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ORIGINAL ARTICLE

A Study on Serum Interleukin 6 Level and Its Relation to Some Oxidative Stress Markers in Experimentally Induced Thyroid Disorders in Adult Male Albino Rats

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ABSTRACT

Background: Thyroid hormones have shown to affect mitochondrial oxidative activity, synthesis of protein, and differentiation of muscle fibers and capillary growth. the aim of the current study is to explore the effect of experimentally induced thyroid dysfunction (hyperthyroidism, hypothyroidism) on IL6 levels and some of oxidative stress markers in order to clarify some of underlying possible mechanisms, and link these events with metabolic and histological changes.

Methods: Thirty adult male albino rats (fed ordinary laboratory along this 4 weeks' study), were divided randomly into 3 equal groups; control group, experimentally-induced hypothyroid group this group (rats received a single daily dose of 2 mg carbimazole/100g body weight diluted in drinking water by oral gavage for 4 weeks) and experimentally-induced hyperthyroid group (rats received L-thyroxin at a dose of 2µg/ml diluted in drinking water for 4 weeks). At the end of the experiment body mass index (BMI) were estimated for all rats.

Results: There was statistical significant difference between hypothyroidism, hyperthyroidism and control groups as regard oxidative stress markers and thyroid hormones levels; also, there was a statistical significant increase in serum interleukin-6 (IL-6) and serum tumor necrosis factor alpha (TNF-α) in both hypothyroidism and hyperthyroidism groups. There was a significant positive correlation between serum IL-6 with serum insulin and TNF-α with malondialdehyde (MDA).

Conclusions: hypothyroidism and hyperthyroidism were associated with the deterioration of serum IL-6 and TNF-α, and impairment of oxidation state. These data provide new insights into the role the antioxidant defense system and the use of various supplements to improve thyroid dysfunction.

Keywords: Serum Interleukin 6; oxidative stress; Albino Rats; thyroid disorders; Albino Rats

INTRODUCTION

Oxidative stress defined as an imbalance in the redox features of some cellular environment which can be the result of either biochemical processes leading to the production of reactive species, exposure to damaging agents (i.e., environmental pollutants and radiations), or limited capabilities of endogenous antioxidant systems **[1]**. Thus, several defense systems have been involved within the cells to prevent uncontrolled reactive oxygen species (ROS) increase. These systems include non-enzymatic molecules [glutathione, vitamins A, C, and E, and several antioxidants present in foods] as well as enzymatic scavengers of ROS [superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX)] being the best-known defense systems **[2]**.

Free oxygen radicals are general mediators of signal transduction pathways, which are able to induce cytokine production from various cell types **[3].** Interleukins are cytokines that act primarily on leukocytes; nearly 40 interleukins have been identified. Interleukin-6 (IL-6) acts as a systemic hormone that may mediate the well-documented inhibitory effect of IL-1 on thyroid cell functions **[4]**.

Thyroid hormones have shown to affect mitochondrial oxidative activity, synthesis of protein, and differentiation of muscle fibers and capillary growth **[5]**. However, the ability of thyroid hormones to prevent or ameliorate oxidative stress biomarkers is controversial**.**

Few studies were conducted to investigate the association between thyroid dysfunction (hyperthyroidism, hypothyroidism) on IL6 levels and some of oxidative stress markers. Previous reports assessed the contribution between ROS and thyrotoxicosis and their results showed some controversies **[6]**.

Thus, this study was planned to explore the effect of experimentally induced thyroid dysfunction (hyperthyroidism, hypothyroidism) on IL6 levels and some of oxidative stress markers in order to clarify some of underlying possible mechanisms, and link these events with metabolic and histological changes.

METHODS

In Physiology Department, Zagazig College of Medicine, this study was carried out in the period between April 2020 and August 2021. Thirty adult male albino rats of local strains weighing 180-200 g, were obtained from the animal house of Faculty of Veterinary Medicine of Zagazig University.

The animals were kept in steel wire cage (5 animals/ cages) in a light- and temperature-controlled room on a12 h/12 h light–dark cycle and fed a standard pellet lab chow with ad libitum access to tap water. Rats were kept under observation for 15 days before the onset of the experiment.

The experimental protocol was approved by physiology department and by local medical ethics committee in Faculty of Medicine of Zagazig University (The Institutional Animal Care and Use Committee, Zagazig University, ZU-IACUC) approval number: ZU-IACUC/3/F/11/2020

After acclimatization period rats were divided randomly into three equal groups. **Group I** (control group); rats were fed on normal diet consisted of 25.8 % protein, 62.8 % carbohydrate and 11.4 % fat and supplied in separate clean containers obtained from Zagazig Agriculture college and administered normal saline orally 1 ml/day using oral gavage for 4 weeks (study period). **Group II** experimentally-induced hypothyroid group; were fed on the same diet, this group received a single daily dose of 2 mg carbimazole/100g body weight diluted in drinking water for 4 weeks. The dose was introduced orally by gastric tube **[7]**. **Group III** experimentally-induced hyperthyroid group; were fed on normal diet, this group received L-thyroxin at a dose of 2µg /ml diluted in drinking water for 4 weeks **[8]**.

At the end of the experimental protocol, BMI index was calculated which equals body weight (gm) / length2 (cm2) where rat length was notified by estimating the distance between the anus and the nose **[9]**. Blood samples were collected from the tail vein **[10]** under ether anesthesia, left for 30 min at room temperature to clot and then centrifuged at 3000 rpm for 15 min and serum was separated and stored at -80oC for estimation of biochemical parameters.

Biochemical measurements were done in the Biochemistry Laboratory, Faculty of Medicine, Zagazig University. Collected serum was used to estimate levels of serum levels of glucose, insulin, total cholesterol (TC), triglycerides (TG), free T3, free T4, TSH, high density lipoprotein (HDL), interleukin 6 (IL6), tumor necrosis factor alpha (TNFα). Also, malondialdehyde (MDA), reduced Glutathione (GSH), superoxide dismutase (SOD) using commercial ELISA kits (Sigma, Aldrich).

Insulin resistance (HOMA-IR) was estimated using the following formula = (Fasting glucose in mg/dl x Fasting insulin in µIU/ml)/405 **[11]**, also, LDL was calculated by the following formula: LDL (mg/dl) = [TC] – [(HDL) + (TG / 5)] **[12].**

After the animals were sacrificed at the end of the experiment, thyroid glands were harvested and disected into 3 equal sized slices then fixed in 10% formalin solution. After automated dehydration, thyroid slices were embedded in paraffin, sectioned at 5um and stained with hematoxylin and eosin stain (HE) for histopathological examination.

Statistical analysis

The results were expressed as mean ± standard deviation (SD). For statistical significance, one-way analysis of variance (ANOVA) and Tukey HSD for Post hoc multiple comparisons were used to compare means. The software, IBM Statistical Package for Social Sciences (SPSS) Version 26 Software for Windows (SPSS, Inc., Chicago, IL, USA), was used for that purpose.

Also, Graph Pad Prism (Version 8 Software for Windows) was used to analyze the Pearson's correlation coefficient between serum levels of IL-6 and TNFα some studied parameters within the

hypothyroid and hyperthyroid groups. Significance was considered with P value ≤ 0.05.

RESULTS

There was a statistically significant difference in BMI between hypothyroid, hyperthyroid and control groups, hypothyroid group had the highest final BMI and hyperthyroid had the lowest final BMI. Glucose was a significantly higher in both hyperthyroid and hypothyroid groups in comparison to that in the control group. In hyperthyroid group, insulin was higher than hypothyroid group and control group. In hypothyroid group, TC, TG and LDL were significantly higher than hyperthyroid group and control group. Free T3 and Free T4 were significantly low in hypothyroid group and significantly high in hyperthyroid group in comparison to that in the control group, while TSH in hypothyroid group was significantly higher than control group and hyperthyroid group.

In hypothyroid and hyperthyroid groups, serum MDA, and serum SOD were significantly higher than control group. In hypothyroid group, serum reduced glutathione was significantly higher than control and hyperthyroid groups. In hyperthyroid group serum reduced glutathione was significantly lower than control group and hypothyroid group. Serum IL-6 and TNF-α level in hypothyroid and hyperthyroid groups were significantly higher in comparison to that in the control group; also, in hypothyroid group both of them were found to be significantly higher than that in both control and hyperthyroid group.

There were a significant positive correlation between IL-6 with insulin and TNF-α with MDA. Also a significant negative correlation between IL-6 with TC and TNF-α was found with final BMI of the studied hyperthyroid group.

There were a significant negative correlation between TNF- α with HDL and a significant positive correlation between TNF-α with final BMI of the studied hypothyroid group.

The control group showed normal histological structure, a photomicrograph of control group thyroid gland section shows multiple variable follicles filled with homogenous eosinophilic colloid with peripheral vacuolation. Follicles are lined with flat to cuboidal follicular cells with few interfollicular cells.

But hyperthyroid group, thyroid gland section shows multiple mostly large follicles filled with homogenous eosinophilic colloid and few collapsed follicles. Follicles are lined mostly with flat with excess interfollicular cells.

In addition, hypothyroid group, thyroid gland section shows few follicles filled with homogenous eosinophilic colloid, multiple follicles, and little colloid and empty follicles. Follicles are lined mostly with vacuolated follicular cells with some desquamated cells inside lumen. Figure 1 shows multiple variable follicles filled with homogenous eosinophilic colloid (C) with peripheral vacuolation (green arrow). Follicles are lined with flat (arrow head) to cuboidal (arrow) follicular cells with few interfollicular cells (tailed arrow). Note few capillaries in between follicles (zigzag arrow). Figure 2 shows multiple mostly large follicles filled with homogenous eosinophilic colloid (C) and few collapsed follicles (asterike). Follicles are lined mostly with flat (arrow head) with excess interfollicular cells (tailed arrow). Note few capillaries in between follicles (zigzag arrow)**.** Figure 3 shows few follicles filled with homogenous eosinophilic colloid (C), multiple follicles (asterike), little colloid and empty follicles (green asterike). Follicles are lined mostly with vacuolated follicular cells (arrow) with some desquamated cells inside lumen (curved arrow). Note multiple congested capillaries in between follicles (zigzag arrow)

Table 1: Biochemical changes in different studied groups.

Group / ***Parameter***	Group 1 (Control group)	Group II (Hypothyroid group)	Group III (Hyperthyroid group)
Final BMI (g/cm2)	0.61±0.062	0.83±0.074 a	0.53±0.047 a&b
Serum glucose (mg/dl)	75.3±1.34	232.3±2.5 a	190.6±2.3 a&b
Serum insulin (µIU/ml)	11.3±0.5	13.76±0.9 a	28.24±0.9 a&b
HOMA-IR	2.34±1.17	7.90±2.36 a	13.06±8.07 a&b
TC(mg/dl)	104±3.3	132.6±5.5 a	71.1±3.3 a&b
TG(mg/dl)	61±2.9	83.3±3.7 a	42±3.4 a&b
HDL(mg/dl)	30.9±2.8	29.4±3.4	29.4±3.03
LDL(mg/dl)	53.8±3.8	78.6±5.4 a	33±2.9 a&b

Free T3 (pg/dl)	3.01±0.3	0.9±0.05 a	8.7±0.7 a&b
Free T4 (ng/dl)	1.5±0.2	0.8±0.09 a	5.6±0.99 a&b
TSH (mIU/ml)	1.1±0.1	4.7±0.7 a	.05±0.02 a&b

Data was expressed as mean±SD. a P<0.05 when compared with control group. b P<0.05 when compared with hypothyroid group. BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance; TC, total cholesterol, TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; TSH, thyroid stimulating hormone.

Table 2: Oxidative stress markers in all studied groups.

Group / ***Parameter***	Group 1 (Control group)	Group II (Hypothyroid group)	Group III (Hyperthyroid group)
Serum MDA (mmol/l)	1.23±0.1	2.023±0.06 a	4.01±0.2 a&b
Serum reduced glutathione (Unit/ml)	44.6±2.12	60.7±2.5 a	33.1±1.4 a&b
Serum SOD (Unit/ml)	16.7±0.9	22.06±1.4 a	32.2±1.02 a&b
IL-6 (ng/ml)	4.1±0.2	59.3±2.6 a	29.2±3.1 a&b
"TNF- α (pg/ml)	46.5±3.9	1410.5±207.4 a	724.3±95.8 a&b

Data was expressed as mean±SD. a P<0.05 when compared with control group. b P<0.05 when compared with hypothyroid group. MDA, malondialdehyde; SOD, superoxide dismutase; IL-6, interleukin-1 beta; TNFα, tumor necrosis factor alpha.

Table 3: Pearson's correlation coefficient (r) between IL-6, TNF-α and other laboratory findings within the hyperthyroid group included in the study.

variables	**IL-6 (ng/ml)**		**TNF-α (pg/ml)**	
	r	**p**	**r**	**P**
IL-6(ng/ml)	1		-.006	0.988
"TNF- α(pg/ml)	-.006-	0.988	1	
Final BMI(g/cm2)	-0.281	0.431	-0.895-**	0.061
glucose(mg/dl)	-.580-	0.079	-.073	0.84
insulin(µIU/ml)	.703*	0.023	-.085	0.816
HOMA-IR	-0.305	0.391	-0.129	0.772
TG(mg/dl)	0.431	0.214	-.054	0.883
TC(mg/dl)	-.648*	0.043	-.073	0.841
HDL(mg/dl)	0.245	0.495	-.485-	0.155
LDL(mg/dl)	0.425	0.221	0.165	0.649
MDA(mmol/l)	-.107	0.769	.661*	0.037
reduced glutathione(units/ml)	-.002	0.995	0.31	0.384
SOD (units/ml)	-.472	0.168	-.38	0.278
free T3(pg/dl)	-.496	0.144	-.079	0.827
free T4(ng/dl)	-.064	0.862	-.593	0.071
TSH(mIU/ml)	-.415	0.233	-.215	0.551

BMI, body mass index; HOMA-IR, homeostasis model assessment insulin resistance; TC, total cholesterol, TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; TSH, thyroid stimulating hormone; MDA, malondialdehyde; SOD, superoxide dismutase.

Table 4: Pearson's correlation coefficient (r) between IL-6, TNF-α and other laboratory findings within the hypothyroid group included in the study.

variables	IL-6 (ng/ml)		TNF-α (pg/ml)	
	r	p	r	P
"TNF- α(pg/ml)	0.515	0.127	1	
Final BMI(g/cm2)	-0.107	0.769	0.710*	0.021
glucose(mg/dl)	0.518	0.125	0.573	0.083
insulin(µIU/ml)	0.286	0.423	0.451	0.191
HOMA-IR	0.414	0.234	0.531	0.114
TG(mg/dl)	0.152	0.676	-.031-	0.933
TC(mg/dl)	0.127	0.727	-.128-	0.726
HDL(mg/dl)	-.590	0.072	-.814**	0.004
LDL(mg/dl)	0.545	0.103	-.130-	0.72
MDA(mmol/l)	-.187	0.606	-.300	0.399
reduced glutathione(units/ml)	-.089	0.806	0.179	0.621
SOD (units/ml)	0.317	0.372	0.199	0.582
free T3(pg/dl)	0.302	0.396	0.43	0.214
free T4(ng/dl)	0.133	0.715	0.187	0.604
TSH(mIU/ml)	0.285	0.425	0.304	0.393

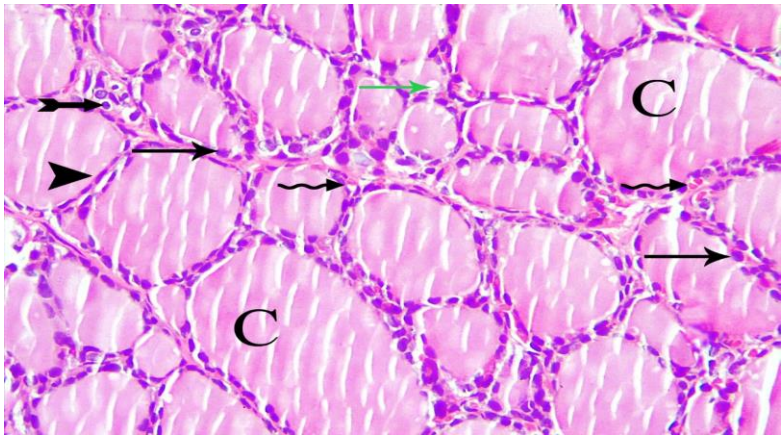

Figure 1: photomicrograph of control group thyroid gland section shows multiple variable follicles filled with homogenous eosinophilic colloid (C) with peripheral vacuolation (green arrow). Follicles are lined with flat (arrow head) to cuboidal (arrow) follicular cells with few interfollicular cells (tailed arrow). Note few capillaries in between follicles (zigzag arrow).

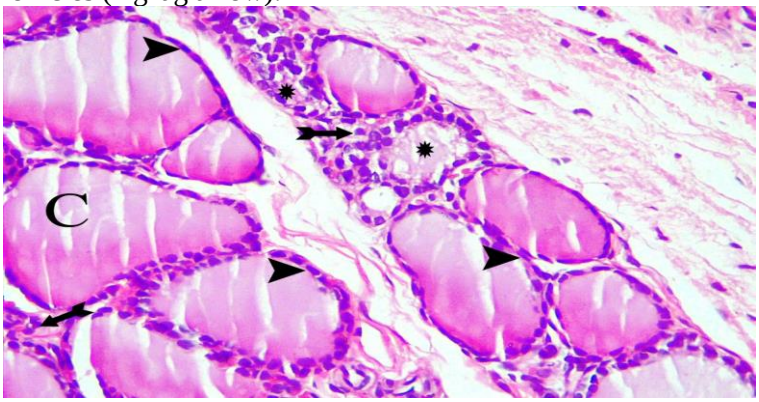

Figure 2: photomicrograph of hyperthyroid group thyroid gland section shows multiple mostly large follicles filled with homogenous eosinophilic colloid (C) and few collapsed follicles (asterike). Follicles are lined mostly with flat (arrow head) with excess interfollicular cells (tailed arrow). Note few capillaries in between follicles (zigzag arrow).

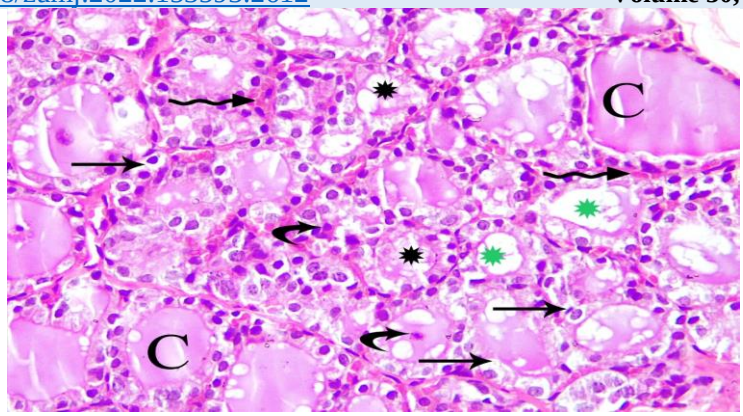

Figure 3: photomicrograph of hypothyroid group thyroid gland section shows few follicles filled with homogenous eosinophilic colloid (C), multiple follicles (asterike), little colloid and empty follicles (green asterike). Follicles are lined mostly with vacuolated follicular cells (arrow) with some desquamated cells inside lumen (curved arrow). Note multiple congested capillaries in between follicles (zigzag arrow)

DISCUSSION

Thyroid hormones play an important role in the oxidation state. Therefore, their regulatory role in the production of free radicals is prominent. On the other hand, these hormones are effective in the synthesis of antioxidant enzymes, vitamins, and regulatory proteins. The production of thyroid hormones is an oxidative biochemical reaction that depends on the formation of peroxides. The thyroid hormones can be a physiological regulator of oxidative stress in cells due to their effect on mitochondrial respiration **[13]**. Moreover, the available data concerning oxidative stress in both hypothyroidism and hyperthyroidism are still controversial **[14]**.

The aim of the present study was to explore the effect of experimentally induced thyroid dysfunction (hyperthyroidism, hypothyroidism) on IL6 levels and some of oxidative stress markers in order to clarify some of underlying possible mechanisms, and link these events with metabolic and histological changes.

The results of the present study revealed that there was a statistically significant difference in final BMI between hypothyroid, hyperthyroid and control groups. These results were supported by **Yeldu and Ishaq [15]** and **Venditti et al. [16]** who found that body gain has been reported to occur in hypothyroidism.

In contrast, **Kim and Lee [17]** found that in the hyperthyroid group, the mean weight was increased significantly after the intervention period, similar to the control group. Although levothyroxine increases the rate of metabolism, it may also increase food intake in animals, and so this could be a reason for gaining weight in the hyperthyroid group

The results of the current study showed that fasting blood glucose, fasting insulin, and HOMA-IR were significantly higher in both the hypothyroid and the hyperthyroid groups; moreover, revealed that both hyperthyroidism and hypothyroidism deteriorate insulin sensitivity as indicated by the significant increase in HOMA-IR, which in turn was associated with a significant increase in serum insulin levels.

This came in agreement with **Yeldu and Ishaq [15]** who confirmed that metabolism disorder of glucose in hyperthyroid is mainly attributed to oxidative stress which already approved in this study by exerting deleterious effects on pancreas and liver. Hyperthyroidism is accompanied with marked increase of oxidative impact on hepatic lipid peroxidation and cell damage markers (AST, ALT, LDH, and ALP activities) **[18]**.

Vazquez-Anaya et al. [19] study has confirmed that hypothyroidism is associated with insulin resistance. In hypothyroidism, the mechanism of insulin resistance was attributed by the study of **Ormazabal et al., [20]** to a decrease in insulin-mediated glucose disposal and decreased ability of insulin to increase the blood flow to the hyperthyroid tissues, which leads to lower glucose disposal.

In the present study, TG, TC, LDL were significantly higher in hypothyroid group than control group, while they were lower in hyperthyroid group than control group. No significant difference was found between the studied groups regarding HDL.

In agreement with the present study, **Oktay et al. [21]** study found that the mean levels of TC, TG and LDL-c in the hyperthyroid rats were significantly lower than those in the control group, and in the hypothyroid group, it was significantly higher than the control group.

In the present study, lipid peroxidation products such as MDA and superoxide dismutase (SOD) concentrations showed a significant increase in the hyperthyroid rats when compared to controls. Finally, reduced glutathione was significantly increased in hypothyroidism and significantly decreased in hyperthyroidism when compared to control group.

Previous studies have evidenced that free radicals increase during hyperthyroidism **[21, 22]**. **Yeldu and Ishaq [15]** found that lipid peroxidation products such as MDA and hydroperoxide concentrations did not show any significant change in the hypothyroid individuals compared to controls, whereas those of hyperthyroid rats were significantly higher than those of controls. A significant reduction in reduced glutathione levels in hyperthyroid rats were observed compared to those of controls. SOD activities in hyperthyroid rats did undergo a significant increase when compared to that recorded in both hypothyroid and control rats.

Also, **Najafi et al. [14]** found that the mean levels of MDA in the hyperthyroid group were significantly higher than the hypothyroid group. This can be due to the increased rate of metabolism in hyperthyroidism relative to hypothyroidism and as a result of increased lipid peroxidation rate of the active group. Moreover, hyperthyroidism leads to a rise in oxygen consumption, inducing in turn, an increase in the level of oxidative stress in the heart and in the skeletal muscles; consequently, lipid peroxidations and hydroperoxides formation **[16]**.

As revealed in his study, the MDA serum level decreased in the hypothyroid group compared to the control group. The study of **Erdamar et al. [23]** was showed that the levels of MDA increased in the hypo and hyperthyroid groups, while it diminished in the hyperthyroid group after Propylthiouracil (PTU) treatment. Also, in the study by **Chesere et al. [24]** showed that after hypothyroidism induction, the level of lipid peroxidation did not change, while after treatment with T3, it increased.

The acquired results reveal also a marked increase in SOD activity in hyperthyroidism, indicating the presence of oxidative stress due to the increasing mitochondrial oxidation rate, characterized by an overproduction of superoxide anion. The latter is known for its harmfulness to the cell membrane. The SOD is also known for its role in transforming (O2-) into inorganic hydroperoxide (H2O2), which will, in turn, be reduced by both CAT and GPx enzymes **[16].**

In the present study, Free T3 and T4 underwent a highly significant increase in the hyperthyroid rats compared to the control ones, whereas in hypothyroid animals the concentrations were remarkably reduced compared to those of untreated animals.

Najafi et al. [14] found that the mean levels of T3 and T4 hormones were lower in the hypothyroid group but in the hyperthyroid group, it was significantly higher than those in other groups.

Minakhina et al. [25] clarified that thyroid gland activity is regulated by the hypothalamic–pituitary– thyroid axis, including the negative feedback loop. The authors pointed to TSH as a major growth factor for the thyroid. The thyroid gland under TSH undergoes enlargement, hyperplasia, neovascularization and morphological alterations of thyrocytes related to their involvement in the production, processing and release of thyroid hormones.

Finally, in the present study, TNF-α level were higher and positively associated with MDA. On the other hand, it was negatively associated with HDL of the studied hypothyroid group. As regard levels of IL-6, they were high and positively associated with insulin, also; negatively associated with TC in the hyperthyroid group.

This came in agreement with **Baldissarelli et al. [26]** who found that thyrotoxicosis stimulates the oxidative stress response and the production of inflammatory cytokines (IL-6 and TNF-α); in addition to the positive significant correlation between TNF-α with MDA.

However, **Zhou, et al. [27]** showed that IL-6 and TNF-α increased with longer duration of radioactive iodine (131I)-induced hypothyroidism. They showed that the levels of TNF-α and IL-6 were still continually increasing, indicating that the elevated levels of the pro-inflammatory cytokines are probably associated with hypothyroidism.

Levothyroxine (L-T4) treatment of hypothyroid rats markedly decreased the elevated serum levels of TNF-α and IL-6 **[28]**. **Marfella et al. [29]** also observed significantly lower plasma TNF-α and IL-6 levels in patients with subclinical hypothyroidism treated with L-T4 compared to the untreated individuals.

In our study; the histopathological findings of hyperthyroid group showed multiple mostly large follicles filled with homogenous eosinophilic colloid and few collapsed follicles. Serum levels of T4 and T3 act as reliable indicators of the thyroid function in both human

and experimental animals. Any change in their levels reflects disturbancein the glandular synthesis and/or secretion, as well as disorders in the extrathyroidal metabolism **[30].**

In hypothyroid group a picture showed few follicles (filled with homogenous eosinophilic colloid), multiple follicles, and little colloid and empty follicles. This was concomitant with the results of other researchers, Ferreira **et al., [31]** who confirmed a significant increase in the follicular epithelium in the hypothyroid group. This may be attributed to the low level of T4 that led to increased TSH levels, which was responsible for the proliferative activity of follicular cells. Also, some researchers **Rajab et al. [32]** clarified that thyroid gland activity is regulated by the hypothalamic–pituitary– thyroid axis, including the negative feedback loop.

Limitations of this study included that it was achieved on rats and the results obtained may be different from human. Also, small numbers of rats were used. Thus, further studies should be conducted to confirm the current results.

CONCLUSIONS

hypothyroidism and hyperthyroidism are associated with the deterioration of IL-6 and TNF-alpha, and impairment of oxidation state. These data provides new insights into the role the antioxidant defense system and the use of various supplements to improve thyroid dysfunction

Conflict of Interest: None

Financial Disclosures: None

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