STUDY OF TOXIC EFFECT OF METHIMAZOLE ON THE CORTICAL STRUCTURE OF ADULT MALE ALBINO RATS KIDNEYS AND THE AMELIORATED EFFECT OF THYROXIN

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ABSTRACT

Kidney and thyroid functions interact with each other. Drugs used in treatment of any of them could have side reactions on any other organ. The effects of antithyroid medications on extrathyroidal organs could be due to oxidative stress and to damage in the renal cells.

Aim: This work is designed to demonstrate the role of T4 in protection against the increase in oxidative stress caused by methimazole, and to detect if antithyroid drug-induced hypothyroidism (methimazole) or removal of thyroid by surgery causes damage of kidney cells or not.

Methods: Twenty-five healthy adult male albino rats were used in the study. The animals were randomly separated into groups. Each group contained five rats: Group I (control group): This group received no drugs or treatment. Group II included rats with false thyroidectomy. Group III included thyroidectomized albino rats. Group IV included methimazole-induced hypothyroidism albino rats through receiving 60 mg/kg/day of methimazole in drinking water. Group V were administered methimazole (60 mg/kg/day) and l-thyroxine (T4) subcutaneous injection (20 µg/kg/day).The animals were anasethized and their abdomens were opened and both kidneys were removed, and immediately processed for histological & immunohistochemical study. Also oxidative enzymes were estimated.

Rresults: Light microscopic examination of H&E stained sections showed marked damage of the structure of renal cortex in methimazole induced hypothyroidism group. This damage was concomitant with a decrease in kidney antioxidant enzymes. This damage was less pronounced in group of rats administrated T4 in association with methimazole. The cortex of kidney in rats of thyroidectomized group did not show any alterations in its micro structure.

Conclusion: Methimazole causes both of hypothyroidism and alteration of the kidney cortex. This alteration is not noticed in case of surgical thyroidectomy inducing hypothyroidism. L-Thyroxine (T4) could decrease the effect of methimazole on kidney cortex.

Keywords: *Methimazole, hypothyroidism, thyroidectomy, kidney cortex.*

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INTRODUCTION

The kidney is an important organ with great complexity in its structure and functional variety. It gets ride of nitrogenous waste and keeps the volume, composition, pressure of the blood, and the density of the bones **[1]**.

Hormones of thyroid gland have a vital role in the physiology, differentiation and development of any organism **[2]**.

There are interactions between renal and thyroidal functions **[3]**. Dysfunction of thyroid results in disturbance of kidney functions and development, while renal disease can cause dysfunction of thyroid. Renal disorders and thyroid dysfunction may coexist with same causes **[4]**. Moreover they add that decrease of thyroid hormones can disturb blood pressure and is accompanied with decrease in glomerular filtration, hyponatremia, and change in the excretion of water. Thionamides are antithyroid drugs which are simple molecules and have a thiourea moiety and a sulfhydryl group within a heterocyclic structure. Their main function is to inhibit synthesis of thyroid hormone by interacting with vital step in triiodothyronine and thyroxine synthesis which is iodination of tyrosine in thyroglobulin **[5]**.

This antithyroid drug may cause antioxidant imbalance **[6]**. Moreover, methimazole increases free radicals production and decrease the capacity of the antioxidative protection, so it is accompanied with oxidative stress **[7, 8]**.

Imbalance between oxidants and antioxidants causes cellular damage. High level of reactive oxygen species (ROS) and reactive nitrogen species, lipid peroxidation, nitration, carbonylation, or glutathionylation of

proteins, and DNA fragmentation are caused by activated oxidant system **[9, 10].**

Antithyroid drugs produce ROS and reactive nitrogen species such as peroxynitrite (ONOO–) which may cause injury of kidney **[11, 12]**.Such drugs also cause elevation of malondialdehyde which are significantly less in rats with low thyroid hormones than with normal level of thyroid hormones **[13].**

The protective role of hypothyroidism against kidney injury is clear. The increased release of antioxidant enzymes as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) has been found to decrease kidney damage [14, 5].

The thyroid hormones have role on the control of the cell cycle, so that in methimazole treated rats in combination with T4, the injury of renal cortex is less pronounced [15]. So, this work was designed to demonstrate the role of T4 in protection against the increase in oxidative stress caused by methimazole, and to detect which of hypothyroidism induced by drugs or by surgery can cause injury of renal cortex cells.

MATERIALS AND METHODS

Drugs

The drugs used in the present study were:

- Methimazole (pharmaceutical company, Egypt) with dose (60 mg per kilogram per day in drinking water) [16].
- T4 injection (Sigma Chemical Co., UK) with dose (20 ug/kg/d sc) [7].

Experimental animals

Twenty five healthy adult male albino rats weighting 180-200gm were got from the Laboratory Animals' Unit at the Faculty of Medicine, Zagazig University were used in this study. All animals were kept under hygienic conditions. Standard food and water were allowed. All rats were handled in accordance to the standard guideline for the care and use of laboratory animal. We separated the rats randomly into five groups:

Group I (control group) (n=5): no drugs were given.

Group II (n=5): it underwent false thyroidectomy and received post-operative treatment.

Group III (n=5): Animals underwent into thyroidectomy to induce hypothyroidism, Thyroidectomy was done on rats after giving sodium pentobarbital intraperitoneal (35 mg/kg body weight) [17]. We cut the sternothyroid muscle and expose the trachea then we located parathyroid gland and isolated them from the thyroid gland, and implanted into the surrounding muscle. We dissected out the thyroid gland gently to be careful of laryngeal nerve. After the operation, ketolac (50 mg/kg i.m.) and gentamicin (10 mg/kg) were given to rats for five days to relieve pain and protect against infection [17].

Group IV (n=5): it had rats with hypothyroidism induced by methimazole, as they were given methimazole in dose of 60 mg/kg/day for 4 weeks.

Group V (n=5): It had rats which were given l- thyroxine (T4) injection (20µg/kg/day, subcutaneous) and methimazole (60 mg/kg/day) for 4 weeks.

We measured the serum level of the thyroid hormones (T3 and T4) at the end of the treatment to confirm the hypothyroid state. The samples were taken from retroorbital venous plexus and the serum was separated and kept at-40□C until measuring which was done by enzyme immunoassay.

Methods

At the end of every stage of the experiment which extended for four weeks, all animals were sacrificed by decapitation, their abdominal cavities were opened both kidneys were removed and immediately processed for light microscopic study.

Measuring the activities of the antioxidant system

A sample from the renal tissue from each animal was homogenized in a polytron (Model PT 2000; Brinkmann, Westbury, New York, USA) for 10 s in cold 50 mmol/l potassium phosphate 0.1% triton X-100 (pH=7.0). The homogenate was centrifuged at 19000*g* at 4°C for 30 min and the supernatant was separated to measure the activities of the antioxidant enzymes [17, 18].

Light microscopy technique

Each kidney was cut into two halves across the renal pelvis along its longitudinal axis to expose cortex, medulla and papilla. The specimens were immersed at once in 10% formol saline for 48 hours to be Processed and embedded in paraffin [19]. Coronal cuts of 7

um thicknesses were cut by a standard microtome then stained with H&E.

Immunohistochemical technique

Immunohistochemical reactions were carried out on sections of the kidney using 8-Hydroxydeoxyguanosine (8-OHdG) Monoclonal antibody.8-OhdG is an oxidized derivative of deoxyguanosine which considered a major product of oxidation of DNA. Concentrations of 8-oxo-dG inside the cell are indicator of oxidative stress. Paraffin blocks were cut by a microtome at four micron thickness. Sections were mounted on glass slides then processed [20].

Image analysis and morphometric study

Stained sections with H&E were analyzed morphometrically using image analyzer computer system. The data were collected using **Leica Qwin** 500 image analyzer computer system in the image analysis unit in Histology and Cell Biology Department, Faculty of Medicine, Cairo University.

1- The thickness of Bowman's space of corpuscles the kidney per 200 high power fields:

Using the measuring field menu, in slides stained with haematoxylin and eosin, in random areas under 200 high power fields of light microscope. A mean of fifteen readings was measured from five different sections from slides of each animal in each group**.**

2- The diameter of the convoluted tubules per 200 high power fields:

Using the measuring field menu, the diameter of the convoluted tubules was measured in slides stained with haematoxylin and eosin in random areas under 200 high power fields of light microscope. A mean of fifteen readings was estimated from five different sections from slides of each animal in each group.

Statistical analysis

The obtained data were analyzed statistically by SPSS program (Statistical Package for Social Science) version **18.0**. Quantitative data were expressed as mean ± SD (Standard deviation).ANOVA *F*-test test was used to calculate difference between quantitative variables in more than two groups in normally distributed data.

The significance level of all previous tests was done. The level of significance was fixed at 5% level (P-value).

*P value of >0.05 indicated non-significant results.

*P value of <0.05 indicated significant results.

*P value of <0.01 indicated highly significant results.

RESULTS

Histological Examination

Hematoxylin and eosin (H&E) stained sections examination of kidney cortex of the control and thyroidectomized groups revealed that the cortex of kidney was formed of renal tubules and renal corpuscles. Each renal corpuscle consisted of a glomerulus containing tuft of capillaries and encircled by parietal and visceral layers of Bowman's capsule which were separated by Bowman's space. The outer parietal layer was formed of flat cells while the inner visceral layer was closely related to the glomerular capillaries. The cortical renal tubules were formed mainly of proximal and distal convoluted tubules. They were lined with simple cuboidal epithelium with central rounded nuclei. The lumen of the proximal tubules was irregular and narrower than the distal ones **(Figs. 1,2)**. In methimazole treated group of renal cortex revealed some dilated tubules with flattened epithelium and some of the lining tubular cells showed vacuolation of the cytoplasm and darkly stained nuclei. In addition, the glomeruli appeared shrunken with widened Bowman's space **(Figs. 3,4).** Some tubules exhibited intra-luminal eosinophilic homogenous material **(Fig. 5).** Excess inflammatory cells between tubules **(Fig. 4)** and excess hemorrhage between tubules **(Fig. 5)** were also seen. These changes are less pronounced in rats which received methimazole in combination with thyroxin. There was decrease of vaculation of the tubular cells with hemorrhage and inflammatory cells in between tubules **(Fig. 6)**.

Immunohistochemically, the renal cortex of control group showed few positive immunoreactive nuclei among the tubular lining cells and in the glomeruli **(Figs. 7,8)**. In methimazole treated group revealed many immunoreactive nuclei among the tubular lining cells and in the glomeruli in comparison with control group **(Fig. 9).** This immune

reaction is less noticed in rats which received methimazole in combination with thyroxin **(Fig. 10)**.

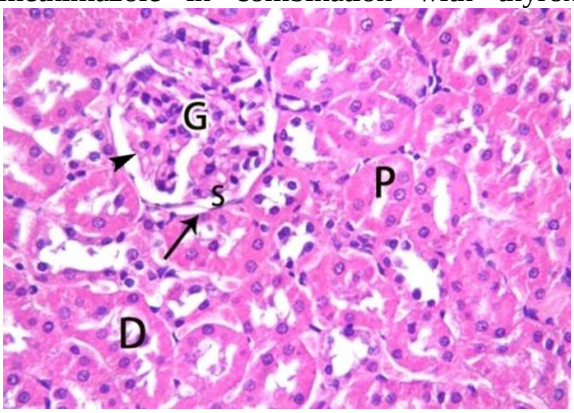


Fig. (1): A photomicrograph of cortex of a kidney in rats of control group showing a glomerulus (G) encircled by parietal (arrow) and visceral layers (arrow head) of Bowman's capsule, separated by renal space (S). Proximal convoluted tubule (P) and distal convoluted tubule (D) are also seen .(H&E ×400)

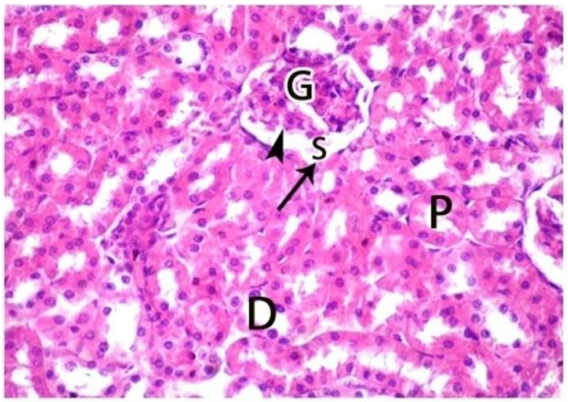


Fig. (2): A photomicrograph of cortex of a kidney in rats of methimazole treated group showing a glomerulus (G) encircled by parietal (arrow) and visceral (arrow head) layers of Bowman's capsule, separated by renal space (S). Proximal (P) and distal (D) convoluted tubules are also seen. (H&E ×400)

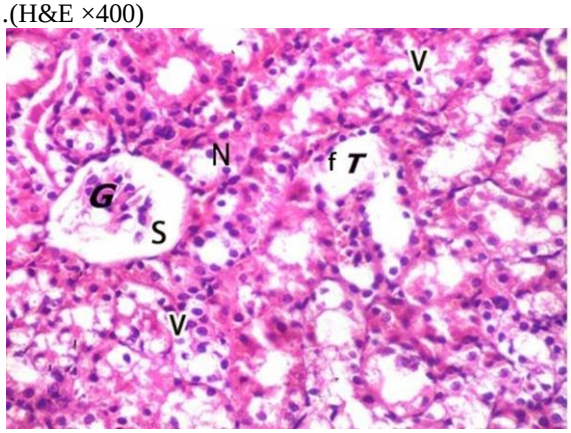


Fig. (3): A photomicrograph of cortex of a kidney in rats of methimazole treated group showing a corpuscle with shrunken glomerulus (G) and widened Bowman's space (S). The cells which lines the tubules exhibit marked rarefaction and vacuolation (V) of the cytoplasm; darkly stained nuclei (N). Many tubules show dilated tubules (T) with flattened epithelium (F). (H&E ×400)

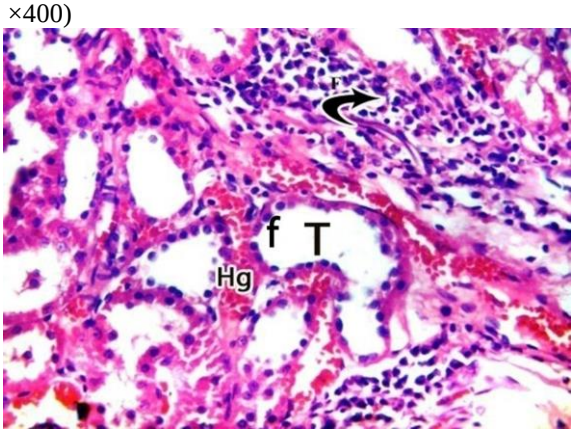


Fig. (4): A photomicrograph of cortex of a kidney in rats of methimazole treated group showing dilated renal tubules (T) with flattened epithelium (f) and area of hemorrhage (Hg) between renal tubules and inflammatory cell infiltration (Curved arrow). (H&E ×400)

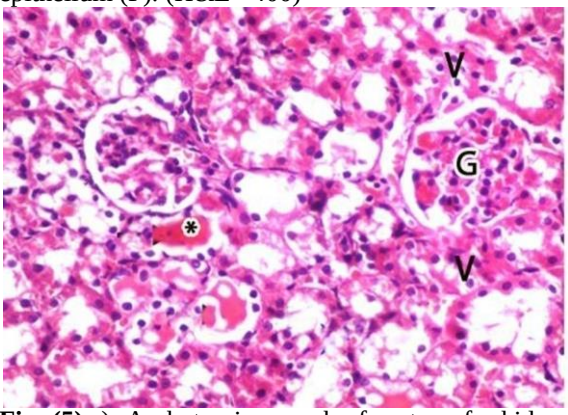


Fig. (5):): A photomicrograph of cortex of a kidney in rats of methimazole treated group showing many tubules with intra-luminal eosinophilic homogenous material (star) and cytoplasmic vacuoles (V) of their lining tubular cells. Congested glomeruli (G) are also seen. (H&E ×400)

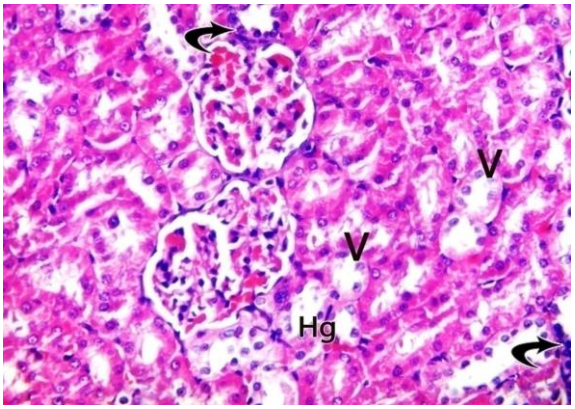


Fig. (6): A photomicrograph of renal cortex of methimazole co-treated with T4 group showing some vaculated cells (V), inflammatory cells (curved arrow) and hemorrhage (Hg) between tubules. (H&E × 400)

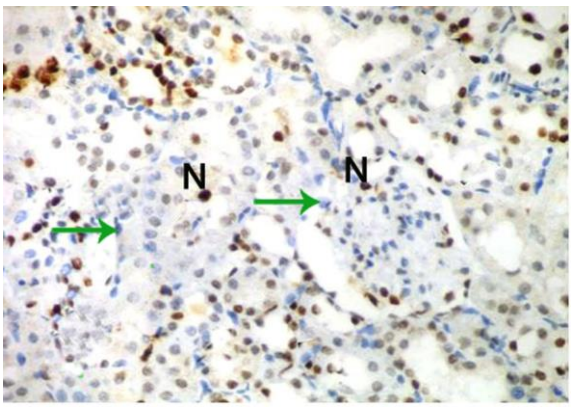


Fig. (7): A photomicrograph of cortex of a kidney in rats of control group showing some positive immunoreactive nuclei (N) among the normal cells lining the tubules and the glomerului (green arrow). (8-OhdG immunostaining ×400)

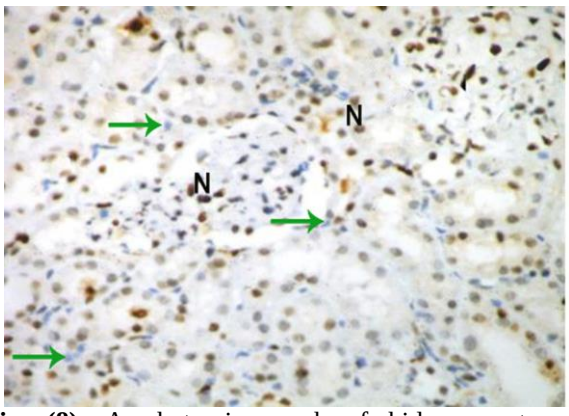


Fig. (8): A photomicrograph of kidney cortex of thyroidectomized adult male albino rat showing some positive immunoreactive nuclei (N) among the normal cells lining the tubules and the glomerului (green arrow). (8-OhdG immunostaining ×400)

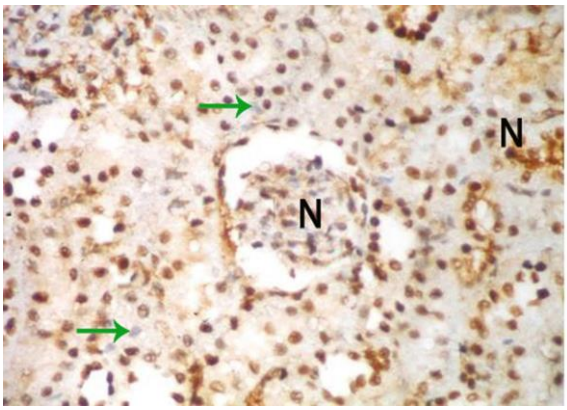


Fig. (9): A photomicrograph of cortex of a kidney in rats of methimazole treated group showing excessive positive immunoreactive nuclei (N) among few normal cells lining the tubules and the glomeruli (green arrow). (8-OhdG immunostaining ×400)

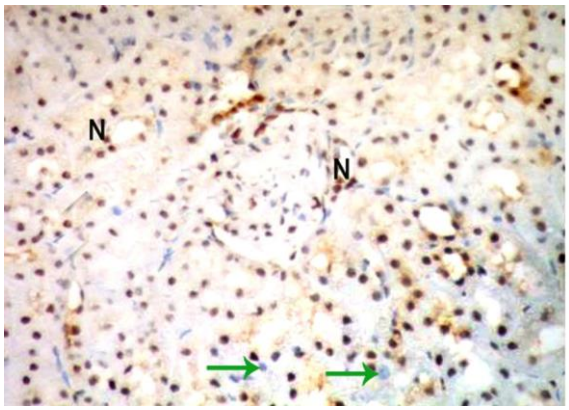


Fig. (10): A photomicrograph of kidney cortex of methimazole co-treated with T4 group showing immunohistochemical stained sections revealed some immunoreacive nuclei (N) among normal cell lining the tubules and glomeruli (green arrow). (8-OhdG immunostaining ×400)

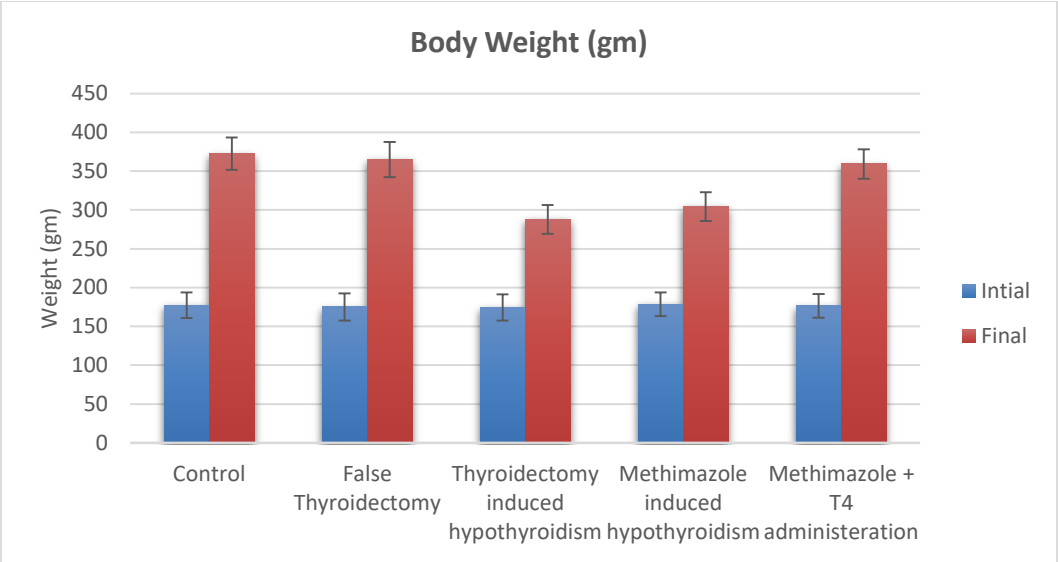
Statistical analysis

There were statistical significance differences between the studied groups in the weight. There was statistically significant difference between control group and methimazole with thyroxin administration group **(Table 1; Graph 1)**. Also, statistical analysis of the T3 and T4 levels in the studied groups revealed that there were significant decrease in their levels in thyroidectomized and methimazole treated groups. **(Table1; Graphs 2,3)**. Also, there was statistical significant decrease in both methimazole treated and methimazole with thyroxin administration groups in antioxidant enzymes (catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) level. **(Table 1; Graph 4).** In addition, there were statistical significant increase in the diameter of convoluted tubules and the thickness of Bowman's space in both methimazole treated and methimazole with thyroxin administration groups. **(Table 1; Graphs 5, 6)**.

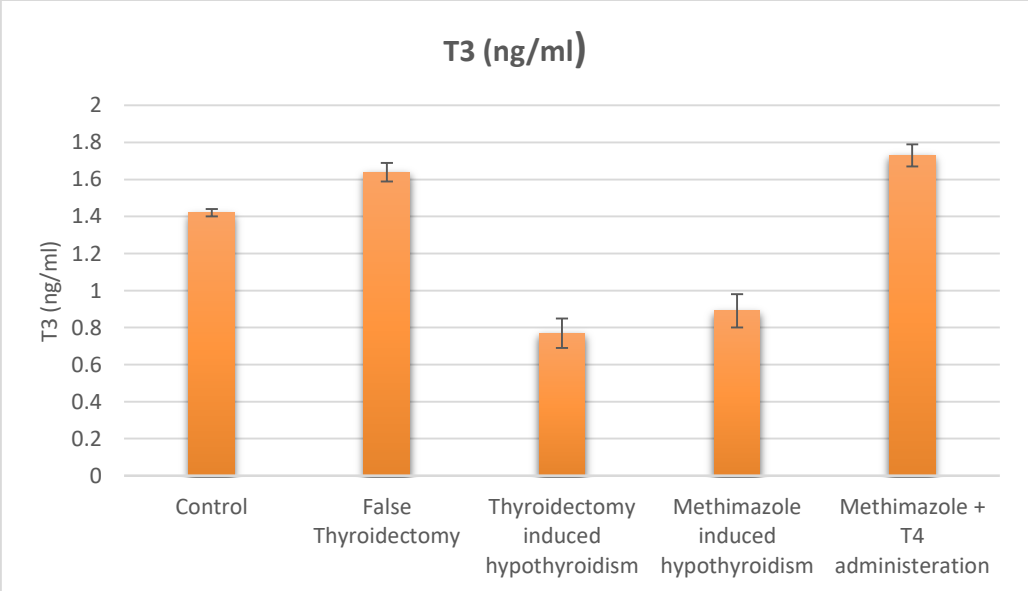
Table (1): Initial and final Body weight, T3, T4, antioxidant, diameter of convoluted tubules and thickness of Bowman's space among the different studied groups:

Variable	Control (*n*=5)	False Thyroidectomy (n=5)	Thyroidectomy induced hypothyroidism (n=5)	Methimazole induced hypothyroidism (n=5)	Methimazole + T4 administration (n=5)
Initial BW (gm)	177.32±16.55[a]	175.16 ± 17.5[a]	174.36 ± 16.89[a]	178.56 ± 15.22[a]	176.61 ± 15.24[a]
Final BW (gm)	372.5±20.74[a]	364.81 ± 22.75[a]	**287.9 ± 18.52** [b]	**304.12 ± 18.57** [b]	359.11 ± 19.01[a]
T3 (ng/ml)	1.42 ± 0.02[a]	1.64 ± 0.05[a]	**0.77 ± 0.08** [b]	**0.89 ± 0.09** [b]	1.73 ± 0.06[a]
T4 (ug/dl)	6.91 ± 0.43[a]	7.43 ± 0.51[a]	**3.57 ± 0.79** [b]	**3.82 ± 0.42**[b]	7.17 ± 0.49 [a]
Antioxidant(Mm/l	1.67 ± 0.22[a]	1.46 ± 0.20[a]	1.53 ± 0.34[a]	**0.64 ± 0.21** [b]	**0.86 ± 0.23** [c]
Diameter(µm)	59.58±9.84[a]	67.87 ± 21.22[a]	62.73 ± 10.2[a]	**147.39 ± 9.45** [b]	**100.02 ± 13.66** [c]
Bowman(µm)	24.31±3.99[a]	29.36 ± 2.39[a]	39.11 ± 8.03[b]	**91.62 ± 20.22** [c]	**70.54 ± 7.44** [d]

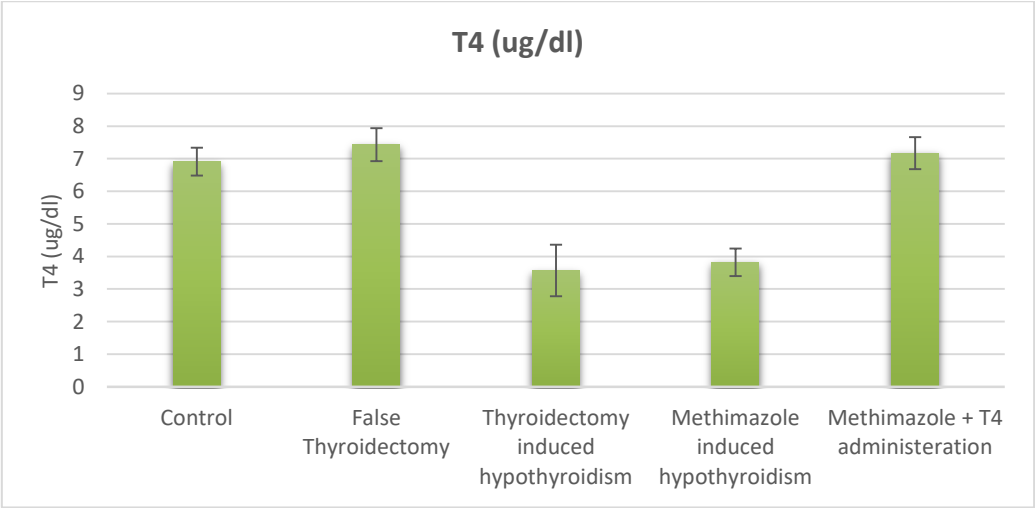
Data expressed as mean ± SD, Groups with different letters are statistically significant (P<0.05)



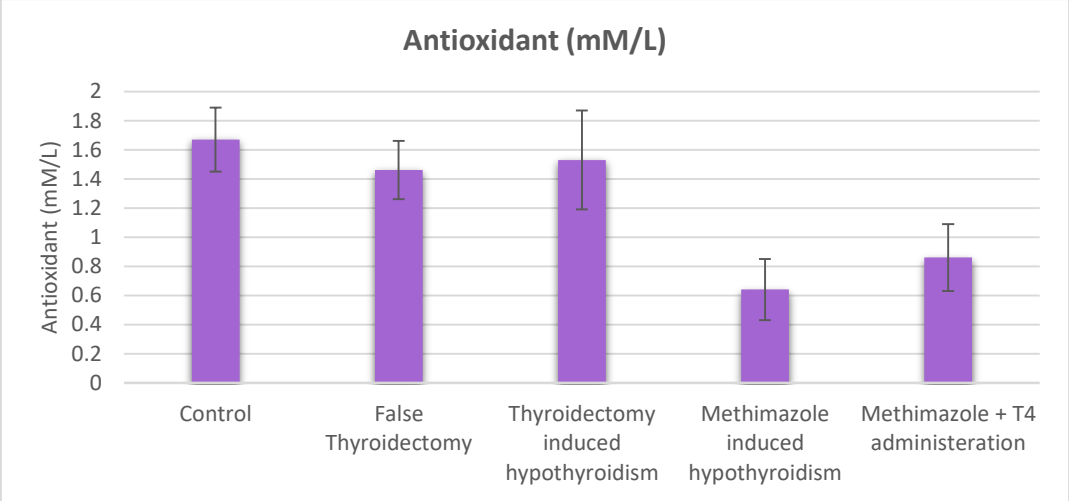
Graph (1): Mean values of initial and final weight in different groups.



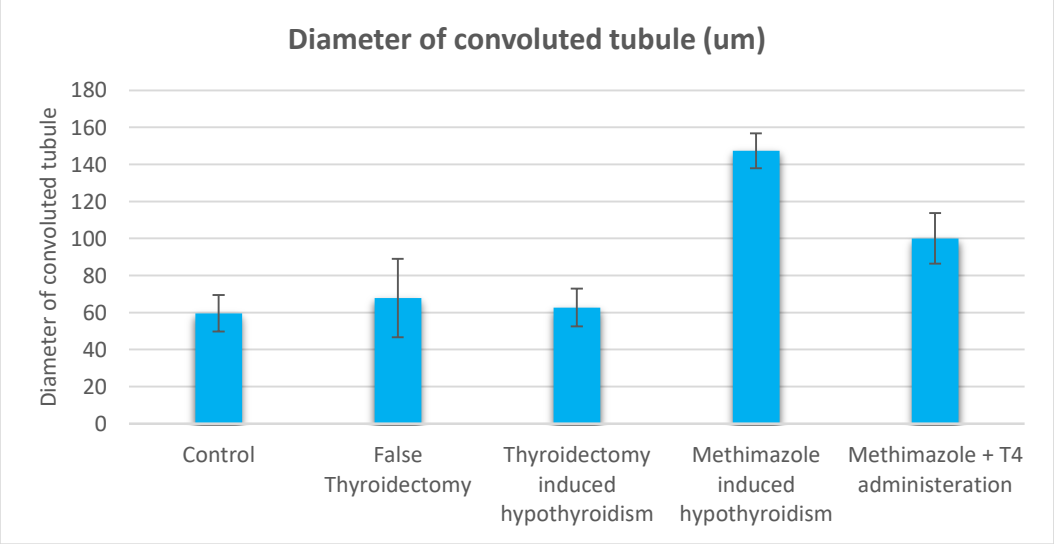
Graph (2): Mean values of T3 level in different groups.



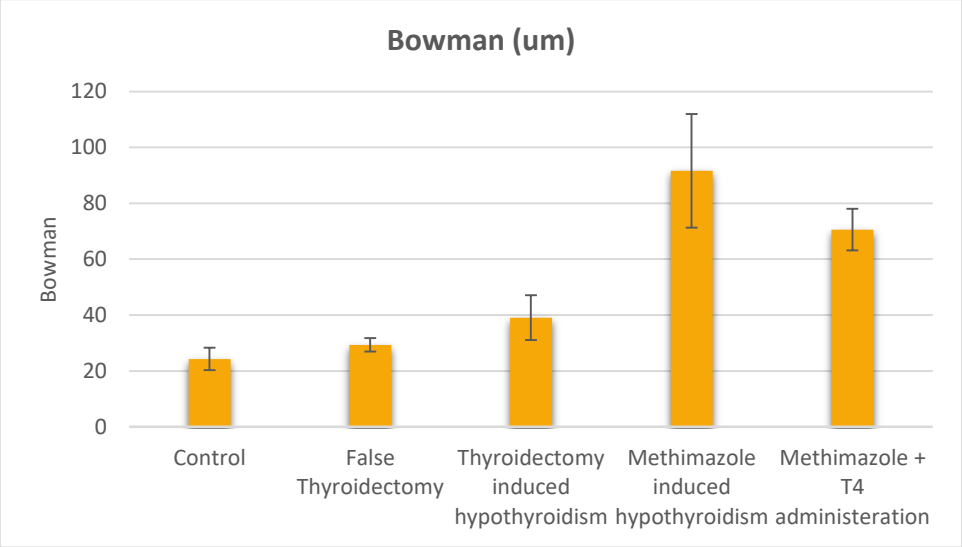
Graph (3): Mean values of T4 level in different groups.



Graph (4): Mean values of antioxidant enzymes level in different groups



Graph (5): Mean values of convoluted tubules diameter in different groups



Graph (6): Mean values of thickness of bowman space in different groups.

DISCUSSION

In this study, the rat was chosen as it is one of the most widely used research animal especially for the urinary physiology **[21]**. They are initially used for experimental purposes since the half of the nineteenth century. Adult male albino rats were chosen in this work because it could be housed, bred and handled without difficulties. In addition, they had a long life span and it was relatively disease free.

The present study showed marked alterations in the structure of kidney cortex of the rat after intake of the drug which induced hypothyroidism (methimazole). Hypothyroidism caused by methimazole was associated with marked lowering in the level of T3 and T4 in serum. A dose of 20 µg T4/kg body weight per day was needed to make the serum T3 levels approximately normal. So the dose of T4 was taken to prove if the injury of the kidney cortex which is caused by methimazole would be prevented by T4 or not.

In present study, examination of haematoxylin and eosin stained sections of the kidney cortex of the control animals showed that the kidney cortex was formed of tubules and renal corpuscles. The corpuscle was composed of glomerulus encircled by Bowman's capsule. Distal convoluted tubules had wider lumen than proximal convoluted tubules. Proximal convoluted tubules had narrow lumen. The normal present results were similar to that identified before **[22, 23]**.

Our result agreed with **Basuony [24]** who registered that the distal convoluted tubule is fewer in number and may be known by the pale cuboidal epithelial cells and with **William et al., [25]** who claimed that the distal convoluted tubules have a smooth internal surface, and not have brush border.

In this work, the immune-stained sections examination of the control group revealed some positive immunoreactive nuclei among the normal cells lining the tubules and the glomerului.

Our results showed that the analysis of histological and immunohistochemical results of the thyroidectomized groups were the same as the results of the control group. This agreed with **Gazia [26]** who reported that, H&E stained sections of the kidney cortex of both groups showed the presence of kidney tubules and corpuscles. Each corpuscle was composed of a glomerulus encircled by double layers of Bowman's capsule with a filtration space between them. The outer layer was composed of a single layer of simple squamous cells, and the inner layer was composed of podocytes which had oval large nuclei. The glomerulus had tufts of capillaries lined by flat endothelial cells. There were proximal convoluted tubules, distal convoluted tubules, and collecting ducts around the renal corpuscles. The amount of renal interstitium was few. In addition, the author reported that examination of the immune-stained sections of the control and thyroidectomized groups showed negative

immunostaining reaction in the convoluted tubules and glomeruli.

Furthermore, **Tenorio-Velázquez et al., 2005 [17]** added in case of hypothyroidism induced by thyroidectomy with parathyroid implant, no kidney tissue damage was detected. This agreed with our work.

Allen and Rana [27] and Isman et al., [28] reported that the protective role of hypothyroidism caused by thyroidectomy against kidney cellular injury in the thyroidectomized group was in agreement with the protective role of hypothyroidism against nitrosative stress, oxidative stress, , and cellular alterations in different experimental models.

In addition, **Halestrap et al., [29]** reported that the hypothyroidism which was caused by thyroidectomy might have protective effect as that mitochondria was known to have an important effect on the pathways of cell death by activating permeability of mitochondrial transition pores and causing the production of cytochrome c and proapoptotic factors, as well as Ca++ overload, which caused nonselective permeability of the inner membrane. Also, **Jena et al., [30]** explained that there were molecular mechanisms by which it might cause a protected state, as decreasing the activity of enzyme associated with mitochondrial respiratory chain rendered mitochondria resistant to the opening of membrane permeability transition pores.

Moreover, **Franco et al., 2011 [31]** reported that hypothyroidism also could increase the formation of polyunsaturated fatty acids which in turn changed plasma membrane composition. **Isman et al. [28]** and **Hataya et al., [32]** were in agreement with that explanation and reported that this change of lipid composition caused lipid peroxidation sensitivity in rats membranes with hypothyroidism and could decrease the vulnerability to oxygen radical which caused cell injury. In contrast to this, **Shin et al. [33]** reported that the state of hypothyroidism predisposed kidney damage due to an increase in synthesis of polyunsaturated fatty acid, which were vulnerable to peroxidation and the decrease of kidney proliferation.

In the present study, light microscopic examination H&E stained sections of group III showed widened Bowman's space, congestion of glomeruli, abnormal shape of glomeruli, and area of hemorrhage in the interstitium between tubules. Kidney tubules appeared with dilated lumen and degenerated epithelium. Some kidney tubules had cytoplasmic vaculations in the cells of lining and hyaline casts in lumen of a lot of tubules. Inflammatory cells in the interstitium between tubules also appeared. In addition, this effect was accompanied with oxidative stress, which was detected by the immunohistochemical stain which showed strong positive immune reaction for 8-OHdG in the renal cells. These changes did not occur in other groups.

These results were the same as the results concluded by **Gazia [26]. Calanas-Continente et al., [34]** reported that five percent of hyperthyroidism patients treated with antithyroid medications were had damage in their kidneys. These results were observed in animals and humans. According to **Becker et al., [35]** two of twelve cats studied suffered from azotemia after intake of methimazole.

These results were in consistent with **Angermüller et al., [36]** who reported that methimazole could cause damage of cells by many ways as chemical structure or because of the interaction between the physiological changes caused by the hypothyroidism and such chemical structure. Under physiological conditions the presence of antioxidant enzymes, in particular peroxidases and dismutases, prevented oxidative stress and tissue damage.

Bandyopadhyay et al., [37] were in accordance with this explanation and stated that some medications as methimazole, affected the physiological state harmfully, change the interior environment of cells, and caused injury of cells because of oxidant generation and reactive oxygen species (ROS); as, lipid peroxidation was not neutralized completely by the decrease of antioxidant system. Methimazole caused inactivation of various peroxidases with a heme group at the active center irreversibly.

Furthermore, **Basu and Mohapatra et al., [3]** explained that methimazole could cause an inactivation of peroxidases heme

group involved in scavenging H2O2, as CAT (catalase; antioxidant) was one of the most essential peroxidases that hindered the metabolism-enhanced H2O2 and CAT inactivation caused high levels of H2O2. The decrease in the antioxidant system might result in an elevation in oxidation reaction and injury of cells because H2O2 participated in the cells that produce it, could cross the plasma membrane, and affected adjacent cells.

In our work, examination of Haematoxylin and eosin (H&E) stained sections of methimazole co-treated with T4 group revealed decrease of vaculation of the tubules with hemorrhage and inflammatory cells between tubules. Immunohistochemical stained sections revealed some immunoreactive nuclei among the tubular lining cells and in the glomeruli. These results were in accordance with **Gazia. [26]** who reported such changes are less evoked in rats with hypothyroidism and received T4 .Also, **Puzianowska-Kuznicka et al [15]** reported that in rats administrated methimazole with T4 supplementation, the changes were incompletely prevented in the renal cortex. This effect was caused by the effect of thyroid hormones on the cell cycle regulation.

In the current study, T3 and T4 concentration decreased in hypothyroidism induced by thyroidectomy and methimazole treated group compared with the euthyroid group. This agreed with **Gazia [26], Cano-Europ et al., [38]** and **Cano- Europa et al., [39]** who reported that the concentration of T3 and T4 decreased in the thyroidectomized group and methimazole-treated group.

In this work, at the end of treatment, the hypothyroidism induced by methimazole caused reduction of the body weight. The thyroidectomized group and the group treated with methimazole and T4 showed differences in the body weight in comparison with the control group. This agreed with **Gazia [26]** and **Sur [40]** who reported that in methimazole treated group there is significant decrease in the body weight.

Statistical analysis of our result showed that there were statistical significance differences between the studied groups in the thickness of Bowman's space and the diameter of the tubules. There was increase in the thickness of Bowman's space and the diameter of the tubules in group III. In addition, group IV showed statistical significance differences Compared with group I. However, there were no change in group I and II. This was proved by **Gazia [26**] who reported that sections in the group treated with methimazole showed some glomeruli with Bowman's space widening, and the kidney tubules with a dilated lumen and degeneration of its lining. Some tubules revealed marked necrosis while others showed defect in cellular continuity, pyknosis of nuclei of tubular cells, and disintegration of cellular content. Kidney tubules lined with vacuolated cells, and hyaline casts in lumen of many tubules were also detected. These changes were less evoked in rats with hypothyroidism and received thyroxine (T4), whereas some tubules showed the vacuolated cells in their lining and hyaline casts in tubular lumen.

The statistical analysis of activity of renal antioxidant enzymes in the studied groups showed that no significant change between the control and thyroidectomized groups, while treatment with methimazole caused decrease in antioxidant enzymes levels. This decrease in the renal antioxidant enzyme levels was not prevented by T4 in the group administrated methimazole with T4. This agreed with **Gazia [26]** who registered that there was significant decrease in the activity of antioxidant enzymes in the group treated with methimazole.

Sarandol et al., [41] reported that the decrease of the antioxidant enzymes levels which detected in the methimazole-induced hypothyroidism group might be due to the oxidant reaction that causes oxidative stress and damage of cells.

There is a proof of extrathyroidal effects of antithyroid drugs, such as thionamides, in animals and humans **Bandyopadhyay et al., [37].** One of these effects of thionamides is a contribution to oxidative stress and cellular damage. In general, cellular injury occurred when the balance between oxidant and antioxidants was disturbed and the antioxidant system did not neutralize the oxidants. An enhanced oxidant system caused lipid peroxidation, an increase of reactive oxygen species, and also nitration, carbonylation or

glutathionylation of proteins and fragmentation of DNA **[9,10].**

In conclusion, methimazole causes hypothyroidism and damage in the kidney cortex. This damage is not caused by hypothyroidism induced by surgical thyroidectomy. L-Thyroxine (T4) could decrease the effect of methimazole on renal cortex.

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