

# EFFECT OF MELATONIN ON HYPERTENSION AND DIABETES INDUCED EXPERIMENTALLY IN ADULT MALE ALBINO RATS

By

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## ABSTRACT

**Background:** Diabetes Mellitus is the most common endocrine disorder. It is a pathological state leads to long term complications causing damage of different tissue and organs as heart and blood vessels. Hypertension is one of the leading causes of mortality and morbidity. Melatonin has extraordinary antioxidant potential and reduce the level of free radical burden on the level of both oxygen and nitrogen species. **Objective:** Evaluation of melatonin on hypertension and diabetes induced experimentally in adult male albino rats. **Materials and Methods:** Seventy adult male albino rats of local strain were divided into equal seven groups as follow: Group I: served as control group received normal saline, Group II: diabetic group, Group III: hypertensive group, Group IV: Diabetic-hypertensive group, Group V: diabetic-melatonin-treated group, Group VI: Hypertensive-melatonin-treated group and Group VII: Diabetic-hypertensive-melatonin-treated group. At the end of experimental period, blood samples were obtained for determination of glycated hemoglobin, plasma glucose, serum lipid profile (total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride (TG)), serum insulin, serum urea and serum creatinine levels. Measurements of blood pressure were performed for the hypertensive rats. Also, cardiac muscles samples were obtained for histopathology study. **Results:** STZ led to significant increase in blood glucose, glycated hemoglobin, cholesterol, TG, LDL, serum urea and serum creatinine levels associated with significant decrease in serum insulin level. Cadmium led to significant increase in total cholesterol, TG, LDL, serum urea and serum creatinine levels associated with significant increase in blood pressure. Melatonin treatment led to significant decrease of blood glucose, glycated hemoglobin, total cholesterol, TG, LDL, serum urea and serum creatinine levels associated with significant increase in serum insulin level associated with significant decrease blood pressure. **Conclusion:** Melatonin has a protective effect against cardiac muscle abnormalities in diabetic, diabetic-hypertensive and hypertensive rats due to its antioxidant properties.

**Keywords:** STZ, Cadmium, Diabetes mellitus, Hypertension, Melatonin

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease, in which the person has high blood sugar due to inefficient insulin secretion or the cells does not respond to the produced insulin. This high blood sugar produces the classical diabetic

symptoms i.e. polyuria, polydipsia and polyphagia (**David and Dolores, 2011**).

Hypertension has been defined by the World Health Organization as a persistent increase of systemic blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic or both. Systemic hypertension is one of

the most prevalent and serious causes of coronary artery and myocardial disease. Hypertension remains a major health problem because of its impact on mortality and morbidity. According to World Health Organization (WHO) report, hypertension is estimated to cause 7.1 million premature deaths and 4.5 % of disease burden annually (**Alamgeer et al., 2015**).

Cadmium (Cd) is a widespread industrial and environmental pollutant. It has been considered a risk factor for cardiovascular diseases (CVDs) including hypertension. Epidemiological study revealed that presence of Cd in urine is correlated with the elevation of systolic and diastolic blood Pressure. In addition, Cd has been observed to increase the prevalence of peripheral arterial diseases (**Wood et al., 2011**).

Melatonin is an endogenous product of the pineal gland. It plays an important role in the regulation of several parameters of the cardiovascular system including blood pressure. It is considered to be a putative antihypertensive agent (**Dominguez-Rodriguez et al., 2012**).

Melatonin has several functions ranging from its ability to coordinate circadian activity (sleep-promoting effect), induces hypothermic effect, stabilizes sleep-wake cycles, stimulates several antioxidative enzymes and acts on bone metabolism (**Sharma et al., 2015**).

The present study was designed to evaluate the effect of melatonin on hypertension and diabetes induced experimentally in adult male albino rats.

## MATERIALS AND METHODS

### Animals and experimental design:

Seventy adult male albino rats of local strain were brought from Nile Pharmaceuticals Company, Cairo, Egypt and chosen to be the model of the present work. All rats were about the same age and healthy, their weight ranging between 130 - 160 gm (average weight 145 gm). They were housed in stainless steel cages (20 × 32 × 20 cm for every 5 rats) at room temperature, good ventilation and received water and commissural rat chow diet with the natural light dark cycle. They were left for two weeks in the laboratory room before the onset of the experiment for acclimatization. Rats were divided into equal 7 groups as follow;

**Group I (Control group):** Normal rats received daily intraperitoneal (I.P.) injection of 0.5ml saline for 6 week.

**Group II (Diabetic group):** Rats of this group subjected to induction of diabetes by I.P. injection of single dose of 60 mg /kg body weight of streptozotocin (**Roy et al., 2013**) followed by I.P. injection of 0.5 ml saline daily for 6 week.

**Group III (Hypertensive group):** Rats of this group subjected to induction of hypertension by daily I.P. injection of cadmium dissolved in 0.9 % saline in a dose of 1mg/kg body weight for 2 weeks (**Kaur et al., 2011**).

**Group IV (Diabetic hypertensive group):** Hypertension was induced firstly as group III, followed by induction of diabetes as group II.

**Group V (Diabetic melatonin-treated group):** Diabetes was induced as group II,

followed by daily I.P. injection of 10 mg/kg body weight of melatonin for 6 week.

**Group VI (Hypertensive melatonin-treated group):** Hypertension was induced as group III, followed by daily I.P. injection of 10 mg/kg body weight of melatonin for 6 week.

**Group VII (Diabetic hypertensive melatonin-treated group):** Hypertension was induced firstly as group III followed by induction of diabetes as group II, followed by daily I.P. injection of 10 mg/kg body weight of melatonin for 6 week.

**Induction of diabetes:** STZ was purchased from Sigma Pharmaceuticals Company in the form of vial contain 100 mg STZ powder and dissolved in 10ml saline to prepare 10 ml STZ solution and given in a dose of 60 mg/kg, body weight in 50 mM citrate buffer (Roy et al., 2013), then the animals were allowed to drink 5% glucose solution overnight. After 72 h these animals tested for diabetes. The animals with fasting blood glucose level more than 190 mg/dl selected for further study (Park and Kang, 2012).

**Induction of hypertension:** Cadmium was purchased from Sigma Pharmaceuticals Company in the form of vial contain 250 mg powder and dissolved in 250 ml 0.9% saline to prepare 250 ml cadmium solution. Hypertension was induced experimentally by intraperitoneal injection of Cadmium (Sigma Pharmaceuticals Company) daily for 2 weeks at a dose of 1 mg/kg (Kaur et al., 2011).

**Blood and tissue collection:** At the end of experimental period, all rats were fasted overnight and anesthetized by placing in an anesthetic box filled with

ether vapor. Ether vapor was maintained by periodically applying liquid ether to a cotton wool on the base of the box. Blood was withdrawn from the retro-orbital plexus using heparinized capillary tube for determination of blood glucose (Braham and Trinder, 1972), and glycated hemoglobin levels (Inouye et al., 1999). To obtain serum, blood was left to clot and centrifuged at 5000 rate per minute for 10 minutes. Serum was sucked out into Eppendorf tubes and stored frozen at -20°C (Shermer, 1968) until assayed for determination of total cholesterol (Tietz, 2011), TG (N?gele et al., 1984), HDL (Tietz, 2011), LDL (Friedewald et al., 1972), serum insulin level (Rydtren and Sandler, 2002), serum urea level (Sands and Layton, 2009) and serum creatinine level (Dunicz, 1964). Measurements of blood pressure were reported to hypertensive rats according to Safaeiana et al. (2016). The blood pressure (BP) was recorded by the non-invasive tail-cuff method (AD Instrument Power Lab Data Acquisition System, Australia). Heart was excised for histopathological examination which preserved in 10% formalin solution. Paraffin blocks were made for the tissue samples and different sections were obtained and slides were stained with hematoxyline and eosin (Hx and E) stains and examined using a light microscope.

**Statistical analysis:** Data input and analysis were done using Statistical Package for the Social Sciences (SPSS) version "24" computer program. All results were expressed as mean  $\pm$  standard error. Mean values of the different groups were compared using one way analysis of variance. 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

Results of the present work showed that induction of diabetes led to significant increase in the mean value of blood glucose level, glycated hemoglobin level, serum cholesterol level, serum triglyceride level, serum LDL level, serum urea level and serum creatinine level in groups II and IV associated with significant decrease in the mean value of serum insulin level and insignificant decrease in the mean value of HDL level (**Table 1**).

Administration of melatonin to diabetic rats led to significant decrease in the mean value of blood glucose level, glycated hemoglobin level, serum cholesterol level,

serum triglyceride level, serum LDL level and serum urea level, associated with significant increase in the mean value of serum insulin level. In addition, it led to insignificant increase in the mean value of HDL level, associated with insignificant decrease in the mean value of serum creatinine level in groups V and VII. Also, administration of melatonin to diabetic-hypertensive rats led to significant decrease in the mean value of blood glucose level, glycated hemoglobin level, serum cholesterol level, serum triglyceride level, serum LDL level, serum urea level and serum creatinine level, associated with significant increase in the mean value of serum insulin level. Also, it led to insignificant increase in the mean value of HDL level (**Table 2**).

**Table (1):** Effects of STZ on studied groups (Mean  $\pm$  SE).

Parameters \ Groups	Group I	Group II	Group IV
Blood Glucose (mg/dl)	100.9 $\pm$ 3.1	337 $\pm$ 9.16*	343.25 $\pm$ 7.31*
Serum insulin ( $\mu$ IU/L)	10.41 $\pm$ 0.53	3.38 $\pm$ 0.15*	3.2 $\pm$ 0.08*
Glycated hemoglobin (%)	4.87 $\pm$ 0.28	10.57 $\pm$ 0.49*	10.6 $\pm$ 0.49*
Cholesterol (mg/dl)	106.5 $\pm$ 3.69	138.3 $\pm$ 3.57*	177.1 $\pm$ 4.12*
TGs (mg/dl)	97.8 $\pm$ 3.55	116.8 $\pm$ 4.11*	153.1 $\pm$ 6.4*
HDL (mg/dl)	40.3 $\pm$ 0.8	38.8 $\pm$ 0.74	39.0 $\pm$ 1.1
LDL (mg/dl)	47.3 $\pm$ 3.3	76.2 $\pm$ 4.1*	107.5 $\pm$ 3.49*
Urea (mg/dl)	42.74 $\pm$ 1.6	47.8 $\pm$ 1.18*	49.97 $\pm$ 1.36*
Creatinine (mg/dl)	0.77 $\pm$ 0.03	1.23 $\pm$ 0.1*	1.9 $\pm$ 0.13*

Number of rats in each group = 10.

Group I: control group.

Group II: Diabetic group.

Group IV: Diabetic- hypertensive group.

\* indicate significance compared to group I.

**Table(2):** Effects of melatonin on diabetic groups (Mean  $\pm$  SE).

Parameters \ Groups	Group II	Group IV	Group V	Group VII
Blood Glucose (mg/dl)	337 $\pm$ 9.16	343.25 $\pm$ 7.31	246.9 $\pm$ 11.4*	271.8 $\pm$ 12.7#
Serum insulin ( $\mu$ IU/L)	3.38 $\pm$ 0.15	3.2 $\pm$ 0.08	6.68 $\pm$ 0.33*	8.7 $\pm$ 0.37#
Glycated hemoglobin (%)	10.57 $\pm$ 0.49	10.6 $\pm$ 0.49	8.9 $\pm$ 0.38*	8.1 $\pm$ 0.26#
Cholesterol (mg/dl)	138.3 $\pm$ 3.57	177.1 $\pm$ 4.12	117.1 $\pm$ 4.18*	141.1 $\pm$ 5.41#
TGs (mg/dl)	116.8 $\pm$ 4.11	153.1 $\pm$ 6.4	99.4 $\pm$ 4.37*	133.4 $\pm$ 4.06#
HDL (mg/dl)	38.8 $\pm$ 0.74	39.0 $\pm$ 1.1	40.4 $\pm$ 1.2	40.2 $\pm$ 0.65
LDL (mg/dl)	76.2 $\pm$ 4.1	107.5 $\pm$ 3.49	57.3 $\pm$ 3.78*	76.8 $\pm$ 3.09#
Urea (mg/dl)	47.8 $\pm$ 1.18	49.97 $\pm$ 1.36	40.9 $\pm$ 1.8*	42.05 $\pm$ 1.46#
Creatinine (mg/dl)	1.23 $\pm$ 0.1	1.9 $\pm$ 0.13	1.15 $\pm$ 0.12*	1.14 $\pm$ 0.08#

Number of rats in each group = 10.

Group II: Diabetic group.

Group IV: Diabetic- hypertensive group.

Group V: Diabetic-melatonin-treated group.

Group VII: diabetic-hypertensive- melatonin-treated group.

\* indicate significance compared to group II.

# indicate significance compared to group IV.

Results of the present work showed that induction of hypertension led to significant increase in the mean value of serum cholesterol level, serum triglyceride level, serum LDL level, serum urea level and serum creatinine level associated with insignificant decrease in the mean value of HDL level. Also, the results of the present work showed that hypertensive and diabetic hypertensive rats led to significant increases in the mean value of systolic blood pressure and diastolic blood pressure. Administration of melatonin to

diabetic rats and also to diabetic hypertensive rats led to significant decreases in the mean value of systolic blood pressure and diastolic blood pressure (**Table 3**).

Administration of melatonin to hypertensive rats led to significant decrease in the mean value of serum cholesterol level, serum triglyceride level, serum LDL level, serum urea level and serum creatinine level, associated with insignificant increase in the mean value of HDL level (**Table 4**).

**Table (3):** Effects of cadmium on studied groups (Mean  $\pm$  SE).

Parameters \ Groups	Group I	Group III	Group IV
Cholesterol (mg/dl)	106.5 $\pm$ 3.69	175.6 $\pm$ 3.44*	177.1 $\pm$ 4.12*
TGs (mg/dl)	97.8 $\pm$ 3.55	145.9 $\pm$ 7.07*	153.1 $\pm$ 6.4*
HDL (mg/dl)	40.3 $\pm$ 0.8	38.8 $\pm$ 0.83	39.0 $\pm$ 1.1
LDL (mg/dl)	47.3 $\pm$ 3.3	107.6 $\pm$ 2.69*	107.5 $\pm$ 3.49*
Urea (mg/dl)	42.74 $\pm$ 1.6	48.33 $\pm$ 1.0*	49.97 $\pm$ 1.36*
Creatinine (mg/dl)	0.77 $\pm$ 0.03	1.77 $\pm$ 0.08*	1.9 $\pm$ 0.13*
Systolic BP (mmHg)	117.5 $\pm$ 2.38	154.0 $\pm$ 2.66*	156.25 $\pm$ 4.09*
Diastolic BP (mmHg)	80.0 $\pm$ 1.97	98.0 $\pm$ 3.2*	106.2 $\pm$ 2.63*

Number of rats in each group = 10.

Group I: control group.

Group III: Hypertensive group.

Group IV: Diabetic- hypertensive group.

\* indicate significance compared to group I.

**Table (4):** Effects of melatonin on hypertensive groups (Mean  $\pm$  SE).

Parameters \ Groups	Group III	Group IV	Group VI	Group VII
Cholesterol (mg/dl)	175.6 $\pm$ 3.44	177.1 $\pm$ 4.12	150.7 $\pm$ 3.55*	141.1 $\pm$ 5.41#
TGs (mg/dl)	145.9 $\pm$ 7.07	153.1 $\pm$ 6.4	121.7 $\pm$ 7.67*	133.4 $\pm$ 4.06#
HDL (mg/dl)	38.8 $\pm$ 0.83	39.0 $\pm$ 1.1	39.3 $\pm$ 0.69	40.2 $\pm$ 0.65
LDL (mg/dl)	107.6 $\pm$ 2.69	107.5 $\pm$ 3.49	86.99 $\pm$ 3.46*	76.8 $\pm$ 3.09#
Urea (mg/dl)	48.33 $\pm$ 1.0	49.97 $\pm$ 1.36	44.15 $\pm$ 1.07*	42.05 $\pm$ 1.46#
Creatinine (mg/dl)	1.77 $\pm$ 0.08	1.9 $\pm$ 0.13	1.03 $\pm$ 0.08*	1.14 $\pm$ 0.08#
Systolic BP (mmHg)	154.0 $\pm$ 2.66	156.25 $\pm$ 4.09	138.5 $\pm$ 3.65*	143.12 $\pm$ 1.87#
Diastolic BP (mmHg)	98.0 $\pm$ 3.2	106.2 $\pm$ 2.63	82.0 $\pm$ 2.26*	93.12 $\pm$ 1.8#

Number of rats in each group = 10.

Group III: Hypertensive group.

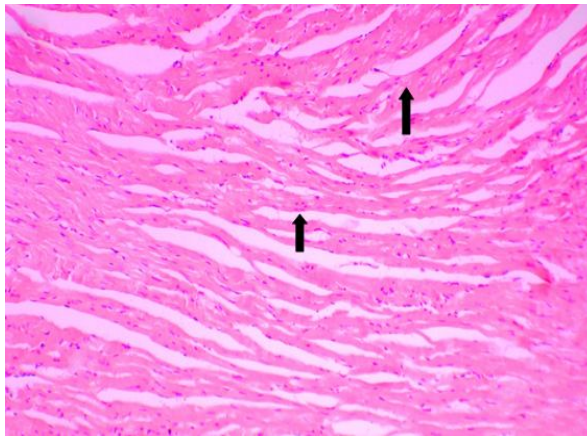
Group IV: Diabetic- hypertensive group.

Group VI: Hypertensive-melatonin-treated group.

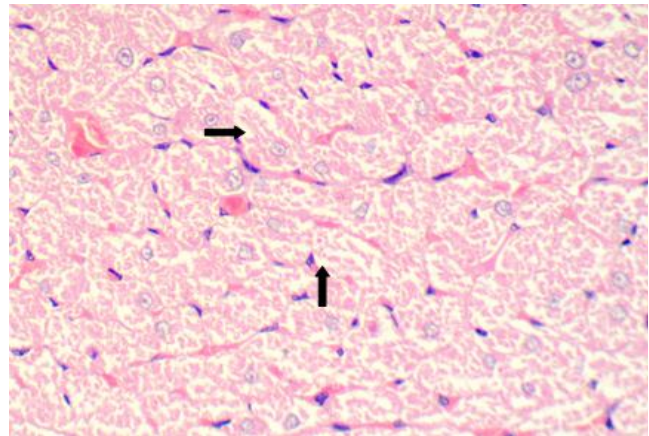
Group VII: diabetic-hypertensive- melatonin-treated group.

\* indicate significance compared to group I.

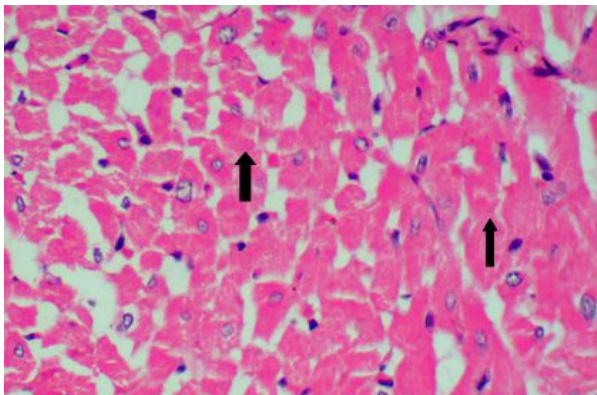
# indicate significance compared to group IV.



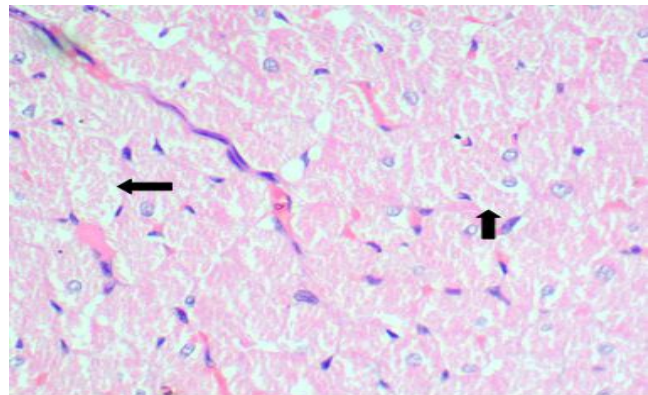
**Figure (1):** Longitudinal section of the cardiac muscles shows bundles of smooth muscles with bright eosinophilic cytoplasm interdigitating with each other (black arrow) of the control group (H&E-×100).



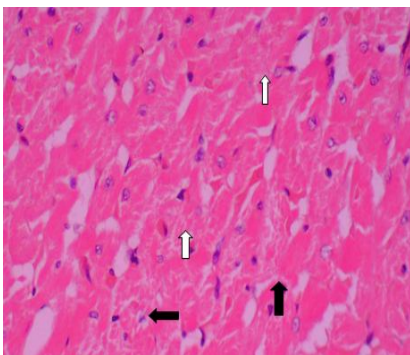
**Figure (2):** Cross section of the cardiac muscles shows degeneration of the smooth muscles bundles with faint eosinophilic granular cytoplasm (black arrow) of the diabetic group (H&E-×400).



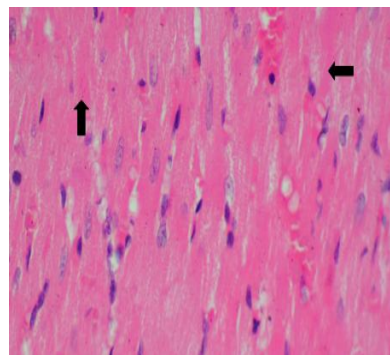
**Figure (3):** Cross section of the cardiac muscles shows smooth muscles bundles with bright eosinophilic cytoplasm (black arrow) of the hypertensive group (H&E-×100).



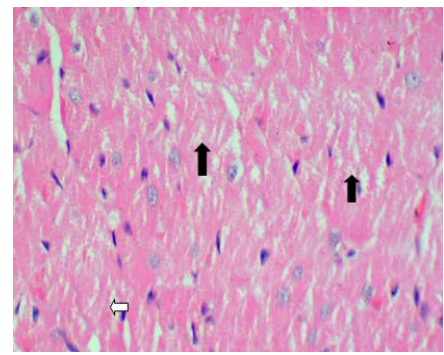
**Figure (4):** Cross section of the cardiac muscles shows degeneration of the smooth muscles bundles with faint eosinophilic granular cytoplasm (black arrow) of the diabetic hypertensive group (H&E-×400).



**Figure (5):** Cross section of the cardiac muscles shows decrease granularity of cytoplasm of smooth muscles (black arrow) with partial recovery of degeneration of some (white arrow) of the diabetic melatonin-treated group (H&E-×400).



**Figure (6):** Longitudinal section of the cardiac muscles shows smooth muscles bundles with bright eosinophilic cytoplasm interdigitating with each other (black arrow) of the hypertensive melatonin-treated group (H&E-×400).



**Figure (7):** Cross section of the cardiac muscles shows decrease granularity of cytoplasm of smooth muscles (black arrow) with partial recovery of degeneration of some muscle bundles (white arrow) of the diabetic hypertensive melatonin-treated group (H&E-×400).

## DISCUSSION

The present work was designed to evaluate the effect of melatonin on hypertension and diabetes induced experimentally in adult male albino rats

Results of the present work showed that STZ injection led to significant increase of blood glucose level and glycated hemoglobin associated with significant decrease in insulin level in diabetic and diabetic-hypertensive groups when compared with the control group. These results were in agreement with **Khaneshi et al. (2013)** and **Sekkin et al. (2015)** who found that a single injection of STZ leads to development of DM indicated by elevated blood glucose, glycated hemoglobin (HbA1c) and decreased serum insulin levels. This occurs due to destruction of  $\beta$  cells within 24 hour, damage of islets cells, and triggering of inflammatory process leading to macrophage and subsequent lymphocyte infiltration caused by STZ (**Arora et al., 2009** and **Szkudelski, 2012**). Oxidative damage induced by STZ in rats is closely associated with chronic inflammation leading to potential tissue damage (**Rochette et al., 2014** and **Xu et al., 2014**).

Streptozotocin (STZ) is an antibiotic produced by *Streptomyces achromogenes*. However, STZ is a widely used chemical for induction of experimental diabetes in rodents. STZ-induced type I diabetes in rodents is a well-established and well-accepted practice for studying pathogenesis of diabetes and its complications. The cytotoxic effect of STZ is mediated by free radicals, toxic and carcinogenic effects on the pancreas,

liver, brain and kidneys (**Jangra et al., 2013** and **Wu and Yan, 2015**).

In the present work, there were significant increases in cholesterol, triglyceride (TG) and low density lipoprotein (LDL), associated with insignificant decrease in high density lipoprotein (HDL) in diabetic and diabetic-hypertensive rats when compared with the control rats. These results were compatible with **Vishnu et al. (2009)** and **Saleh & Maged (2010)** who reported that cholesterol, TGs and LDL levels showed significant elevations in diabetic animals when compared with normal one.

The results of the present work showed that cadmium injection led to disturbed lipid profile in hypertensive rats. These results were in agreement with **Ghosh & Indra (2015)** and **Samarghandian et al. (2015)** who noticed that the cadmium toxicity leads to significant increase in the cholesterol, TGs and LDL levels. These changes occurred as a result of alterations in lipid metabolism by increasing the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), reductase (HMG-CoA) by production of inflammatory cytokines as well as interleukins. These enhance hepatic lipogenesis and suppress oxidation of fatty acids (**Rogalska et al., 2009** and **Prabu et al., 2010**).

In the present work, urea and creatinine levels increased in diabetic, hypertensive and diabetic-hypertensive rats when compared with the control group. These results were in agreement with **Akinnuga et al. (2014)** and **Kumaresan et al. (2014)** who noticed that the urea and creatinine level increased significantly in diabetic rat when compared with normal



rat due to close association between oxidative stress and diabetic renal damage. **Nasim et al. (2015) and Mbarki et al. (2016)** reported that urea and creatinine levels increased in hypertensive rats when compared with normal one. These might be due to nephron destruction due to toxic effect of cadmium (**Weaver et al., 2011**). This occurs due to severe oxidative damage induced by Cd leading to renal tubular dysfunction and decreased glomerular filtration (**Ding et al., 2011 and Dhana et al., 2012**).

In the present study, there was increased systolic and diastolic blood pressure in hypertensive and diabetic-hypertensive groups when compared with control group. These results were in agreement with **Kukongviriyapan et al. (2014)** who reported that the cadmium (Cd) injection led to increased systolic and diastolic blood pressure. These result from complex actions on both vascular endothelial cells and vascular smooth muscle cells (**Prozialeck et al., 2008**). Cd decreases the functional availability of the potent vasodilator NO which may lead to vascular dysfunction (**Gokalp et al., 2009**).

Results of the present work showed that melatonin administration led to significant decrease in blood glucose and glycated hemoglobin levels, associated with significant increase in insulin level in diabetic melatonin-treated group and diabetic hypertensive melatonin-treated group when compared with diabetic and diabetic hypertensive groups respectively. These results were in agreement with **Sekkin et al. (2015)** who mentioned that administration of melatonin led to significant reduction of blood glucose and

glycated hemoglobin levels, and increased insulin level due to melatonin administration to diabetic rats led to prevention of oxidative damage.

Results of the present work showed that melatonin administration led to significant decrease in cholesterol, triglyceride, LDL and urea levels, whereas HDL level showed insignificant increase in diabetic melatonin-treated, hypertensive melatonin-treated and diabetic hypertensive melatonin-treated groups when compared with diabetic, hypertensive and diabetic hypertensive groups respectively. These results were in agreement with **Agil et al. (2011)** who reported improvement of lipid profile after administration of melatonin. This was explained by anti-oxidant, anti-hyperlipidemic and anti-inflammatory effects of melatonin which reduces the oxidative stress involved in the pathogenesis of metabolic syndrome (**Huang et al., 2013**).

In the present study, melatonin administration led to insignificant decrease in creatinine level in diabetic melatonin-treated rats when compared with the diabetic group. Significant decrease in creatinine level occurred in hypertensive melatonin-treated and diabetic hypertensive melatonin-treated groups when compared with the hypertensive group and diabetic hypertensive group respectively.

**Alabbassi et al. (2008)** has reported that therapeutic administration of melatonin in lead acetate-treated rats significantly reduces serum urea and creatinine concentrations. Moreover, **Preet and Dua (2011)** reported that administration of melatonin in cadmium chloride-exposed rats results in significant decrease in serum urea and creatinine levels compared

to animals administered cadmium chloride alone. The decreased plasma creatinine concentration observed in alpha-lipoic acid and melatonin-treated cadmium intoxicated rats could be attributed to the protective effect of alpha-lipoic acid and melatonin against kidney damage produced by cadmium toxicity (**Hussein et al., 2014**).

In the present study, melatonin administration led to significant decrease in systolic and diastolic blood pressure in hypertensive melatonin-treated group and diabetic hypertensive melatonin-treated group when compared with the hypertensive and diabetic hypertensive groups respectively. These results were in agreement with the findings of **Grossman et al. (2011)** who noticed that melatonin administration decreases systolic and diastolic blood pressure. The hypotensive effect of melatonin might be due to decreasing renal oxidative stress and vascular reactivity (**Ilhan et al., 2015**).

Histopathological examinations of the heart showed degeneration of smooth muscles bundles with faint eosinophilic granular cytoplasm in diabetes and diabetic hypertensive groups. However, there were normal smooth muscle bundles with bright eosinophilic cytoplasm in hypertensive group.

These results were compatible with **Khong et al. (2011)** who found a significant increase in myocardial fibrosis, as evidenced by greater proportional area of interstitial collagen I and III immunostaining, and presence of cellular hypertrophy with increased cardiomyocyte cross-sectional area in diabetic rats. **Alpsoy et al. (2014)** noticed degenerative changes as myofibrillar loss, vacuolization of cytoplasm and irregu-

larity of myofibrils in the cardiac tissues in Cd administered to rats.

A study carried out by **Olaiya et al. (2013)** showed that administration of cadmium chloride orally for four weeks induces hypertension in a rat model and reported that cardiac tissue section showed foci of necrosis with cellular infiltration by mononuclear cells in the hypertensive group.

In the present study, melatonin administration led to decreased granularity of the cytoplasm of smooth muscles bundles with partial recovery of degeneration in diabetic melatonin-treated and diabetic hypertensive melatonin-treated groups. These results were in agreement with **Alghasham (2013)** who reported that melatonin effectively prevented the rise of malondialdehyde levels, nitrite and creatine kinase isoenzyme which act as indicator of oxidative stress in the heart and this protect the cardiac tissue. The protective effect of melatonin could be due to its potent antioxidant activity.

## CONCLUSION

Melatonin has a marked enhancing effects on blood glucose, insulin, blood urea, creatinine, lipid profile and blood pressure levels in adult male albino rats. This might be due to increasing insulin secretion, enhanced sensitivity, and decreasing hepatic fat biosynthesis. These effects of melatonin could improve diabetic and hypertensive mortality and morbidity.

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## تأثير الميلاتونين على مرض ضغط الدم المرتفع ومرض البول السكري المستحدث تجريبياً في ذكور الجرذان البيضاء البالغة

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**خلفية البحث:** يعتبر مرض البول السكري هو أكثر اضطرابات الغدد الصماء شيوعاً وهو عبارة عن حالة مرضية تؤدي إلى مضاعفات كثيرة على المدى الطويل مما يسبب بعض الأضرار التي تلحق بالقلب والأوعية الدموية أو غيرها. ويعتبر الإجهاد التأكسدي هو العامل الأكثر أهمية المسؤول عن الإضطرابات الناتجة عن مرض البول السكري ويعتبر مرض ضغط الدم المرتفع هو واحد من الأسباب الرئيسية للوفيات والميلاتونين له أهمية في علاج الأمراض وذلك بسبب امتلاكه لخواص مضاد الأكسدة.

**الهدف من البحث:** تقييم تأثير تناول الميلاتونين على مرض البول السكري وكذلك ضغط الدم المرتفع.

**مواد وطرق البحث:** إستخدم في هذا البحث سبعون ذكراً أبيضاً من ذكور الجرذان البيضاء البالغة كنموذج للدراسة. و قد قسمت الجرذان إلى سبعة مجموعات متساوية كالاتي: المجموعة الأولى: مجموعة ضابطة أعطيت محلولا ملحياً، والمجموعة الثانية مصابة بالسكري والمجموعة الثالثة مصابة بضغط الدم المرتفع والمجموعة الرابعة مصابة بالسكري و ضغط الدم المرتفع والمجموعة الخامسة مجموعة الميلاتونين مع البول السكري والمجموعة السادسة مجموعة الميلاتونين مع ضغط الدم المرتفع والمجموعة السابعة مجموعة الميلاتونين مع البول السكري و ضغط الدم المرتفع. وفي نهاية التجربة تم قياس كل من نسبة السكر بالدم والهيموجلوبين السكري و هرمون الإنسولين والكوليستيرول والدهون الثلاثية والبروتين الدهني عالي الكثافة والبروتين الدهني منخفض الكثافة ونسبة اليوريا والكرياتينين بالدم. كما تم قياس ضغط الدم الإنقباضي والإنبساطي لدى الجرذان المصابة بضغط الدم المرتفع. كما تم قتل الجرذان لأخذ عينات من القلب من كل مجموعة لدراستها هستولوجياً.

**النتائج:** أدى حقن ستريبينوزوتوسين الى إرتفاع نسبة كل من السكر بالدم والهيموجلوبين السكري والكوليستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة واليوريا والكرياتينين بالدم إرتفاعاً

ذو دلالة إحصائية كما إنخفض هرمون الإنسولين بالدم إنخفاضا ذو دلالة إحصائية. وقد أدى حقن الكادميوم إلى إرتفاع نسبة كل من الكوليستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة واليوربا والكرياتينين بالدم مع إرتفاع ضغط الدم الإنقباضي والإنبساطي إرتفاعا ذو دلالة إحصائية. وقد أدى حقن الميلاتونين الى إنخفاض نسبة كل من السكر والهيموجلوبين السكري والكوليستيرول والدهون الثلاثية والبروتين الدهني منخفض الكثافة واليوربا والكرياتينين بالدم مع إنخفاض ضغط الدم الإنقباضي والإنبساطي انخفاضا ذو دلالة إحصائية كما إرتفع هرمون الإنسولين بالدم ارتفاعا ذو دلالة إحصائية.

**الإستنتاج:** الميلاتونين أدى إلى خفض نسبة السكر والهيموجلوبين السكري والدهون واليوربا والكرياتينين في دم الجرذان المصابة بالبول السكري وضغط الدم المرتفع، كما أدى أيضا إلى تحسين نسبة هرمون الإنسولين بالإضافة إلى إنخفاض ضغط الدم المرتفع مما يعنى أن إستخدام الميلاتونين يمكن أن يكون ذا فائدة تطبيقية وعملا مساعداً في علاج مرض السكر وضغط الدم المرتفع والوقاية من مضاعفاتهم.