The effect of melatonin on adrenal gland and pancreas function in alloxan – induced diabetes in adult female rabbits

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Summary

The present study was carried out to investigate the ameliorative effect of melatonin on pancreatic and adrenal dysfunction induced by alloxan in adult female rabbits. Twenty four adult female rabbits were randomly divided into four equal groups treated for 42 days as follows: control group received 2 ml of distal water intraperitoneally, animals of the second group received single dose of 150 mg /kg of alloxan (group T1), while the third group received single dose of 150 mg/kg of alloxan and after 7 days received 10mg/kg I/P of melatonin for 42 days of experiment (T2 group). The fourth group received 10 mg/kg I/P of melatonin for 42 days .After the 7 days of alloxan injection the blood is collected from (T1) and (T2) animals, to investigate of diabetes induction in these groups. Also blood samples were collected at zero time, 14, 28 and 42 days of the experiment for measuring the serum concentration of glucose, total protein, total cholesterol, reduce glutathione and hormones concentration (insulin and cortisol). The result of present study indicated that melatonin administration is not affected in body weight in rabbits to T2 and T3 as compared with control group, while (T1) group showed significant decrease in these parameters as compared with other groups. The adrenal gland weight to body weight ratio showed significant increase in adrenal weight in (T1) as compared with all other group while T2 and T3 groups showed significant decrease as compared with T1 groups. While the pancreas gland weight to body weight ratio showed significant increase in pancreas weight in (T3) group as compared with other groups. Animals T1 and T2 groups showed significant decrease as compared with T3 and control groups. Animals T1 group showed significant elevation in serum glucose, total cholesterol and serum cortisol concentration as compared with control, T2 and T3 groups. The results also showed a significant decrease in total serum protein, serum insulin and reduce glutathione concentrations in alloxan treated group (T1) as compared with control, T2 and T3 animals. Inferred from the result of this experiment is treatment of diabetic female rabbits with melatonin (10 mg /kg .B.W) for 42 days lead to improve the function of adrenal gland and pancreas gland. Also it showed the possibility of reducing oxidative stress triggered by alloxan through the use of melatonin.

Keywords: Melatonin, Diabetes, Alloxan, Pancreas, Adrenal gland.

Introduction

Diabetes Mellitus is a chronic metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin action or insulin production or both. Diabetes mellitus is largely prevalent almost in all countries and persists to elevate in numbers and significance (1-3). The Diabetes mellitus can be induced chemically in experimental animal by using alloxan (4). It is very famous as diabetogenic agent for using in induction Type I diabetes in experimental animals (5). Alloxan is urea derivative which causes selective necrosis in the pancreatic B – cell of islet. The cytotoxic effect of alloxan on pancreatic beta cells is made by several mechanism including the generation of free radicals (6 and 7). The study antioxidant effects of melatonin on adrenal gland and pancreas function in case of diabetes mellitus type 1 is largely unknown, and considered as first study in Iraq. Therefore, this experiment designed to demonstrate the role of melatonin in suppression of oxidative stress of alloxan-induced diabetic in adult rabbits female.

Materials and Methods

Twenty four female rabbits were divided randomly into four equal groups. Control group: they were received 2cc of distal water for 42 days i/p, group T1: rabbits were received single dose of alloxan monohydrate (150 mg/kg B.W) i/p for diabetic induction

(8), third group (Alloxan – melatonin) group T2: received single dose of alloxan monohydrate (150 mg/kg B.W) i/p, after 7 days were received (10mg/kg B.W) of melatonin for 42 days and group T3: they were received (10 mg/kg B.W) of melatonin for 42 days (9 and 10). The blood samples were collected at zero, 14, 28 and 42 days of experiment, the blood were uptake via cardiac puncture technique, then samples were centrifuged at 3000 rpm for 15 minute to obtain serum stored in 20 °C. The serum was used for determination the concentration of glucose, cholesterol, total protein using enzymatic kits (Biosystem, Spain), cortisol using enzymatic kit (Human, Germany), insulin using Insulin ELIZA kit (Sigma, USA) and reduced glutathione according to (11).

Results and Discussion

The results in (Table, 1) showed non-significant decrease of body weight in the alloxan treated group (T1) as compared with the control group at all period of experiment except at days 42 the T1 showed significant ($P<0.05$) decrease in body weight as compared with control and two treated group (T2 and T3) also results showed that melatonin caused increased in body weight as compared with alloxan group (T1) but not reach the significant degree. In all groups, there were no significant differences ($P>0.05$) in total serum protein concentration at zero time (Table, 4). While at other periods of experiment, T1 group (alloxan treated group) showed significant ($P<0.05$) decrease in total protein as compared with control and T3 group. On other hand, at 28 and 42 days of experiment the T2 (alloxan – melatonin group) exhibited significant ($P<0.05$) decrease in total protein as compared with control and T3 group. At days 14 and 28 of experiment, there were significant ($P<0.05$) increase in T3 (melatonin treated group) as compared with (T1and T2 group) and non -significant increase as compared with control groups.

Table, 1: Effect of alloxan and melatonin on body weight (g) in female rabbits.

Group Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	1592.14±38.33 A a	1583.28±105.03 A a	1561.65±48.50 A a	1550.50±40.16 A a
14 day	1561.14±34.40 A a	1467.50±89.68 A a	1518.15±42.71 A a	1539.50±39.33 A a
28 day	1533.50±34.09 A a	1408.32±81.98 A a	1500.65±40.46 A a	1546.65±39.18 A a
42 day	1516.18±33.1247 A a	1287.50±92.50 B b	1509.28±40.92 A a	1573.50±40.47 A a

-L.S.D = 151.3

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group ($P<0.05$). The different small letters denote significant differences within group ($P<0.05$).

In (Table, 2) the results showed significant ($P<0.05$) increase in serum glucose concentration in the alloxan treated group (T1) as compared with the control group at all period of experiment, also the T1 group showed significant ($P<0.05$) increase in serum glucose, as compared with (T2 and T3 group) at all period of experiment except at zero time. While in T2 group there were a significant increase in serum glucose concentration as compared with the control group and T3 at 14 and 42 days of experiment and no significant differences ($P>0.05$) at (zero time and day 28). T2 showed significant decrease in serum glucose as compared with alloxan treated group (T1). Furthermore, the T3 group (melatonin treated group) showed significant decrease in serum glucose concentration as compared with T1 group at all period of experiment.

There was a significant ($P<0.05$) increase in serum cholesterol concentration in T1 group as compared with control and T3 group. At day 42 there were significant ($P<0.05$) increase in serum cholesterol in alloxan treated group (T1) as compared with all other groups. The alloxan – melatonin treated group (T2) showed significant ($P<0.05$) decrease as compared to alloxan treated group (T1) at days 28 and 42 while exhibited significant increase as

compared to (T3 group). Whereas melatonin treated group (T3) showed significant decrease in serum cholesterol concentration as compared with T1 and T2 groups all periods except zero day. Within the time there was a significant (P<0.05) increase in this parameter in T1 group at 14, 28 and last period of experiment as compared with zero time (Table, 3). The results also showed a significant (P<0.05) decrease in total serum protein concentration in T1 and T2 groups as compared with control and T3 group. At day 42 there were significant (P<0.05) decrease in total serum protein in alloxan treated group (T1) as compared with all other groups. The alloxan treated group (T1) showed significant (P<0.05) decrease as compared to alloxan – melatonin treated group (T2) at days 28 and 42 (Table, 4).

Table, 2: Effect of alloxan and melatonin on serum glucose (mg/dl) in female rabbits.

Group / Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	132.67±2.71 A a	141.35±1.44 A d	141.41±5.62 A b	140.75±10.83 A a
14 day	131.65±2.89 C a	224.70±3.79 A c	175.20±4.11 B a	137.82±7.24 C a
28 day	128.90±2.70 B a	251.66±5.11 A b	125.65±9.99 B c	121.57±5.38 B b
42 day	130.91±3.49 C a	278.91±4.56 A a	147.31±3.67 B b	115.75±5.02 D c

L.S.D = 14.1

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

Table, 3: Effect of alloxan and melatonin on serum cholesterol concentration (mg/dl) in rabbits.

Group / Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	55.91±1.61 A a	56.50±1.75 A c	58.37±2.59 A c	54.75±3.14 A a
14 day	56.82±2.14 B a	108.95±4.59 A b	101.70±3.24 A a	53.15±1.07 B a
28 day	55.32±1.62 C a	113.07±4.16 A ab	77.15±3.83 B b	52.08±2.33 C a
42 day	57.50±1.75 C a	120.30±3.05 A a	71.92±2.84 B b	49.65±1.30 D a

L.S.D = 7.5

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

Table, 4: Effect of alloxan and melatonin on total serum protein (g/dl).

Group / Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	64.00±1.70 A a	60.65±3.01 A a	60.17±1.35 A a	63.37±1.98 A c
14 day	66.15±1.54 AB a	55.65±2.26 C ab	61.25±1.28 B a	69.23±3.24 A bc
28 day	67.32±3.91 A a	51.82±1.12 B b	58.15±3.06 B ab	73.62±1.11 A ab
42 day	64.75±2.83 B a	40.52±1.95 D c	54.82±4.08 C b	76.61±0.83 A a

L.S.D = 6.5

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

Results in (Table, 5) illustrate a significant (P<0.05) decrease in serum reduced glutathione concentration in T1 group which treated with alloxan in comparison with control and other two treated groups (T2 and T3) group but melatonin treatment caused

significant (P<0.05) increase in reduce glutathione (T2 group) as compared with (T1 group). While, T3 animals which treated with melatonin only showed significant (P<0.05) increase in reduce glutathione in comparison with T1 and T2 groups, and the concentration tended closely to control group. Also there was significant decrease within T1 group and significant (P<0.05) increase within T3 group at all periods of experiment as compared with zero time. Alloxan caused a significant increase (P<0.05) in serum cortisol concentration in group T1 at day 14 until the end of experiment as compared with control group. While treatment of animals with melatonin beside alloxan (T2 group) and melatonin alone (T3 group) caused significant (P<0.05) decrease of cortisol concentration especially at 28 and day 42 as compared with other groups (Table, 6). There were a significant increase of serum cortisol concentration of T1 group at all periods as compared with zero time, while there were a significant (P<0.05) decrease within T3 group at the end of experiment as compared with other periods.

Table, 5: Effect of alloxan and melatonin on serum reduced glutathione concentration (µmol/l)

Group Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	48.16±1.86 A a	48.00±2.88 A a	48.50±1.65 A a	48.50±2.53 A b
14 day	49.16±1.98 A a	30.33±2.66 C b	34.66±2.60 B c	51.16±3.27 A ab
28 day	51.66±2.15 A a	26.82±2.24 C c	39.00±2.17 B b	54.50±2.39 A a
42 day	51.80±0.786 A a	27.00±2.09 D c	36.83±2.50 B b	53.83±3.73 A a

L.S.D = 2.9

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

At 14, 28 and day 42 of experiment T1 treated group showed a significant (P<0.05) decrease in insulin concentration as compared with control group and (T2 and T 3) group (Table, 7). While T2 (melatonin + alloxan group) showed significant (P<0.05) increase in insulin concentration as compared with alloxan treated group (T1). Furthermore, T3 (melatonin treated group) exhibited non-significant differences at all period as compared with control group.

Table, 6: Effect of alloxan and melatonin on serum cortisol (m.mol/l) in rabbits

Group Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	18.99±1.11 A b	19.20±.=0.89 A d	19.32±.86 A b	19.67±0.82 A a
14 day	20.93±1.46 B ab	25.03±1.40 A c	22.02±1.06 AB b	18.17±0.57 B a
28 day	19.37±1.52 C ab	31.75±1.66 A b	26.38±0.83 B a	15.50±1.36 D ab
42 day	22.33±1.61 C a	37.67±1.64 A a	29.38±0.83 B a	12.51±1.02 D b

L.S.D =3.5

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

At the end of experiment the results showed significant increase (P<0.05) in ratio of adrenal gland weight to body weight in group T1 as compared with all other group. T2 and T3 showed significant (P<0.05) decrease as compared with T1 group. While the result showed a significant increase (P<0.05) in this parameter in both group (T1 and T2) as compared with control group (Table, 8).

Table, 7: Effect of alloxan and melatonin on serum insulin (µÚ) in rabbits.

Group / Time	Control group	(T1) group	(T2) group	(T3) group
Zero time	52.68±1.77 A a	58.94±3.76 A a	56.34±2.88 A a	58.79±1.69 A a
14 day	56.68±2.98 A a	41.94±2.91 C b	49.57±3.13 B a	57.10±1.40 A a
28 day	58.79±3.27 A a	35.00±1.87 C b	42.75±3.51 B b	57.97±1.62 A a
42 day	56.89±4.15 A a	27.99±1.86 D c	35.31±0.85 B b	56.98±1.31 A a

L.S.D = 7

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

The pancreas gland weight to body weight ratio showed significant increase (P<0.05) in in T3 group as compared with all other group (Table, 9). Whereas T1 and T2 showed significant decrease as compared with T3 group and control group.

Table, 8: Effect of alloxan and melatonin on adrenal gland weight to body weight (g) in rabbits.

Group / Time	Control group	(T1) group	(T2) group	(T3) group
42 day	1.22±2.50 C	1.65±1.55 A	1.32±4.78 B	1± 4.08 D

L.S.D = 0.002

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

Table, 9: Effect of alloxan and melatonin on pancreas weight to body weight (g).

Group / Time	Control group	(T1) group	(T2) group	(T3) group
42 day	0.130±0.031 B	0.112±0.012 C	0.113±0.001 C	0.133±0.003 A

L.S.D =0.0012

T1: group given single dose of alloxan 150 mg/kg B.W., T2 = given alloxan(150mg/ kg.B.W) and melatonin 10 mg /kg . B.W i/p, T3: given melatonin (10 mg /kg B.W i/p. The different capital letters denote significant differences between group (P<0.05). The different small letters denote significant differences within group (P<0.05).

Weight loss which is one of the clinical features of diabetes mellitus may be due to the degeneration of the adipocytes and muscle tissues to make up for the energy lost from the body due to frequent urination and over conversion of glycogen to glucose. Weight loss is a very serious issue in the management of diabetes mellitus (12). There were no changes in the body weight of rabbits in all groups except in T1 group, this might be explained by the fact that exogenous melatonin causes no effect on the overall body weight in rats (13 and 14). This is probably because the food intake does not affected by melatonin administration (15). But others studies showed that melatonin was effective in the improving the food intake, body weight gain, serum total protein and albumin in the rats fed an ochretoxin A contaminated diet (16). High blood glucose, as the main features of diabetes, effects on all body systems (17). The increase in the serum glucose concentration in diabetic rabbits is agreement with (18 and 19).

In the present study, elevated serum glucose was decreased with dietary melatonin supplementation. Similar effects of different antioxidants on the glucose metabolism have been reported (20). Various studies showed that the stress led to increase total serum cholesterol (21). Melatonin inhibits cholesterol absorption across the intestinal epithelium and by increasing the conversion of cholesterol to bile acids (22). The antihyperlipidimic actions of MT has been several reports showed that type 1 and type 2 diabetes-induced hyperglycemia augment the levels of cholesterol, triglycerides, LDL and VLDL, and diminishes the level of HDL (23). The free

radical leads to inhibit protein synthesis by weakening the beginning of the peptide chain and by preventing the production of peptide chains in ribozomes (24). Free radicals may also be implicated in the observed decline in protein content since exposure to the free radicals leads to protein fragmentation, protein peroxides generation, enzymatic oxidation and degradation of proteins (25).

The total protein decreased significantly in alloxan - diabetic rats (26). The decrease in total protein concentrations in the serum of diabetic rats may be ascribed to (i) a decreased amino acid uptake (27) (ii) a greatly decreased concentration of a variety of essential amino acids (28) and (iii) an increased conversion rate of glycogenic amino acid to CO2 and H2O (29). Treatment with melatonin ameliorated the decline in the plasma protein content probably by scavenging the free radicals and improving the antioxidative status and in turn the process of protein synthesis.In liver melatonin administration leads to the rise in the activities of three enzymes of glutathione metabolism: c-glutamylcysteine synthetase, glutathione reductase and glutathione peroxidase, affecting both GSH content and GSH/GSSG ratio (30). Melatonin induced enhancement of liver c-glutamylcysteine synthetase activity might also be responsible for elevated blood GSH content observed in melatonin-treated diabetic rabbits.

In patients with diabetes, autonomic nervous system imbalance leads to increased activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, and consequently hypercortisolism and adrenocortical growth. These alterations are probably due to reduced relative feedback sensitivity to glucocorticoids in different parts of the axis, changes in 11-beta hydroxysteroid dehydrogenase (11B-HSD) enzyme activity, and increased expression of corticotropin-releasing hormone in hypothalamus (31). In this regard, it has been shown that there is an increase in cortisol secretion and adrenocortical hypertrophy in type 2 diabetic patients who suffer parasympathetic neuropathy, compared with type 1 diabetics with sympathetic neuropathy (32). Thus, it seems that the degree of HPA axis dysfunction in diabetic patients is associated with the damage of neuronal pathway of the HPA axis and weakening response of glucocorticoids negative feedback (33). In Alloxan diabetic rabbits, the blood glucose levels are raised due to permanent destruction of pancreatic B cells, moreover, the serum insulin levels are decreased in Alloxan diabetic rabbits due to destruction of pancreatic B cells (34). The decrease in insulin level is clearly related to induction of diabetes due to necrosis of B cells of pancreatic islets by the cytotoxin alloxan. A decrease in insulin level in chemically induced diabetes was reported in animal models (35).

The adrenal gland hypertrophy-hyperfunction that accompanies early experimental diabetes has been well documented (36 and 37), and there is further evidence for a role for insulin-like growth factor I (IGF-I) in adrenal cell function and steroidogenic response from studies on cultured bovine adrenal fasciculata cells (38). The increased pancreas weight provides an indirect evidence for the increased IGF concentration. This is hypothesized with the reports of increased levels of IGF after exogenous melatonin administration (39). IGFs have been implicated in general growth, definite role in pancreas development. IGF -1 signaling can bring about antiapoptosis, protein synthesis, cell growth and mitogenesis (40). These properties of IGF are definitely the reason behind the increased weight of pancreas.

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تأ ثير الميلاتونين في وظيفة الغدة الكظرية والبنكرياس في إناث الأرانب البالغة المصابة بالسكري المستحدث بالالوكزان

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الخلاصة

صمّمت هذه التجربة لمعرفة تاثير الميلاتونين للحد من الإجهاد التأكسدي للآلوكسان على وظيفة غدة البنكرياس والغدة الكظرية في إناث الأرانب البالغة. استعمل (24) من إناث الأرانب البالغة وقسمت عشوائياً إلى أربع مجاميع متساوية وعوملت لمدة 42 يوم كالآتي: حيوانات مجموعة السيطرة جرعت 3 مل من الماء المقطر حقنا بداخل غشاء الخلب يوميا ولمدة 42 يوم. حيوانات المجموعة الثانية (T1) حقنت 150 ملغم/كغم من المحلول المائي للالوكزان داخل غشاء الخلب بواقع جرعة واحدة، حيوانات المجموعة الثالثة (T2) حقنت بجرعة واحدة من 150 ملغم / كغم من آلوكسان داخل غشاء الخلب وبعد 7 أيام أعطيت 10 ملغم/

كغم داخل غشاء الخلب من الميلاتونين لمدة 42 يوما من التجربة أما المجموعة الرابعة فقد أعطيت 10 ملغم / كغم من الميلاتونين لمدة 42 يوم داخل غشاء الخلب. حُسِبَتْ أوزان الحيوانات وسُحِبَتْ عينات الدم من القلب في الأيام (0 و14 و28 و42) من مدة العلاج لغرض حساب المعايير الآتية في مصل الدم: الكولسترول، الكلوكوز، البروتين، كلوتاثيون، هرموني الانسولين والكورتزول. في نهاية التجربة تم التضحية بالحيوانات المعاملة لغرض تقدير أوزان البنكرياس والغدة الكظرية .أظهرت الدراسة أنّ إعطاء هرمون الميلاتونين سبب زيادة غير معنوية في وزن الجسم في حيوانات المجاميع (T2 و T3) مقارنة مع مجموعة السيطرة، بينما المجموعة (T1) أظهرت انخفاضا معنويا في وزن الجسم مقارنة مع كل المجاميع الأخرى. أما نسبة وزن الغدة الكظرية الى وزن الجسم فقد أظهرت النتائج زيادة معنوية في وزن الغدة في المجموعة (T1) مقارنة مع باقي المجاميع. بينما اظهرت المجموعتان (T2 و T3) انخفاضا معنويا مقارنة مع المجموعة (T1). من جهة أخرى أظهرت المجموعة (T3) زيادة معنوية في نسبة وزن البنكرياس إلى وزن الجسم مقارنة مع باقي المجاميع بينما المجموعتين (T1 وT2) أظهرت انخفاضا معنويا مقارنة مع المجموعة (T3) ومجموعة السيطرة. أيضا أظهرت المجموعة (T1) ارتفاعا معنويا في تركيز مصل الكلوكوز، الكولسترول وهرمون الكورتزول مقارنة مع باقي المجاميع. كذلك أظهرت النتائج انخفاضا معنويا في تركيز مصل البروتين، هرمون الانسولين والكلوتاثايون في المجموعة (T1) مقارنة مع باقي المجاميع. نستنتج من هذه التجربة أن إعطاء الميلاتونيين (10 ملغم / كغم من وزن الجسم) لإناث الأرانب المصابة بالسكري لمدة 42 يوما أدى إلى تحسين وظيفة الغدة الكظرية وغدة البنكرياس. كذلك تبيّن إمكانية تقليل أثار الإجهاد التاكسدي المستحدث بواسطة الالوكسان عن طريق استخدام الميلاتونين.

الكلمات المفتاحية: الميلاتونين، السكري، الالوكزان، بنكرياس، الغدة الكظرية.