Original Article

Adverse Effect of Dexamethasone on the Thyroid Gland of Adult Male Albino Rat and the Possible Protective Role of Curcumin: Histological, Immunohistochemical and Biochemical Study

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ABSTRACT

Introduction: The thyroid gland is a vital endocrine gland that regulates metabolism, growth, and development of the human body. Dexamethasone (Dex) is a synthetic glucocorticoid that is used to treat a variety of metabolic and inflammatory diseases, but there are insufficient data on how it can adversely affect the thyroid gland. Curcumin (Cur) is a powerful natural antioxidant with a variety of medical benefits.

Aim of the Work: To demonstrate the histological, immunohistochemical, and biochemical changes induced by dexamethasone in the thyroid gland of adult male albino rat and to investigate the possible protective effect of curcumin.

Material and Methods: Forty male albino rats were randomly divided into 4 groups (10 rats each): the control group, Cur-group, Dex-group, and Dex+Cur group. Dexamethasone was injected subcutaneously three times per week for thirty days at a dose 0.1 mg/kg/day. Curcumin was given orally at a dose 100 mg/kg/daily for the same period. The thyroid tissues were processed for light and transmission electron microscopic studies. Serum levels of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were assayed.

Results: Dex-group showed vacuolated, multilayered follicular cells, desquamated cells in the follicular lumen, disrupted follicular basement membrane and congested blood vessels. Ultrastructurally, follicular cells showed cytoplasmic vacuolations, destructed mitochondria, dilated rough endoplasmic reticulum, shrunken irregular nuclei and disturbed normal architecture compared to the control group. There was a significant increase in (collagen deposition and Ki67 immunoexpression) and a significant decrease of (serum levels of T3, T4 and TSH) in Dex group versus control group. Co-treatment with curcumin in Dex+Cur-group restored the normal glandular structure and biochemical parameters.

Conclusion: Dexamethasone induced adverse effects on both structure and function of the thyroid gland of adult albino rats that could be ameliorated by co-treatment with curcumin. So, concomitant intake of curcumin with dexamethasone is recommended to protect the thyroid gland.

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Key Words: Curcumin, dexamethasone, Ki67, thyroid, ultrastructure.

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INTRODUCTION

Glucocorticoids (GCs) are steroid hormones that are known as "stress hormones" due to their role in the primary physiological response to stress[1,2]. Dexamethasone (Dex) is a synthetic corticosteroid drug that is used for suppressing the immune system of the human body. It belongs to the GC family, and its efficacy can exceed cortisol by 20-30 times[3,4]. Dexamethasone is an anti-inflammatory medication that relieves inflammation and treat a variety of metabolic and inflammatory diseases[5,6]. Additionally, it is used to treat acetonemia / ketosis, non-specific skin illnesses, trauma, and stress in animals[7,8]. Whereas treatment with steroids for long duration has numerous health risks as insufficient adrenal function, increase the susceptibility to infection, hyperglycemia, high blood pressure, osteoporosis, and diabetes mellitus[9].

Thyroid gland synthesizes tyrosine-based hormones (triiodothyronine (T3) and thyroxine (T4)) which have a fundamental role in the human health. These hormones are mainly responsible for regulating vital metabolic processes such as cell growth, development, and differentiation in the human body[10,11]. Thyroid hormones affect nearly every metabolically active cell in the body, therefore thyroid disturbance can induce adverse effects on all body systems[12].

The thyroid axis (hypothalamus-pituitary-thyroid axis) is a hormone regulatory system starting from the hypothalamus to the pituitary and eventually to the thyroid gland. Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and then stimulates the secretion of TSH from the pituitary gland which in turn, stimulates thyroid gland to release T3 and T4[13]. GCs can affect thyroid metabolism through its impact on the hypothalamus- pituitary-thyroid-axis as thyroid gland has α and β glucocorticoid receptors, which have an essential role in the differentiation of thyroid cells[14,8].

Curcumin is a yellow pigmented natural polyphenol that is extracted from the rhizome of turmeric

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(Curcuma longa), a member of the ginger family (Zingaberaceae)[15]. It has multiple therapeutic benefits related to its antioxidant and anti-inflammatory properties. It protects against oxidative damage that is induced by many toxicants and oxidative materials and can modulate over 700 genes as well as slow or stop inflammatory enzymes including cyclooxygenase-2 and 5-lipoxygenase[16]. Curcumin is used widely as a spice and as natural food coloring substance. It is also characterized by having many pharmacological and physiological effects such as antibacterial, antifungal, antiviral, antiproliferative, proapoptotic, and antiatherosclerotic. Moreover, curcumin has many therapeutic benefits for Alzheimer's disease, arthritis, allergy, asthma, psoriasis, diabetes, multiple sclerosis, nephrotoxicity, cancer, inflammatory bowel disease as well as cardiovascular disease[17]. It is available in the form of powder, capsules, tablets, ointments, energy drinks, and even in soap and cosmetics. Further, the curcuminoids are approved by the US Food and Drug Administration (FDA) as "Generally Recognized As Safe" (GRAS)[18].

Based on the previously mentioned data, this study aimed to demonstrate the histological, immunohistochemical, and biochemical changes induced by dexamethasone in the thyroid gland of adult male albino rats and to evaluate the possible protective effect of curcumin.

MATERIALS AND METHODS

Experimental animals

The experiment was performed in the animal house of the Histology and Cell Biology Department in the Faculty of Medicine, Tanta University. Forty adult male albino rats aged 2-3 months, weighing 180 – 200 grams were used in this experiment. They were fed a standard laboratory animal feed and were adapted in clean properly ventilated cages for a week without receiving any treatment before starting the experiment. The experiment was performed following the standard of the ethical committee of Tanta University, which are in agreement with the national guidelines for animal care and use (Approval number: 35160/12/21.).

Reagents

Dexamethasone was purchased from Amriya for pharmaceutical industries (No. 941, Alexandria, Egypt) in a solution form dexamethasone sodium phosphate. Dexamethasone solution was at a concentration of 4 mg/1ml. The target dose was reached by adding 19 ml of distilled water to each 1 ml solution.

Curcumin was purchased from Herbal House Company (No. HHC092020, Dakahlia, Egypt). It was in the form of bright yellow to orange powder and was dissolved in distilled water as a vehicle. Dissolved curcumin solution was prepared at a concentration of 20mg/1ml by dissolving 1000 mg curcumin powder in 50 ml of distilled water.

Experimental design

Animals were randomly divided into 4 equal groups (10 rats each) as following:

Group I (Control group): included 10 rats were subdivided randomly into 3 subgroups as following:

- Subgroup Ia: rats were kept without any treatment through the experimental period.
- Subgroup Ib: rats were given 1ml distilled water, the diluting vehicle for curcumin, daily using gastric tube for 30 days.
- Subgroup Ic: rats were injected 0.1ml of distilled water, the diluting vehicle for dexamethasone, subcutaneously three times per week for 30 days.

Group II (Cur-group): included 10 rats received 1ml of curcumin solution daily using gastric tube in a dose of 100 mg/kg/day for 30 days[16].

Group III (Dex-group): included 10 rats that were injected 0.1 ml of dexamethasone solution subcutaneously three times per week for 30 days at a dose 0.1 mg/kg/day[19].

Group IV (Dex+Cur group): included 10 rats received curcumin concomitantly with dexamethasone in the same dose and duration as group II & III.

At the end of the experimental period, rats were anaesthetized with sodium pentobarbital at a dose of 50 mg/kg through intraperitoneal injection[20]. To expose the trachea, a midline incision was made with dissection of the neck to separate the sternomastoid and sternohyoid muscles. After that, trace upward until the thyroid gland was visible and gently dissected. Each gland was divided into two parts; one of each was processed for light microscopic study and the other for electron microscopic study.

Hormonal assay

Blood samples were collected immediately from the heart of anaesthetized rats by 5 ml syringes between 9.00 to 10.00 A.M to avoid the diurnal variation of hormones levels. Serum was obtained by centrifugation at 3000 rpm for 15 minutes, then serum samples were separated into small glass tubes and stored at -20 ºC until analysis. Chemiluminescence immunoassay (CILA) on a Cobas e601 immunoassay analyzer (Roche-Hitachi Diagnostics, Mannheim, Germany) was used for measuring T3, T4, and TSH serum levels. The hormones were evaluated using Biodiagnostics (Cairo, Egypt) commercially available kits following the manufacturer's instructions[21]. The results were collected and statistically analyzed.

Processing for light microscopy

Specimens were immediately fixed in 10% formal saline solution for 24 hours, dehydrated in ascending series of ethyl alcohol, cleared in xylene, impregnated and paraffinized. Subsequently, sections of 5 µm thickness were cut and mounted on slides. Then, sections were

stained with hematoxylin & eosin (H&E) and Masson trichrome stains[22].

Some specimens were used for immunohistochemical staining for detection of Ki67 protein which is a nuclear marker for evaluation of cellular proliferation. Antigen retrieval of deparaffinized sections was done by adding citrate buffer (pH 6.0) in the microwave. The sections were incubated with rabbit anti-Ki67 monoclonal antibody (Thermo Fisher Scientific,USA, Cat. No. RM-9106-R7) after incubation in 3% hydrogen peroxidase to block endogenous peroxidase activity. Then the sections were incubated with anti-rabbit immunoglobulins for 30 min. Incubation of the sections with diaminobenzidine (DAB) was done for visualization of antibody binding. Negative control was done by the similar preceding steps without adding the primary antibody. Positive control was tonsil. The positive immunoreactivity for Ki67 appeared as brown nuclear staining in the immunoreactive cells[23,24].

Processing for electron microscopy

Thyroid specimens were finely cut and fixed using 4% phosphate buffered glutaraldehyde (0.1 mol/L, pH 7.4), then post-fixed using 1% phosphate-buffered osmium tetroxide. Subsequently, specimens were dehydrated in ascending grades of alcohol then embedded at the apex of inverted polythene beam capsule filled with liquid resin. Semithin sections (0.5 µm) and ultrathin sections (80-90nm) were cut using ultramicrotome. Semithin sections were stained with 1% toluidine blue for light microscopic examination. Ultrathin sections were double-stained with uranyl acetate and lead citrate to be examined and photographed by Transmission Electron Microscope[25]. JEOL-JEM-100 transmission electron microscope (Tokyo, Japan) was used to examine the grids at the Electron Microscopy Unit, Tanta Faculty of Medicine, Egypt.

Morphometric study

The morphometric study was performed using the software "ImageJ" (version 1.48v National Institute of Health, Bethesda, Maryland, USA) for image analysis. The following measurements were quantitatively evaluated in randomly selected 10 nonoverlapping fields at 400 x magnification for each slide:

1. The mean follicular diameter in H & E stained slides[26].
2. The mean area% of collagen fibers in Masson's trichrome stained slides[27].
3. The mean number percentage (%) of Ki67-positive cells in Ki67 immunostained slides[24].

Statistical analysis

The collected morphometric and biochemical data were presented as {Mean ± SD} for all groups and were statistically analyzed by one-way analysis of variance ANOVA followed by Tuckey post hoc test to compare between the different groups. The data was statistically analyzed using statistical package for social sciences statistical analysis software (version 11.5; SPSS Inc., Chicago, Illinois, USA). Results were considered significant when probability value {*P value*} was ≤0.05[28].

RESULTS

The histological, immunohistochemical and electron microscopic results revealed similar findings in the three subgroups of the control group I (Ia, Ib and Ic) with no significant statistical differences in the morphometric results in-between them. Also, biochemical results showed non-significant statistical difference in-between these subgroups. Therefore, they were represented as control group (I) in text, tables and figures to simplify the presentation of our results.

Light Microscopic Examination

Histological Results

1-Hematoxylin & Eosin (H&E) and Toluidine blue (Tb) stained sections

Group I (Control group) and group II (Cur-group): Examination of H&E (Figure 1A) and Tb (Figure 2A) stained thyroid sections of both control and Cur groups revealed similar findings and showed the typical architecture of the thyroid gland. It consisted of lobules separated by CT septa and each lobule was composed of spherical or oval variable sized follicles. The Lumina of thyroid follicles were filled with homogenous acidophilic colloid and were surrounded by one layer of flattened to cuboidal cells with central rounded nuclei. Additionally, in toluidine blue stained sections, we noticed parafollicular C cells with pale cytoplasm and pale vesicular nuclei resting on the follicular basement membrane. Also, capillaries were observed in the connective tissue surrounding the follicles.

Group III (Dex-group): Hematoxylin & eosin (Figures 1 B,C,D,E,F) and Toluidine blue (Figures 2 B,C,D,E) stained sections of Dex-group showed variable structural alterations in the thyroid glands. Follicles revealed swollen vacuolated follicular cells with reduction of colloid or completely empty lumina. Numerous follicles were lined by numerous layers of vacuolated cells that nearly obliterate their lumina, some of which have darkly stained nuclei and the others with pale nuclei. The apical membranes of some follicular cells were disrupted with spilled cytoplasmic content, desquamated cells, and cellular debris in the follicular lumen. Disturbed follicular basal lamina with fusion of some follicles was also noticed. Some follicles showed complete loss of their lining follicular epithelium with scattered nuclei in the colloid. Other follicles appeared with lining epithelium having irregular outlines, vacuolated cytoplasm, and irregular nuclei. There was marked variation in the follicular size that varied from huge, distended follicles to very small shrunken ones. Moreover, dilated congested blood vessels

and inflammatory cellular infiltration were observed in the interstitial tissue in-between the follicles. In addition to loss of the regular lobular architecture of the gland.

Group IV (Dex+Cur group): Examination of H&E (Figures 1 G,H), and Tb (Figures 2 F,G) stained thyroid sections in Dex+Cur group showed more or less preservation of the normal histological structure of the thyroid gland. Normal lobular architecture was observed with follicles of variable sizes and homogenous acidophilic colloid filling their lumina. Most of the follicular cells appeared with normal nuclei and cytoplasm while others showed mild vacuolated cytoplasm. Few areas showed inflammatory cellular infiltration and sporadic shrunken distorted follicles.

2- Masson's trichrome stained sections

Showed minimal amount of collagen fibers in the interstitial tissue between lobules and in between the follicles in both control and Cur-groups (Figure 3A). The deposition of collagen fibers was markedly increased in Dex-group (Figure 3B), whereas in Dex+Cur group moderate amount of collagen fibers was deposited between the gland lobules and between the follicles (Figure 3C).

Immunohistochemical Results

Concerning Ki67 immunostained sections of both control and Cur groups, the immunohistochemical results were nearly similar and revealed weak Ki67-positive immunoreaction that appeared as brown nuclear deposits in the nuclei of few follicular cells (Figure 4A). On the other hand, strong Ki67-positive immunoreaction was noticed in the nuclei of numerous follicular cells in Dex-group (Figure 4B). Dex+Cur group revealed moderate positive immunoreaction in the nuclei of some follicular cells (Figure 4C).

Electron Microscopic Examination

Group I (The control group) and group II (Cur-group): Ultrathin sections of the thyroid glands of rats of the control group (Group I) and Cur-group (Group II) revealed the same ultrastructure picture of normal thyroid follicular cells which appeared flattened to cuboidal in shape. Their cytoplasm revealed apparently normal mitochondria, regular cisternae of rER, and secretory granules. The follicular cells also showed oval or rounded euchromatic nuclei and their apical membrane exhibited short regular microvilli projecting into the colloid cavity. They were resting on regular intact basement membrane (Figures 5 A,B,C).

Group III (Dex-group): Follicular cells in Dex-group showed mild to marked dilated rough endoplasmic reticulum. Mitochondria with disrupted cristae and electron dense bodies were also observed. Some follicular cells showed normal euchromatic nuclei while the others exhibited changes varied from small, irregular, indented and dark nuclei as well as dilatation of the perinuclear cisterna. Dilated intercellular spaces between the follicular cells and disrupted basal lamina were also encountered. Moreover, dilated congested blood capillaries were seen between distorted follicles and some blood capillaries contained inflammatory cells (Figures 5 D,E,F,G,H).

Group IV (Dex+Cur group): Most of follicular cells in this group showed almost normal histological structure. They appeared flat to cuboidal with regular apical microvilli. The cytoplasm showed normal rER, however some cells appeared with mild dilated rough endoplasmic reticulum and multiple lysosomes. Their nuclei were euchromatic and flat to rounded in shape. The basement membrane appeared more or less intact (Figures 5 I,J).

Biochemical Results

No significant statistical differences in the biochemical results were noticed between the control group (group I) and Cur-group (group II). In Dex-group (group III), serum levels of T3 (1.705 ± 0.083), T4 (1.538 ± 0.295) and TSH (0.582 ± 0.06) exhibited a significant decrease (P = .000) compared to the control group (3.432 ± 0.172, 3.012 ± 0.187, 1.165 ± 0.05; for T3, T4, and TSH respectively). On the other hand, Dex+Cur group (group IV) showed a significant increase (P = .000) in the level of T3 (3.317 ± 0.097), T4 (2.805 ± 0.091), and TSH (1.123± 0.041) compared to the Dex-group with no significant difference (P =. 339, .102, .234; for T3, T4, and TSH respectively) compared to the control group (Table 1; Histogram 1).

Morphometric Results

In the present study, no significant statistical differences in the histological and immunohistochemical results were noticed between the control group (group I) and Cur-group (group II). Furthermore, the mean values of the follicular diameter in H&E stained sections and the mean area percentage of collagen fibers in Masson trichrome stained sections as well as, the percentage of ki67- positive cells of Dex+Cur group (group IV) (40.723±5.688; 3.511 ± 0.988; 15.644±1.871 respectively) and in control group (37.353 ± 4.399; 2.445 ± 0.799; 12.731±1.87 respectively) revealed non-significant difference (P = .341 ; P = .081; P = .095 respectively) versus each other. These values significantly increased (P = .000) in Dex-group (group III) (76.29±3.437; 6.984±1.29; 35.991±4.21 respectively) versus control and Dex+Cur groups (Table 2; Histogram 2,3,4).

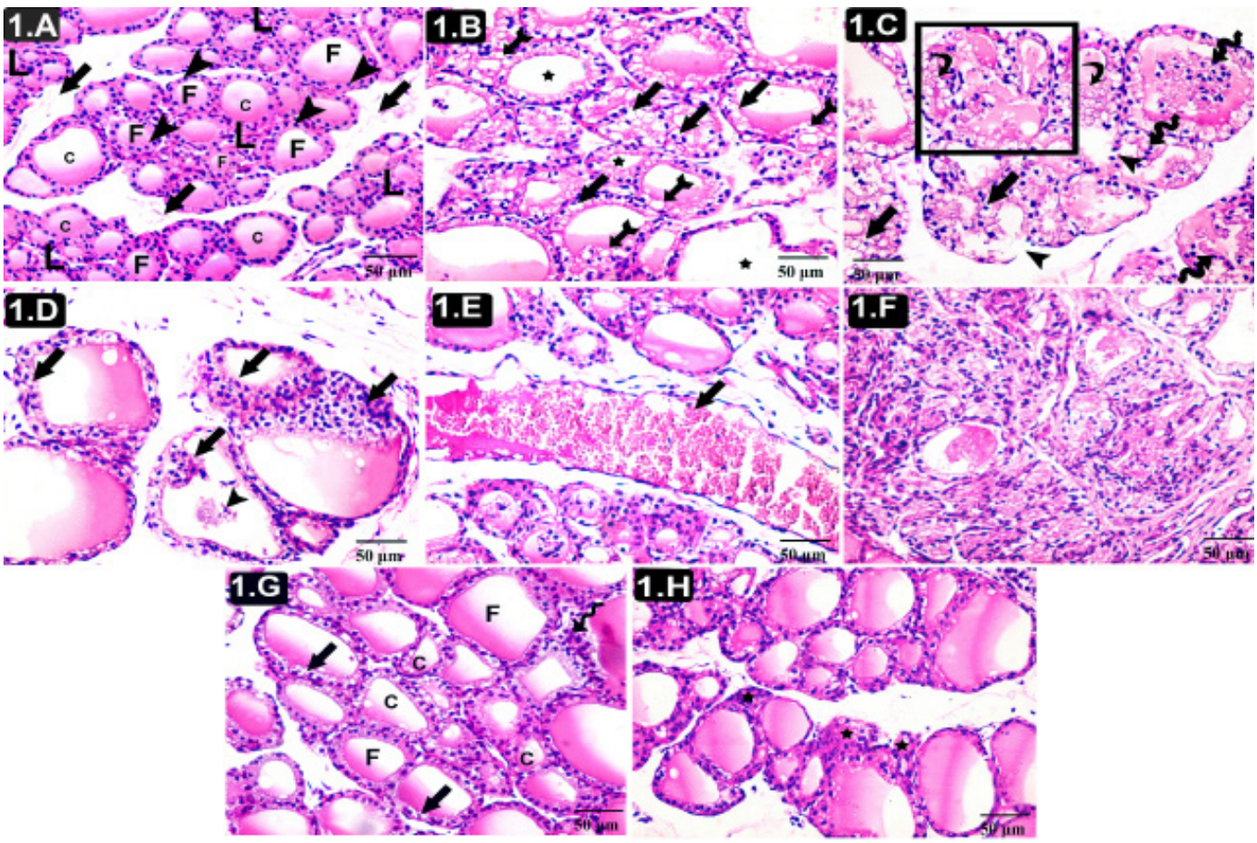


Fig. 1: Photomicrographs of H&E stained thyroid sections of rats in control group (group I) (A) shows lobules (L) separated by CT septa (arrows) and each lobule consists of variable sized follicles (F). Follicles are lined by one layer of flattened to cuboidal epithelium with central rounded nuclei (arrowheads) and their lumina are filled with colloid (C). Dex-group (group III) (B) reveals follicles lined by vacuolated epithelium (arrows) with some follicular cells lost their nuclei (bifid arrows). Notice colloid reduction or totally empty lumina (stars). (C) In some follicles, several follicular cells with pale nuclei and vacuolated cytoplasm obliterate the follicular lumen (curved arrows). Some follicles are fused together (in square) and others show desquamated cells scattered in the lumen (wavy arrows). Notice the disrupted basement membrane (arrowheads) and vacuolated follicular cells (arrows) (D) marked variation in the follicular size with many distended follicles lined by numerous layers of follicular cells (arrows). Notice cellular debris in the lumen of the follicle (arrowhead). (E) dilated congested blood vessel is observed (arrow). (F) disruption and loss of the typical architecture of the gland. Dex + Cur group (group IV) is showing (G) homogenous acidophilic colloid (C) filling the follicular lumen. Most of the follicular cells show oval or rounded nuclei and normal cytoplasm (F), while others appear with mild vacuolated cytoplasm (arrows). Notice inflammatory cellular infiltration (wavy arrow). (H) few follicles appear shrunken and distorted (stars) (H&E stain, Mic.Mag. X 400, scale bar = 50µm).

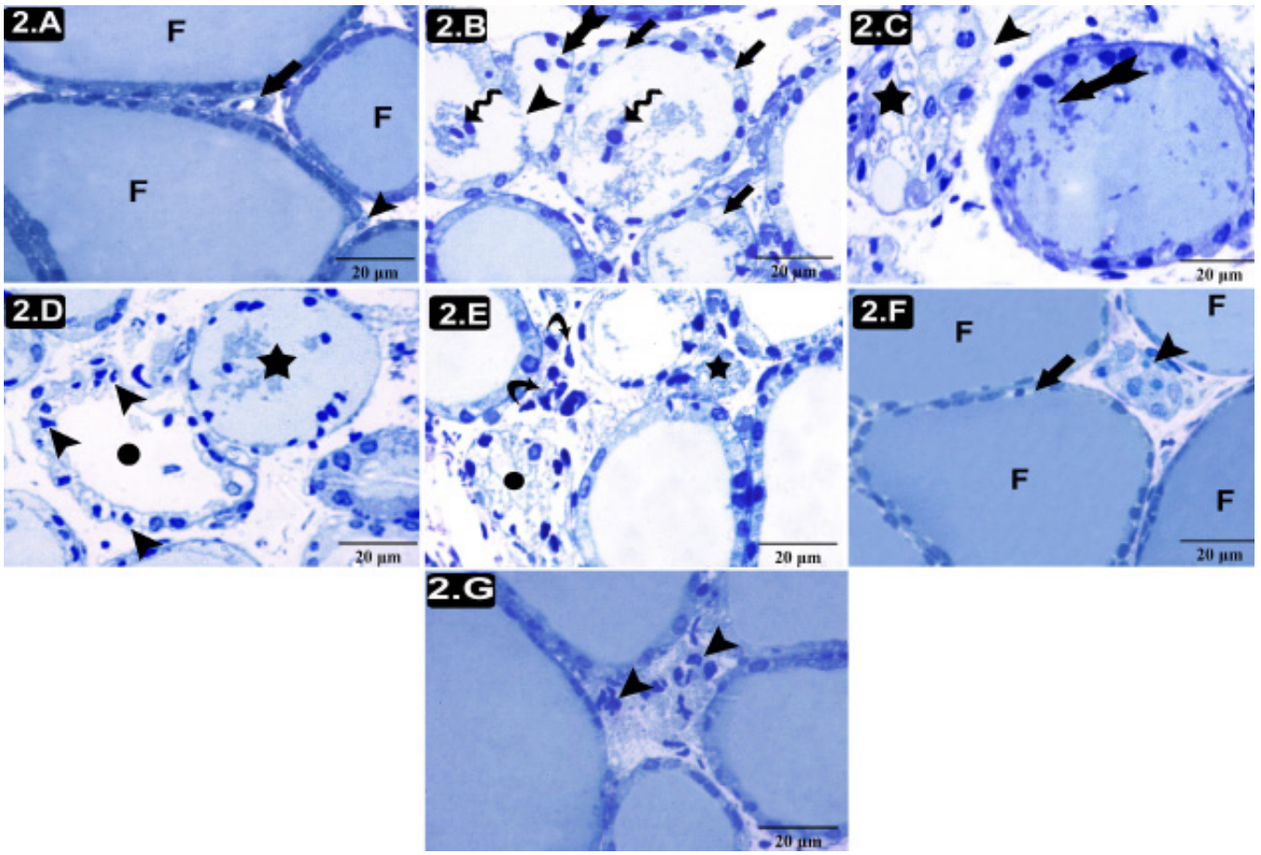


Fig. 2: Photomicrographs of semi-thin sections of the thyroid gland of rats in: control group (A) shows apparently normal thyroid follicles (F) lined with one layer of flattened to cuboidal epithelium and filled with homogeneous colloid. Parafollicular C cell with pale cytoplasm and pale vesicular nucleus is resting on the follicular basement membrane (arrowhead). Notice capillaries in the connective tissue in-between follicles (arrow). Dex-group (B) reveals adherent follicles with disrupted basal lamina (arrowhead), vacuolation of the cytoplasm of the follicular cells with absence of their nuclei (arrows) as well as desquamated cells and cellular debris scattered in the lumen (wavy arrows). Shrunken distorted follicle is seen embedded between follicles (bifid arrow). (c) shows some follicles with disrupted apical membranes and spilled cytoplasmic content in the lumen (bifid arrow). Other follicle (star) exhibits multiple vacuolated follicular cells that nearly obliterate its lumen, some of them shows pale nuclei and the others appear with darkly stained nuclei. Notice disrupted basal lamina (arrowhead) (D) shows a follicle (star) exhibits complete loss of the lining follicular epithelium with scattered nuclei in the colloid. Another follicle (circle) appears with an empty lumen and a lining epithelium shows irregular outlines, irregular nuclei and vacuolated cytoplasm (arrowheads). (E) shows inflammatory cellular infiltration in the interstitial tissue in-between the follicles (curved arrows). Notice shrunken distorted (star) and irregular (circle) follicles. Dex+Cur group (F) is showing thyroid follicles (F) filled with homogenous colloid. Most of the follicular cells show oval or rounded nuclei and normal cytoplasm, while others exhibit mild vacuolated cytoplasm (arrow). Few follicles appear shrunken and distorted (arrowhead). (G) inflammatory cellular infiltration is observed in the interstitial tissue in-between the follicles (arrowheads) (Toluidine blue stain, Mic.Mag. X 1000, scale bar = 20 µm).

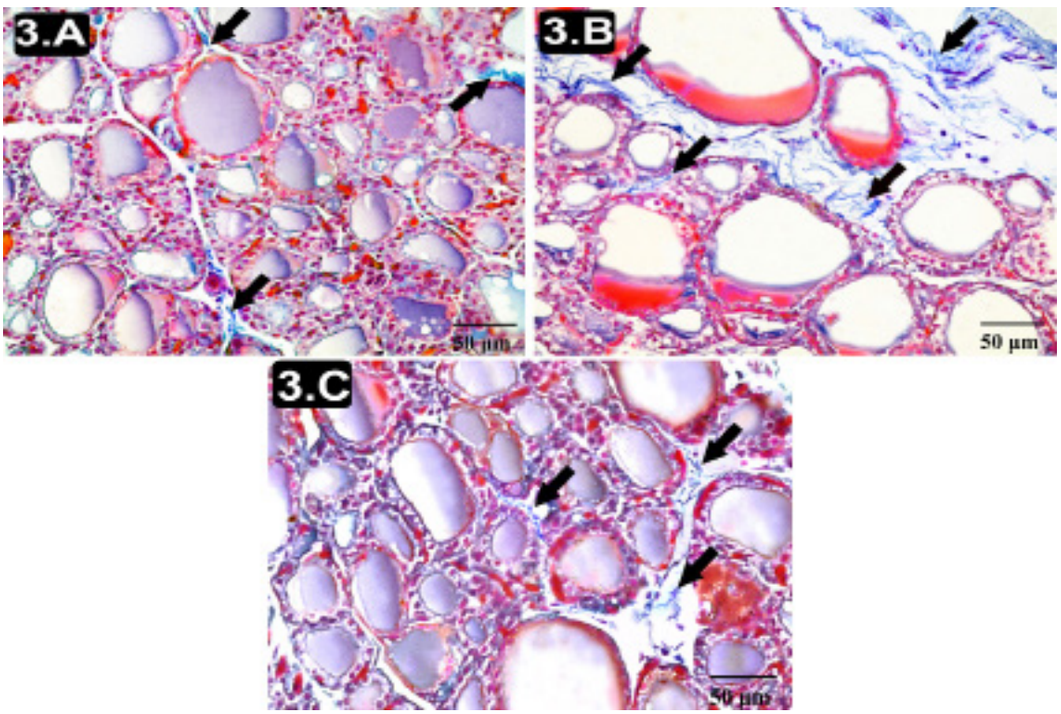


Fig. 3: Photomicrographs of Masson's trichrome stained thyroid sections of the studied groups. Control group (A) shows minimal amount of collagen fibers in-between the lobules and in between the follicles (arrows). Dex-group (B) shows excessive accumulation of collagen fibers (arrows). Dex+Cur group (C) shows moderate amount of collagen fibers (arrows) (Masson's trichrome stain, Mic.Mag. x400, scale bar = 50µm).

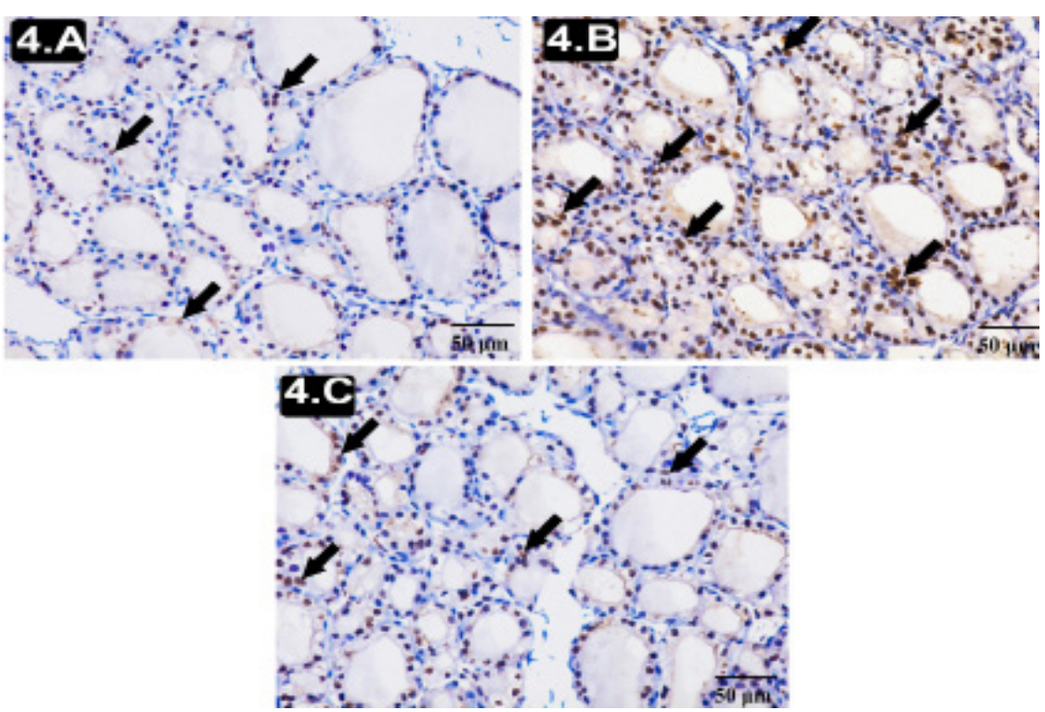


Fig. 4: Photomicrographs of Ki67- immunostained sections of the thyroid gland of (A): Control group shows weak Ki67 positive immunoreaction in the nuclei of few follicular cells (arrows). (B): Dex-group reveals strong Ki67-positive immunoreaction in numerous follicular nuclei in multiple follicles (arrows). (C): Dex-Cur group demonstrating moderate Ki67 positive immunoreaction in few follicular nuclei of some follicles (arrows) (Ki67 immunostaining, Mic.Mag. x400, scale bar = 50µm).

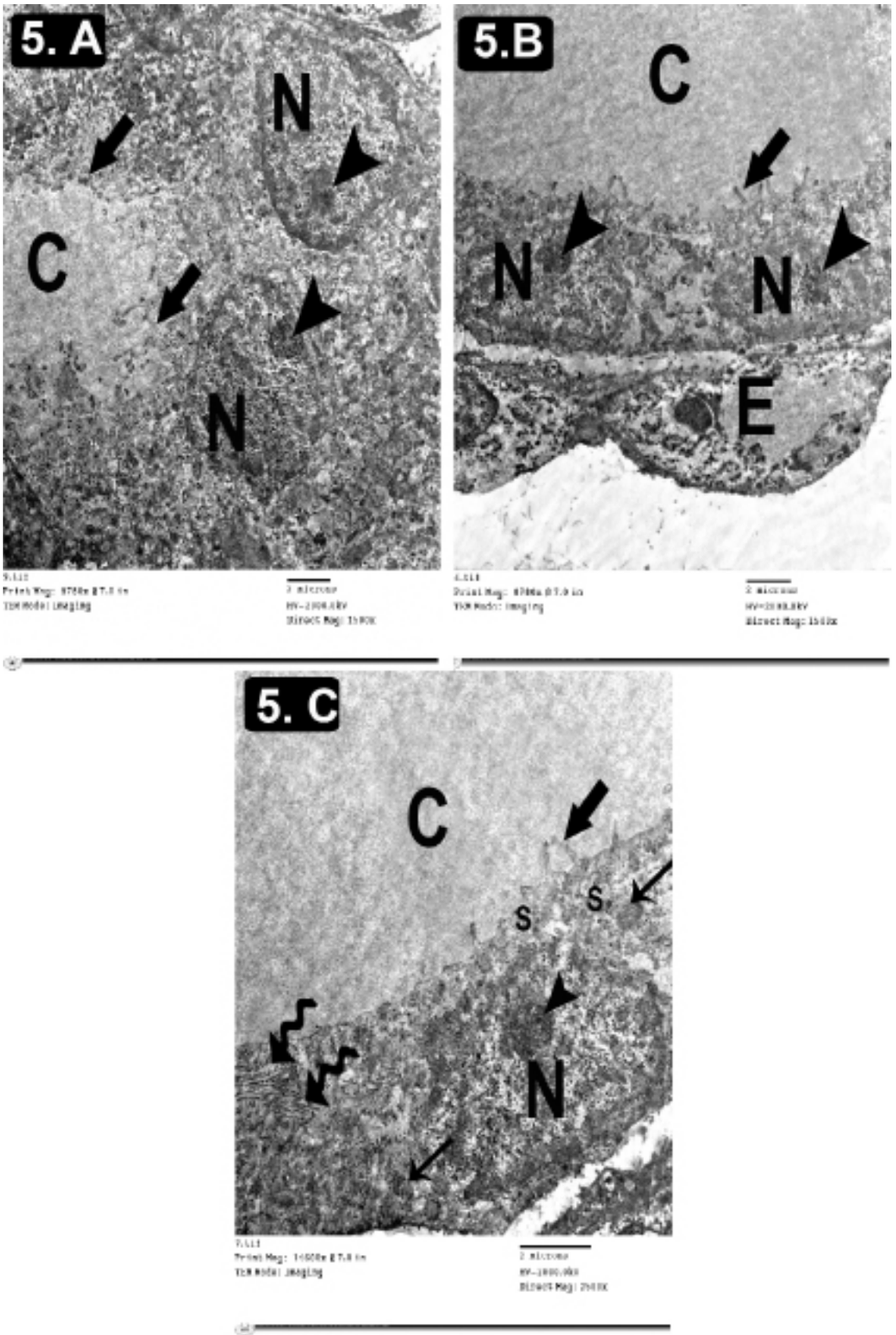


Fig.5 (A, B & C): Electron micrographs of follicular cells of rats in control group (Group I) (A&B) shows parts of thyroid follicles lined with follicular cells having euchromatic nuclei (N) with prominent nucleolus (arrowheads), apical microvilli (thick arrows), and filled with a homogenous colloid (C). Notice endothelial cell (E) presents under the basal lamina (Mic. Mag. X1500). (C) Higher magnification of a follicular cell shows regular rER (wavy arrows), intact mitochondria (thin arrows) and secretory granules (S) (Mic. Mag. X2500).

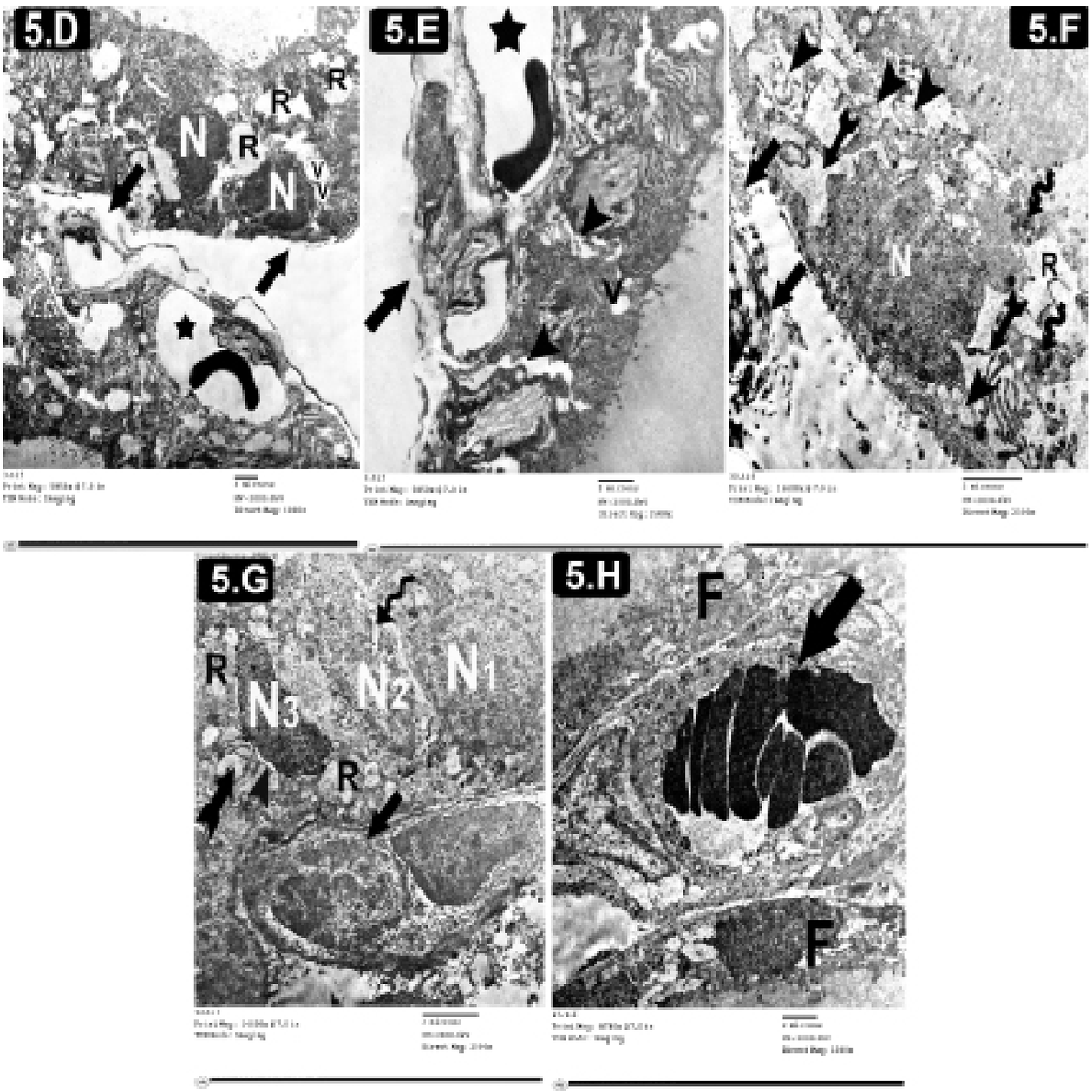


Fig. 5 (D, E, F, G & H): Electron micrographs of follicular cells in Group III (Dex-group) (D) shows follicular cells with rarified (R) vacuolated (V) cytoplasm, shrunken irregular hyperchromatic nuclei (N), and disrupted basal lamina (arrows). Notice dilated blood capillary (star) (Mic. Mag. X1000). (E) reveals dilated intercellular spaces between follicular cells (arrowheads) and cytoplasmic vacuoles (v). Notice dilated blood capillary (star) and disrupted basal lamina (thick arrow) (Mic. Mag. X1500). (F) shows mitochondria with disrupted cristae (arrowheads), electron dense bodies (wavy arrows), dilated profiles of rough endoplasmic reticulum (bifid arrows), and irregular nucleus (N). Notice rarefaction of the cytoplasm (R) and collagen fibers in the interstitium (thick arrows) (Mic. Mag. X2500). (G) shows cytoplasmic rarefaction (R) and dilated rough endoplasmic reticulum (bifid arrow). Nuclei of three follicular cells; (N1) normal euchromatic nucleus, (N2) indented nucleus (wavy arrow), and (N3) hyperchromatic nucleus with dilated perinuclear cisterna (arrowhead) are also seen. Notice blood capillary contains inflammatory cells (thick arrow) (Mic. Mag. X2500). (H) reveals dilated congested blood capillary (thick arrow) between distorted follicles (F) (Mic. Mag. X1500).

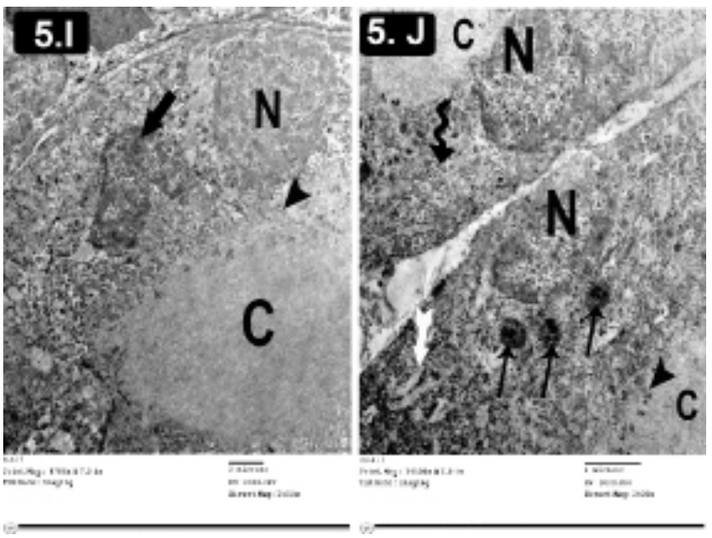


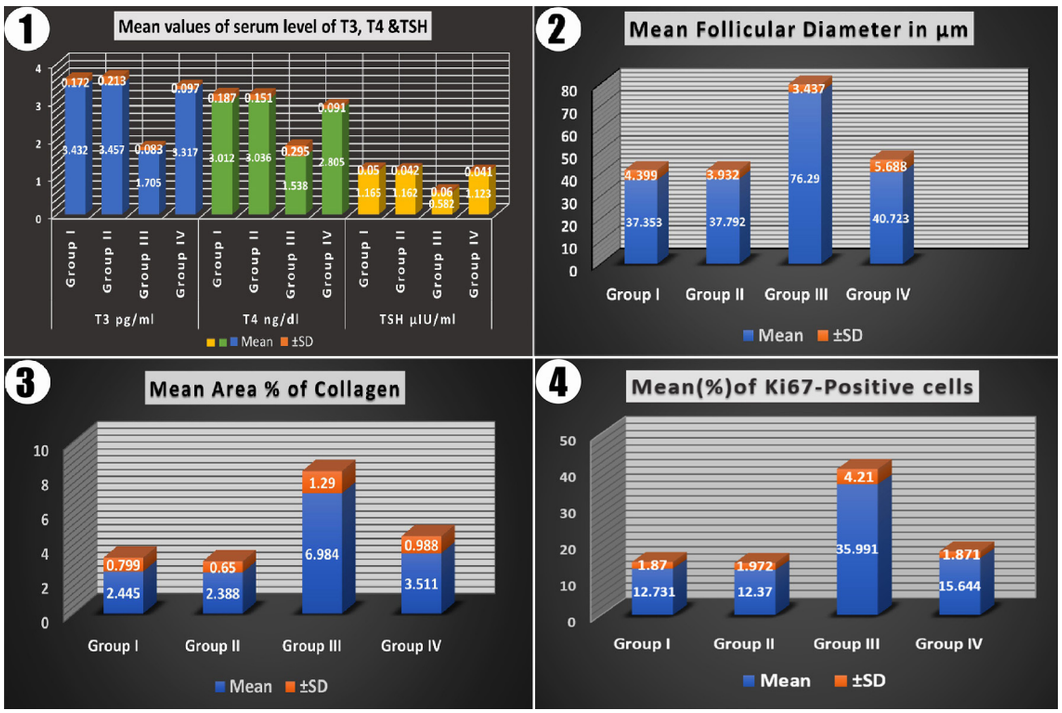
Fig. 5 (I&J): Electron micrographs of follicular cells in Dex+Cur group (I&J) reveals parts of thyroid follicles appear more or less as the control group with flattened to cuboidal follicular cells having euchromatic nuclei (N), apical microvilli (arrowhead), and filled with a homogenous colloid (C), while few nuclei appear shrunken and irregular (thick arrow). (J) a higher magnification of follicular cells shows normal (wavy arrow) to mild dilated rER (bifid arrow) and secondary lysosomes (thin arrows) in the cytoplasm (Mic. Mag. X1500 I & X 2500 J).

Table 1: Mean ± SD of the serum levels of T3, T4 and TSH hormones in all groups (one way ANOVA followed by Tukey's post-hoc test were used). [a]P: vs. control; [b]P: vs. group III; S: significant $P \leq 0.05$; NS: non-significant $P > 0.05$

Groups \ Parameters		T3 (pg/ml)	T4 (ng/dl)	TSH (µlU/ml)
Group I	Mean ± SD	3.432 ± 0.172	3.012 ± 0.187	1.165 ± 0.05
Group II	Mean ± SD	3.457± 0.213	3.036 ± 0.151	1.162 ± 0.042
	P value and significance	[a]*P* = .983 NS	[a]*P* = .993 NS	[a]*P* = .999 NS
Group III	Mean ± SD	1.705 ± 0.083	1.538 ± 0.295	0.582 ± 0.06
	P value and significance	[a]*P* = .000 S	[a]*P* = .000 S	[a]*P* = .000 S
Group IV	Mean ± SD	3.317±0.097	2.805 ± 0.091	1.123± 0.041
	P value and significance	[a]*P* = .339 NS [b]*P* = .000 S	[a]*P* = .102 NS [b]*P* = .000 S	[a]*P* = .234 NS [b]*P* = .000 S

Table 2: Mean ± SD of the follicular diameter (um), area % of collagen and percentage of ki67- positive cells in the thyroid gland of all groups (one way ANOVA followed by Tukey's post-hoc test were used). [a]P: vs. control; [b]P: vs. group III; S: significant $P \leq 0.05$; NS: nonsignificant $P > 0.05$

Groups \ Parameters		The mean follicular diameter (um)	The mean area % of collagen	ki67- positive cells (%)
Group I	Mean ± SD	37.353±4.399	2.445±0.799	12.731±1.87
Group II	Mean ± SD	37.792±3.932	2.388±0.65	12.37± 1.972
	P value and significance	[a]*P* = .996 NS	[a]*P* = 0.999 NS	[a]*P* = 0.991 NS
Group III	Mean ± SD	76.29±3.437	6.984±1.29	35.991±4.21
	P value and significance	[a]*P* = .000 S	[a]*P* = .000 S	[a]*P* = .000 S
Group IV	Mean ± SD	40.723±5.688	3.511±0.988	15.644±1.871
	P value and significance	[a]*P* = .341 NS [b]*P* = .000 S	[a]*P* = .081 NS [b]*P* = .000 S	[a]*P* = .095 NS [b]*P* = .000 S



Histograms: shows (1) the mean ± SD of the serum levels of T3, T4 and TSH hormones, (2) the mean follicular diameter (um), (3) the mean area percentage of collagen fibers, (4) the mean number percentage of ki67- positive cells in all studied groups.

DISCUSSION

Many studies were conducted to investigate the effect of dexamethasone on different body organs, but how it can adversely affect the thyroid gland needs more research. Some previous studies reported that the polyphenolic compounds as curcumin can minimize or prohibit oxidative hazards induced by toxicants and oxidative materials[29]. So, in this work we intended to investigate the protective effect of curcumin on the hazards induced by dexamethasone on both structure and function of the thyroid gland.

As reported by[30] the administration of dexamethasone is correlated with suppression of numerous aspects of the thyroid functions and its effects on the thyroid follicles are variable as it has distinct differences in its effect from one lobule to another within a single gland. They also explained that glucocorticoids affect the thyroid function relying on both the dose and the endocrine condition.

In the current work, light microscopic examination of the thyroid gland in Dex-group revealed marked histological alterations that were confirmed by the electron microscopic examination. These alterations are compatible with those of[8] who demonstrated similar results in rats treated with dexamethasone.

The increased size and distention of the thyroid follicles that were observed in Dex-group was confirmed by statistical analysis of the morphometric study of the mean follicular diameters. According to the data obtained, the follicle diameters were significantly increased in Dex-group as compared to the other groups. On the other hand, some follicles of Dex-group appeared small and shrunken. Similar results were recorded by[30] who demonstrated that rabbits treated with dexamethasone revealed most of thyroid follicles distended with colloid accumulation and they attributed this finding to suppression of the activity of the thyroid gland. He also observed that glucocorticoids may led to the shrinkage of some thyroid follicles and explained that finding by that the influence of glucocorticoid was a dose and time dependent.

Additionally,[31,32] reported that the increased follicular size could be considered as an adaptive change to meet needs of the increased functional capacity due to chronic injury. Furthermore, in the current study increased follicular size appeared to be in line with the stratification and hyperplasia of the follicular lining epithelium. According to[32], the cellular hyperplasia (motivation of the resting (G0) cells to get in the cell cycle (G1) to begin the multiplication) could be attributed to the altered endocrine milieu. This explanation goes in line with our findings of the proliferative marker Ki67 immunostaining which is a cell proliferation-associated antigen that is expressed in all stages of the cell proliferative cycle except the G0 phase[33]. The morphometrical study clarified significant increase in the mean number of Ki67 positive cells in Dex-group which had the highest percentage of the proliferating cells versus other groups.

The shedding of epithelium lining of some follicles and presence of desquamated cells inside the follicular lumens were explained by[34] as a normal basal thyroid cells turnover to maintain thyroid gland's mass homeostasis through continuous basal proliferation and apoptosis. On the other hand,[35] stated that the exfoliated follicular cells in the follicular lumen could be attributed to apoptosis and thyroid toxicity. Moreover,[36] reported that the desquamation of the lining epithelium of the follicles might lead to destruction of the follicular walls and provoke their collapse.

Vacuolated rarefied cytoplasm that was observed in the follicular cells in Dex-group was previously detected by[37], who related these findings to the fluid accumulation. Whereas[38] reported that small and clear vacuoles within the cytoplasm of the follicular cells might be caused by hydropic and vacuolar degeneration. Another explanation was recorded by[39] who stated that the cytoplasmic vacuolation could be related to apoptosis. Furthermore, cytoplasmic vacuolations with pale nuclei could be caused by fluid accumulation together with glandular overstimulation. Additionally,[35] attributed the vacuolated or rarefied cytoplasm to the dilatation of rER cisternae.

Dilatation of the endoplasmic reticulum that was observed in the present study could be explained by different mechanisms according to[40]. The first one is the accumulation of the secretory products due to the increase of their synthesis more than their elimination. The second mechanism is due to either mechanical or enzymatic disturbance in the endoplasmic reticulum that prohibit the elimination of the average quantities of synthesized materials (an impairment in this transport system). Finally, may be due to synthesis of abnormal secretory products that can't get rid of them.

Concerning the mitochondria with disrupted cristae that were noticed in Dex-group, it may be an indicator to oxidative stress as recorded by[41] who attributed the damaged cellular functions to the overload on the antioxidant defense system. Moreover,[42] stated that altered mitochondrial membrane permeability in hypothyroid rats led to mitochondrial dysfunctions. Regarding, alteration of the nuclear pattern in the current work which varied from irregular, darkly stained, and shrunken nuclei as well as dilated perinuclear cisterna might denote apoptosis and DNA damage as reported by[29].

Concerning the irregular coalesced thyroid follicles with disrupted basal laminae that were noticed in Dex-group, might be related to degenerative alterations of the follicles and their collapse after colloid depletion as explained by[43]. Widened intercellular spaces between follicular cells in Dex-group might also be considered as degenerative changes as tight junctions are essential for the preservation of epithelial barrier integrity to permit the transport of the essential molecules and to limit the harmful ones[44].

The inflammatory cellular infiltration in the interfollicular septa of Dex-group could be explained by insufficiency of the thyroid hormones and hypoactivity of the thyroid gland as reported by[40]. Additionally,[45] attributed congestion of blood capillaries that was also observed in the same group to increase the need for blood to feed the follicular cells.

As regard Masson's trichrome stain, thyroid glands of rats in Dex-group showed marked deposition of collagen in the interstitial and in the interfollicular C.T. .This finding was confirmed by the morphometrical and statistical results as there was a significant increase in the area percentage of collagen fibers in group III as compared to the control group. This may be attributed to increased fibrinogen as recorded by[46] who observed that dexamethasone tends to increase fibrinogen concentration. Moreover,[47] demonstrated that fibrinogen stimulates the synthesis of transforming growth factor-β (TGFβ), which triggers the collagen production in fibroblasts. This goes in line with[48] who stated that dexamethasone induced extensive renal fibrosis. Whereas, contrary to the results of the current work,[30] noticed a decrease in collagen fibers deposition in thyroid glands of dexamethasone treated rabbits and attributed this finding to that glucocorticoid is considered a fibroblast growth inhibitor factor.

On the other hand, administration of curcumin in the Dex+Cur group showed preservation of the normal histological architecture as the follicular cells appeared more or less as the control group. According to[49,50], it can be attributed to the role of curcumin in modulation of the production of various inflammatory mediators and limitation of neutrophil infiltration as well as restrain of proinflammatory cytokines in macrophages. Furthermore, curcumin has an antiapoptotic effect as it can decrease the expression of some pro-apoptotic and proinflammatory genes as caspase-3 and COX2, while increase the expression of Bcl-2 which is an anti-apoptotic gene[17]. Concerning the noticeable increase in the lysosomes in some follicular cells in Dex+Cur group, it could be attributed to the improvement of the cellular secretory activity as reported by[16].

Additionally, examined sections of thyroid glands from Dex+Cur group revealed neither signs of hyperplasia nor hypertrophy which was confirmed morphometrically by a significant decrease in the mean of both follicular diameter and number of Ki67-positive cells compared to Dex-group and a nonsignificant difference versus control. This could be attributed to the anti-proliferative effect of curcumin exerted through its inhibitory effect on the activity of protein kinases (as protein kinase C) and on the mitogenic effect of growth factor signals in hypertrophic cells. These enzymes have a fundamental role in the signal transduction which causes thyroid cell proliferation[51,52]. Additionally, curcumin has an inhibitory influence on the proliferation of follicular cells as recorded by[29] who observed decreased expression of PCNA in curcumin treated animals after induction of hypothyroidism by potassium dichromate.

As reported by[53], curcumin can improve the fibrosis because of its anti-inflammatory effect which may explain the significant decrease in the area percentage of collagen fibers in Masson's trichrome stained sections in Dex+Cur group as compared to Dex-group. Furthermore,[54] attributed this finding to the modulatory effect of curcumin on TGFβ that induces fibrosis.

Regarding the laboratory results in the present study, there was a significant decrease in the serum T3, T4 and TSH levels in Dex-group compared to the control group. These results are in agreement with[55,8] who recorded that dexamethasone caused hypothyroidism accompanied by lowering in the levels of T3, T4 and TSH. Dexamethasone does not suppress TSH only but also inhibits the hypothalamic- pituitary- thyroid axis activity. The reduced levels of T3 and T4 may be attributed to the direct effect of Dex on T3 and T4 peripheral metabolism through the alteration of their attachment to carrier proteins, changing of their distribution, and interfering with the transforming of T4 to T3 as reported by[8]. Whereas counter to the results of the present work, a study done by[56] recorded a nonsignificant change in the serum level of TSH in rabbits treated with prednisolone versus rabbits in the control group.

Administration of curcumin in the Dex+Cur group revealed a significant increase of T3, T4 and TSH levels toward the normal levels in comparison with Dex-group. This is in consistence with[57,16] who recorded that curcumin can prevent the reduction of thyroid hormones levels and keep their serum levels near the normal range. These results illustrated the improvement of the thyroid function with administration of curcumin.

CONCLUSION AND RECOMMENDATIONS

We can conclude from the present study that the administration of dexamethasone induces evident histological, immunohistochemical and ultrastructural changes in the thyroid gland of albino rats, associated with a decrease in the serum level of thyroid hormones. The co-administration of curcumin with dexamethasone might ameliorate these alterations as it can restore both the normal thyroid histological architecture and hormonal levels. Therefore, we recommend the concomitant intake of curcumin with dexamethasone to protect thyroid gland from its hazards. Meanwhile, this is an experimental study that needs more investigations and more research to be clinically applied. So, further studies are required to confirm the results of the animal studies and to evaluate the molecular mechanisms of curcumin as well as to study its structural analogues.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التأثير الضار للديكساميثازون على الغدة الدرقية لذكر الجرذ الأبيض البالغ والدور الوقائي المحتمل للكركمين: دراسة نسيجية وهستوكيميائية مناعية وكيميائية حيوية

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المقدمة: ان الغدة الدرقية هي غدة صماء حيوية تنظم عملية التمثيل الغذائي والنمو والتطورفي جسم الإنسان. ويعد الديكساميثازون جلوكوكورتيكويد مصنع والذي يستخدم لعلاج مجموعة متنوعة من الأمراض الأيضية والإلتهابية ، ولكن لا توجد بيانات كافية حول تأثيره السلبي على الغدة الدرقية. أما الكركمين فهو أحد مضادات الأكسدة الطبيعية القوية وله مجموعة متنوعة من الفوائد الطبية.

الهدف من البحث: لقد كان الهدف من هذا العمل هو دراسة التغيرات النسيجية والهستوكيميائية المناعية والكيميائية الحيوية التي يسببها الديكساميثازون بالغدة الدرقية للجرذان البيضاء البالغة ودراسة التأثير الوقائي المحتمل للكركمين.

المواد وطرق البحث: لقد تم تقسيم أربعين من ذكور الجرذان البيضاء بشكل عشوائي إلى ٤ مجموعات متساوية (١٠ فئران لكل مجموعة): المجموعة الضابطة ، مجموعة الكركمين ، مجموعة الديكساميثازون ، ومجموعة الديكساميثازون +الكركمين. وتم حقن الديكساميثازون تحت الجلد ثلاث مرات في الأسبوع لمدة ثلاثين يومًا بجرعة ٠,١ مجم / كجم / يوم. كما تم إعطاء الكركمين عن طريق الفم بجرعة ١٠٠ مجم / كجم / يوميًا لنفس الفترة. وتم تحضيرعينات الغدة الدرقية للدراسة باستخدام المجهرالضوئي والإلكتروني، وفحص مستويات ثلاثي يودوثيرونين ورباعي يودوثيرونين وهرمون تحفيز الغدة الدرقية في المصل.

النتائج: لقد لوحظ في مجموعة الديكساميثازون، زيادة في عدد طبقات الخلايا المبطنة لحويصلات الغدة مع ظهور تجاويف بها. ولوحظ ايضا قطع بالغشاء القاعدي للحويصلات مع وجود خلايا متناثرة داخل تجويفها وكذلك احتقان بالأوعية الدموية. وبفحص الغدة باستخدام الميكرسكوب الاليكتروني، اظهرت الخلايا المبطنة لحويصلات الغدة تجاويف بالسيتوبلازم، وتدمير للميتوكوندريا، وتمدد بالشبكة الإندوبلازمية الخشنة ، وانكماش وعدم انتظام بالأنوية ، كما لوحظ تغير في النسيج الطبيعي للغدة مقارنة بالمجموعة الضابطة. وعلاوة على ذلك ،فقد لوحظ زيادة كبيرة في كمية ألياف الكولاجين وزيادة عدد الخلايا المصبوغة مناعيا بمستضد تكاثر الخلايا (Ki٦٧) في أنسجة الغدة الدرقية وانخفاض مستويات ثلاثي يودوثيرونين ورباعي يودوثيرونين وهرمون تحفيز الغدة الدرقية في المصل بشكل ملحوظ للفئران المعالجة بـالديكساميثازون مقارنة بالمجموعة الضابطة. وعلي الجانب الآخر، أعاد العلاج المشترك مع الكركمين في مجموعة (الديكساميثازون +الكركمين) هيكل الغدة الدرقية والعلامات البيوكيميائية لطبيعتهم.

الخلاصة: اظهرت هذه النتائج أن للديكساميثازون تأثيرات ضارة على كل من تركيب ووظيفة الغدة الدرقية للجرذان البيضاء البالغة والتي يمكن الحد منها عن طريق اعطاء الكركمين بالتزامن مع الديكساميثازون .لذلك ، يوصى بتناول الكركمين مع الديكساميثازون لحماية الغدة الدرقية.