 2008).***

An indirect mechanism for the inhibition of glucagon secretion by exendin-4 is through release of endogenous somatostatin which acts on pancreatic α-cells to inhibit glucagon secretion ***(De Heer et al., 2005). Nauk and Meier (2005)*** reported that the inhibition of glucagon secretion is glucose dependent, i.e. when glucose is not high, enough glucagon is not reduced. ***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.

The glucose level was significantly higher in D_4 than C-peptide D_2 and exendin-4 D_3. The insulin hormone level of the rats treated by C-peptide with exendin-4 was nearly equal to the rats treated by C-peptide D_2. It seemed from this work that C-peptide suppresses the effect of exendin-4 on glucose and insulin hormone level when used simultaneously.

The glucagon hormone level in D_4 was significantly lower than that of exendin-4 (D_3) group and higher than that of C-peptide (D_2) group. It seemed that they both slightly interfere with each other regarding glucagon hormone level in comparison to diabetic group. However, they depress the glucagon hormone level in comparison to control group which were compatible with ***Ciell (2008).***

Alloxan-induced diabetes mellitus elevated levels of cholesterol, triglycerides and LDL, while it depressed level of HDL.This was compatible with that of ***Irshaid et al. (2012)*** who revealed that diabetes mellitus lead to elevated plasma levels of cholesterol, triglycerides and LDL, while depressing level of HDL.

The results of lipid profile with C-peptide were in agreement with ***Hills and Brunskill (2009)*** as they demonstrated the presence of physiological protective role of C-peptide when administered to individuals with type I diabetes mellitus. It seemed that C-peptide bind in nanomolar concentrations to a cell surface receptor which is most likely to be G-protein coupled. Binding of C-peptide initiates multiple cellular effects, evoking a rise in intracellular calcium, stimulation of the $Na/^{+}K^{+}$-ATPase and increased endothelial nitric oxide synthase (eNOS) transcription. These observations raise the possibility that C-peptide may serve as a potential therapeutic agent for the treatment or prevention of long-term complications associated with diabetes mellitus including dyslipidemia. This effect is due to up-regulation of endothelial NOs gene transcription by C-peptide which appeared to be dependent on the upstream phosphorylation and activation of extracellular signal-regulated mitogen activated protein kinase.

The reduction in the plasma total cholesterol, LDL and triglycerides levels and elevation of the HDL by chronic administration of exendin-4 in diabetics was previously reported by ***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 acids levels and it caused a significant change in total cholesterol. They also reported that exendin-4 possibly produce its lipid lowering effect through reduced produc-

tion of intestinal triglycerides rich particle after fat rich meal and/or augmentation of lipid mobilization and oxidation.

One of the most effective mechanisms for the lipid lowering effect of exendin-4 in diabetics is through increased insulin secretion. The increased insulin suppresses lipolysis with decrease in triglycerides ***(Meier et al., 2006).*** In addition, depressed glucagon may contribute to the significant reduction of free fatty acids ***(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 acids.

Using C-peptide alone was nearly equal to using C-peptide and exendin-4 regarding decreasing LDL level. As LDL was insignificantly lower in C-peptide group than exendin-4 with C-peptide group, the action of C-peptide predominated regarding plasma LDL level. The use of both exendin-4 with C-peptide was significantly better regarding lowering of cholesterol and triglycerides than using either exendin-4 or C-peptide alone. The results of this work were compatible with those of ***Wu et al. (2012)*** who reported that exendin-4 and C-peptide stimulate insulin secretion and significantly reduce glucose level.

Armstrong et al. (2006) stated that the reduced lipid peroxidation and improved antioxidant status may be one mechanism by which treatment with vitamins C & E contributes to the prevention of diabetic complications. ***Abdel-sattar (2004)*** stated that diabetic rats receiving antioxidants (vitamins C, E and zinc) encountered a significant reduction of blood glucose, cholesterol and triglycerides with significant elevation of HDL-C.

There was no significant statistical difference between use of C-peptide with exendin-4 only and with antioxidants (vitamins C & E) regarding HDL in this work. Using C-peptide with exendin-4 significantly reduced plasma cholesterol, LDL and triglycerides levels than with antioxidants D_6 group. ***Parildar et al. (2008)*** reported that antioxidants (vitamins C & E) effect on lipid profile of rats increase as long as the study period. ***Sethi et al. (2012)*** also reported that alloxan causes liberation of oxygen radicals such as $O2^-$, H2O2 and MDA, with reduction in the antioxidant status.

The results of MDA with C-peptide were compatible with ***Hills and Brunskill (2009)*** who have demonstrated an up-regulation of endothelial nitric oxide synthase (NOs) gene transcription by C-peptide. This effect appeared to be dependent on the upstream phosphorylation and activation of extracellular signal-regulated mitogen activated protein kinase.

The results of MDA with exendin-4 were compatible with those of ***Cai et al. (2012)*** who reported that exendin-4 significantly inhibits the elevation in MDA level induced by high glucose as well as it suppresses the decrease in SOD level. Also, ***Briyal et al. (2012)*** reported that exendin-4 protects the CNS from damage due to cerebral ischemia by reducing oxidative stress.

The results of using MDA with antioxidants were in accordance with ***Armstrong et al. (2006)*** who stated that reduced lipid peroxidation revealed by reduced MDA and improved antioxidant

status may be one mechanism by which dietary treatment in the form of vitamins C, E contributes to the reduction of MDA level and prevention of diabetic complications. ***EL-Seady and EL-Deeb (2012)*** concluded that vitamins C & E treatment may potentiate insulin action on lipid peroxidation in diabetic dogs and so lower serum MDA. The results of this work were also compatible with those of ***Naziroglu and Butterworth (2005)*** as they reported that vitamins C & E could help lowering the markers indicative of oxidative stress and lipid peroxidation in diabetic subjects and animals.

There was no significant statistical difference between the five different lines of therapy regarding MDA level in this work. Hence, there was no apparent interaction between C-peptide and exendin-4 with and without antioxidants (vitamins C & E) regarding action on MDA plasma level.

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خلفية البحث: يعد مرض البوال السكري مشكلة صحية هائلة تتسبب في الإعتلال والموت. ويفرز السي بيبتيد مع الإنسولين ولديه العديد من الخصائص الفسيولوجية والبيوكيميائية الخاصة به. وتناول السي بيبتيد يحسن وظائف الكلى والجهاز العصبي في مرضى السكري والحيوانات. ويفرز الببتيد -١ شبيه الجلوكاجون طبيعيا بعد وجبة الطعام ولديه القدرة على التخلص من زيادة الجلوكوز في ظل ظروف فرط سكر الدم مستقلة عن تأثيره على الإنسولين أو الجلوكاجون. ويعد عقار إكزندين-٤ مناظرا ومماثلا مهما ل الببتيد -1 شبيه الجلوكاجون.

الهدف من البحث: تبحث هذه الدراسة تأثير عقار سي بيبتيد والببتيد -1 شبيه الجلوكاجون بمفردهما أو متحدين مع وبدون فيتامينات ج و هـ على المماثل الحيواني لمرض السكري.

مواد وطرق البحث : إسُتخدم في هذا البحث سبعون فأرا ذكرا من سلالة محلية أبيض تتراوح أوزانها بين ١٥٠-١٨٠جراما، وقد تم تقسيم الفئران إلى سبعة مجموعات متساوية: المجموعة الضابطة: تلقت محلولاً ملحياً عن طريق الحقن داخل الغشاء البريتوني / يوميا لمدة 4 أسابيع، مجموعة السكري: تلقت حقناً تحت الجلد 120ملغ / كغ من وزن الجسم بالألوكسان مع الجلوكوز لتفادي نقص السكر في الدم المميت للحيوانات.

مجموعة السكري والسي بيبتيد: تلقت آلوكسان ٥٠ نانومول / كغ / يوم من السي بيبتيد عن طريق الحقن داخل الغشاء البريتوني يوميا لمدة ٤ أسابيع، مجموعة السكري والببتيد -١ شبيه الجلوكاجون: تلقت آلوكسان و إكزندين -٤المناظر للببتيد -١ شبيه الجلوكاجون بجرعة ١ نانومول / كغ / يوم عن طريق الحقن داخل الغشاء البريتوني يوميا لمدة ٤ أسابيع ، مجموعة السكري، السي بيبتيد و الببتيد-١ شبيه الجلوكاجون: تلقت آلوكسان، السي بيبتيد و إكزندين-٤، مجموعة السكري مع مضادات الأكسدة: تلقت آلوكسان وفيتامين ج 200ملغ / كغ / يوم و ٨٠٠ وحدة دولية / كغ / يوم من فيتامين

هـ في مياه الشرب يوميا لمدة ٤ أسابيع، مجموعة السكري، السي بيبتيد والببتيد - ١ شبيه الجلوكاجون مع مضادات الأكسدة: تلقت آلوكسان والسي بيبتيد و إكزندين - ٤والفيتامينات ج و هـ .

وفي نهاية فترة التجربة (٤ أسابيع) تم قياس المعايير التالية: مستوى الجلوكوز في الدم، الإنسولين في البلازما، الجلوكاجون في البلازما، الكوليسترول الكلي في الدم، الدهون عالية الكثافة في الدم، الدهون منخفضة الكثافة في الدم، الدهون الثلاثية في الدم وإنزيم المالون داي ألداهيد بالدم.

النتائج: تسببت معالجة الفئران المصابة بداء السكري بالسي بيبتيد مع إكزندين - ٤ في إنخفاض في الكولسترول الكلي والدهون الثلاثية بنسبة دالة إحصائيا كما زاد مستوى الدهون عالية الكثافة والإنسولين بنسبة دالة إحصائيا بالمقارنة مع مجموعة السكري بينما لم يؤثر الجمع بين العقارين على مستويات الجلوكوز والجلوكاجون مقارنة بمجموعة السكري. وقد أدى علاج الفئران المصابة بداء السكري بعقاقير السي بيبتيد وإكزندين - ٤ ومضادات الأكسدة إلى خفض نسبة الجلوكوز والكوليسترول والدهون منخفضة الكثافة والدهون الثلاثية والمالون داي ألدهيد مع إرتفاع الإنسولين بشكل دال إحصائيا بالمقارنة مع مجموعة السكري.

الإستنتاج: تسببت معالجة الفئران المصابة بداء السكري بالسي بيبتيد مع إكزندين - ٤ في إنخفاض في الكولسترول الكلي والدهون الثلاثية بنسبة دالة إحصائيا بالمقارنة مع مجموعة إكزندين - ٤، كما تَحسن فيتامينات ج و هـ من مستوى الدهون، وأيضا مستوى المالون داي ألداهيد كمؤشر الأكسدة.