Biochemical study of gender effect on thyroid cancer in the Egyptian population

Faten Zahran[1], Sahar Hamed[2], Mohamed Yosry[2]* and Mohamed El gareeb [3]

Prof of Biochemistry, faculty of science, Zakazik University.[1]

Prof of molecular biology, urology center, Mansoura University [2]

[3] Prof of organic chemistry, faculty of science, Portsaid University

ABSTRACT

Background and Objective: Thyroid is one of the largest glands; its hormones affect almost every cell in the body, the incidence of thyroid cancer has raised in recent years, About 52,070 new cases of thyroid cancer in the United States in 2018 only. This study was undertaken to determine if gender was associated with susceptibility of thyroid cancer. **Material and Methods**: This study was carried out on 174 cases divided into 108 thyroid patients and 66 healthy as controls. The mean age of cases was (40.58±1.46) they include 48 female and 18 males .All participants were subjected to an estimation of thyroid stimulating hormone (TSH), free thyroxine (FT4), total antioxidant capacity (TAC), in addition to malondialdehyde (MDA).**Results:** For TSH results that was an obvious effect of gender on TC, while for FT4 there was an effect of gender on thyroiditis and TC, for TAC there was a bite effect on thyroiditis and TC, for MDA there was an effect also on thyroiditis and TC, for tissue TAC (TTAC) that was a clear effect of gender on both thyroiditis and TC, and for TMDA there was a little effect. **Conclusion:** Gender of TC patients effects on biochemical investigations of the thyroid.

Key words: *Thyroid cancer, gender, Thyroid hormones, Thyroiditis, Total antioxidant capacity, Malondialdehyde.*

ABBREVIATIONS :Thyroid cancer (TC),Thyroid stimulating hormone (TSH),Free thyroxine (FT4), Total antioxidant capacity (TAC),Malondialdehyde (MDA),Reactive oxygen species (ROS), Tissue TAC (TTAC),and Tissue MDA (TMDA).

INTRODUCTION

The incidence of thyroid cancer has increased by 50% in the United States during the past 25 years (1). Thyroid cancer is a cancer originating from Oxidative stress, caused by imbalance in reactive oxygen species (ROS) produced during normal cell metabolism and /or efficiency scavenger antioxidant defense, is implicated in the pathogenesis of many chronic diseases (2). In hyper metabolic state the tissue oxidative injury was associated with hyperthyroidism. Available data indicate that hyperthyroidism tissue exhibit and increased (ROS) production .when hyperthyroid tissues increase their metabolic capacity, mitochondrial ROS generation is increased as a side effect of enhanced electron carrier level. Investigations of antioxidant defense system have returned controversial results (3) .Tissue susceptibility to oxidative challenge was increased with any thyroid hormone-linked biochemical changes. This may explain the injury and dysfunction of the tissue suffer under stressful conditions .Mitochondria, as a primary target for oxidative stress, might account for hyperthyroidism linked tissue dysfunction (4); there are four types of thyroid cancer Papillary, Follicular, medullary and the Anaplastic thyroid cancer(5).

E-mail address: Mohammed.memco@gmail.com

MATERIALS AND METHODS

Study group: To conduct this study; 174 volunteers were divided into 3 groups healthy (n=66; 18 males and 48 female) thyroiditis (thyroid inflammation) (n=56; 8 males and 48 female) and TC patients (n=52; 14 males and38 female) underwent surgical thyroidectomy. This study was approved by the Mansoura University's Ethical Committee and informed, written consent was obtained from all patients 'volunteer participants.

Assessment of thyroid function: Thyroid stimulating hormone (TSH) and free thyroxine (FT4) were determined in plasma samples by ELISA (IMMUNOSPEC, CA, USA) following manufacturer's instructions. Normal thyroid function (euthyroidism) was defined as normal TSH levels (0.4-4.5 u IU / m L) and FT4 (0.7-1.9 ng / d L)

Evaluation of oxidative stress: Total antioxidant capacity (TAC) and lipid peroxidation products, malondialdehyde (MDA) were determined both in plasma samples as well as tissue homogenate of thyroid using corresponding diagnostic kit (Biodiagnostgic , Egypt)following manufacturer's instructions. TAC and the pink chromogen produced by the reaction of thiobarbituric acid with MDA were measured spectrophotometrically (SpectraMax M5, Molecular Devices) at 520 nm and 532 nm, respectively. Tissue oxidation was assessed by measuring both TTAC and TMDA in thyroid tissue homogenate for diseased groups only. The thyroid tissue homogenized in 10% (w /v) PBS (pH 7.4) using minihard held homogenizer. The homogenates were centrifuged at 14000 rpm, 4°C, for 15 minutes, and the supernatants obtained were collected and stored at 80°C for further analysis, TAC unit was mM/L and MDA unit was nmol/ml

Statistical analysis

Statistical analysis of data was performed using the software statistical package (SPSS program version17.0).The Student –t test was used to compare the numerical values, a minimum of 50 participants was found to be adequate, thus our study population (n =52) was readily in the correct power. A *P*=0.05 was defined to be statistically significant.

RESULTS

There was significant increase in TSH level in male thyroiditis and male thyroid cancer groups when compared to male control group (p=0.001& 0.012) respectively. On the other hand, there was no significant change in TSH level in male thyroiditis when compared to male thyroid cancer group (P=0.33) (Table 1 and Figure 1). For female, there was significant increase in TSH level in female thyroiditis and female thyroid cancer groups when compared to female control group (p=0.001).Also, there was significant increase in mean TSH level in female thyroiditis when compared to female thyroid cancer group (P=0.001) (Table 1 and Figure 1).

E-mail address: Mohammed.memco@gmail.com

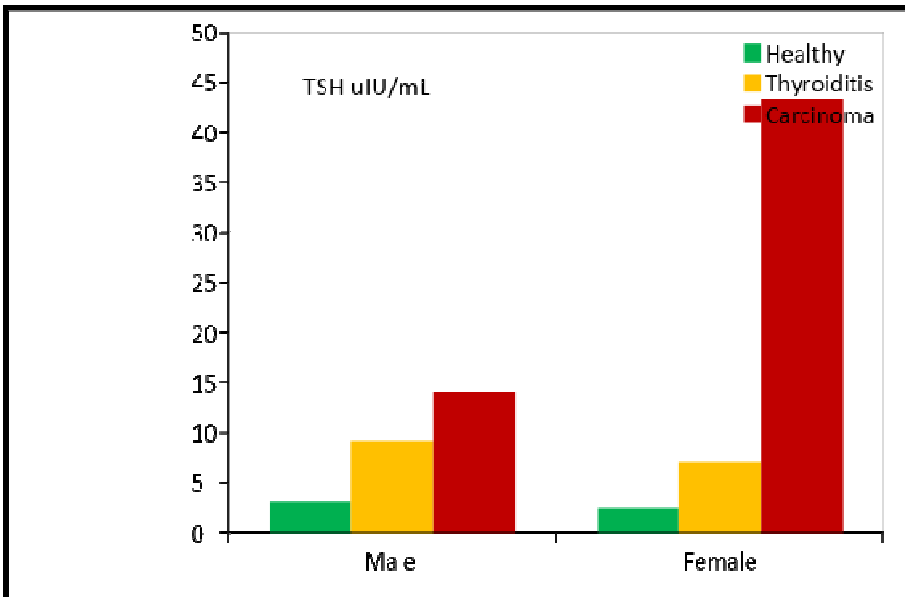

Figure 1: Effect of gender on TSH level in different studied groups.

Table 1: Effect of gender on TSH level in different studied groups:

	Male	SD	*P*	*P1*	Female	SD	*P*	*P1*
Healthy	18	0.46			48	0.69		
Thyroiditis	8	2.60	0.001		48	4.57	0.001	
Carcinoma	14	17.39	0.012	0.33	38	30.45	0.001	0.001

N: Number of cases in each group, SD= Standard Deviation, *P*: significance of diseased groups against healthy group, *P1*: Significance between diseased groups.

There was significant increase in FT4 level in male thyroiditis and male thyroid cancer groups when compared to male control group (p=0.001) for both. On the other hand, there was no significant change in FT4 level in male thyroiditis when compared to male thyroid cancer group (P=0.33) (Table 2 and Figure 2). For female, there was significant increase in FT4 level in female thyroiditis and female thyroid cancer groups when compared to female control group (p=0.001) (Figure 2). Also, there was significant increase in FT4 level in female thyroiditis when compared to female thyroid cancer group (P=0.04).

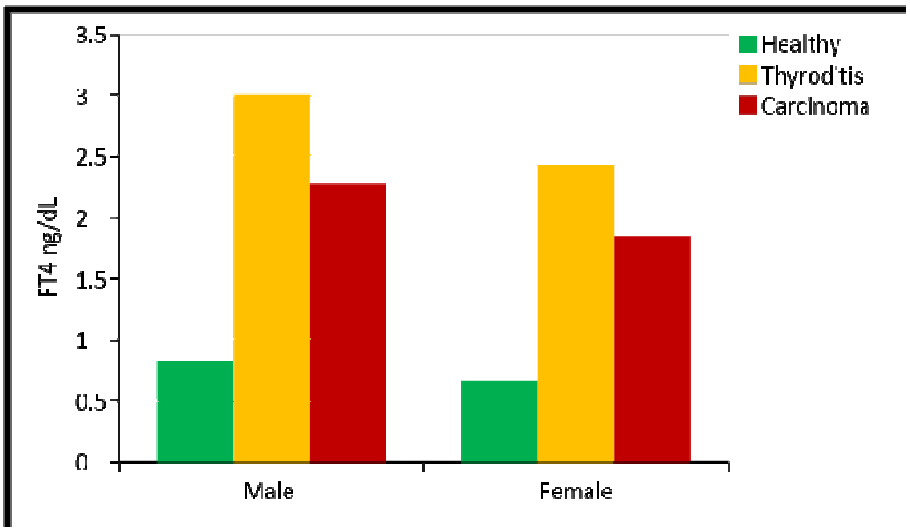

Figure 2: Effect of gender on FT4 level in different studied groups.

Table 2: Effect of gender on FT4 level in different studied groups:

	Male	SD	*P*	*P1*	Female	SD	*P*	*P1*
Healthy	18	0.33			48	0.41		
Thyroiditis	8	1.89	0.001		48	1.66	0.001	
Carcinoma	14	0.67	0.001	0.33	38	0.92	0.001	0.04

N: Number of cases in each group, SD= Standard Deviation, *P*: significance of diseased groups against healthy group, *P1*: Significance between diseased groups.

Association of TAC Level and MDA Level to Different Gender in Different Studied Groups:

There was significant decrease in TAC level in male thyroiditis and male thyroid cancer groups when compared to male control group (p=0.001) for both. While, there was significant increase in TAC level in male thyroiditis when compared to male thyroid cancer group (P=0.001) (Table 3 and Figure 3), for female; there was significant decrease in mean TAC level in female thyroiditis and female thyroid cancer groups when compared to female control group (p=0.001) for both (Figure 3). While, there was significant increase in mean TAC level in female thyroiditis when compared to female thyroid cancer group (P=0.001).

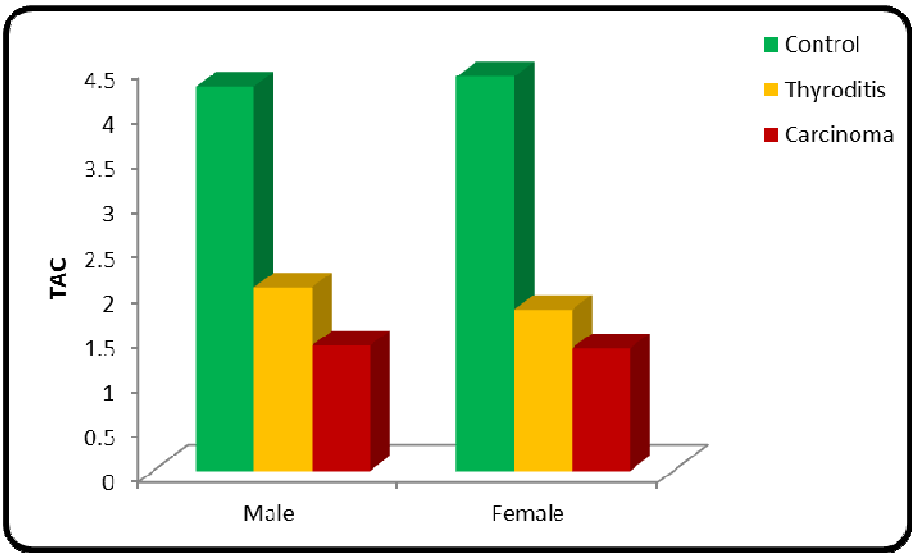

Figure.3: Effect of gender on TAC level in different studied groups.

Table 3: Effect of gender on TAC level in different studied groups:

	Male	SD	*P*	*P1*	Female	SD	*P*	*P1*
Healthy	18	1.61			48	1.52		
Thyroiditis	8	0.11	0.001		48	0.34	0.001	
Carcinoma	14	0.07	0.001	0.001	38	0.31	0.001	0.001

N: Number of cases in each group, SD= Standard Deviation, *P*: significance of diseased groups against healthy group, *P1*: Significance between diseased groups.

There was a significant increase in MDA level in male thyroiditis and male thyroid cancer groups when compared to male control group (p=0.001) for both. While, there was no significant difference in MDA level in male thyroiditis when compared to male thyroid cancer group (P=0.57) (Table 4 and Figure 4). For female, there was significant increase in MDA level in female thyroiditis and female thyroid cancer groups when compared to female control group (p=0.001) for both (Figure 4). While, there was significant decrease in MDA level in female thyroiditis when compared to female thyroid cancer group (P=0.003).

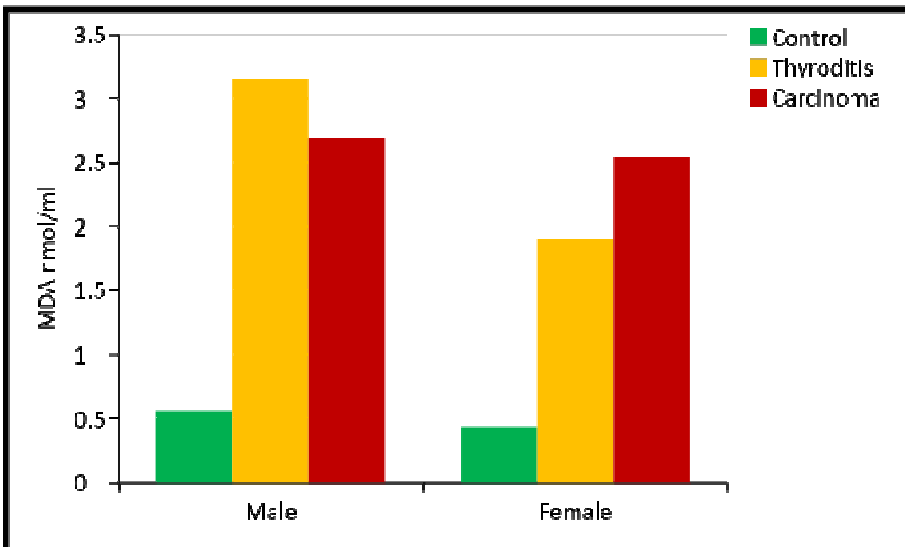

Figure 4: Effect of gender on MDA level in different studied groups.

Table 4: Effect of gender on MDA level in different studied groups:

	Male	SD	*P*	*P1*	Female	SD	*P*	*P1*
Healthy	18	0.42			48	0.27		
Thyroiditis	8	2.77	0.001		48	1.04	0.001	
Carcinoma	14	0.97	0.001	0.57	38	0.92	0.001	0.003

N: Number of cases in each group, SD= Standard Deviation, *P*: significance of diseased groups against healthy group, *P1*: Significance between diseased groups.

Tissue TAC and Tissue MDA (TTAC & TMDA): There was no significant difference in male TTAC level in thyroiditis when compared to thyroid cancer groups (p=0.48). As well as, for female TTAC level there was no significant difference in TTAC level in thyroiditis when compared to thyroid cancer groups (p=0.06) (Table 5 and Figure 5).

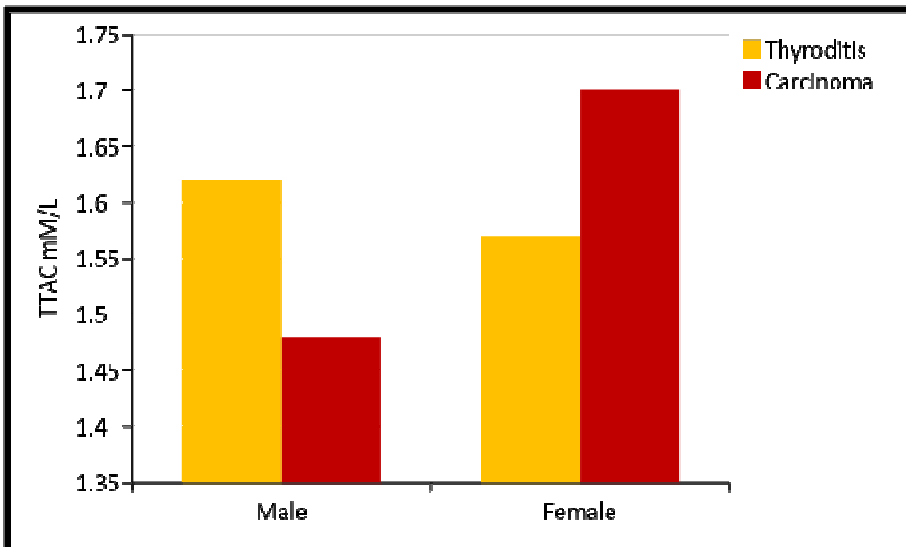

Figure 5: Effect of gender on TTAC level in different studied groups.

Table 5: Effect of gender on Tissue TAC & Tissue MDA level in different studied groups:

		Male	SD	*P1*	Female	SD	*P1*
TTAC	Thyroiditis	8	0.42		48	0.34	
	Carcinoma	14	0.41	0.48	38	0.24	0.03
TMDA	Thyroiditis	8	0.31		48	0.76	
	Carcinoma	14	1.16	0.06	38	1.91	0.01

N: Number of cases in each group, SD= Standard Deviation, *P*: significance of diseased groups against healthy group, *P1*: Significance between diseased groups.

There was significant decrease in male TMDA level in thyroiditis when compared to thyroid cancer groups (p=0.03). As well as, for female TMDA level there was significant decrease in the TTAC level in thyroiditis when compared to thyroid cancer groups (p=0.001) (Table 5 and Figure 6)

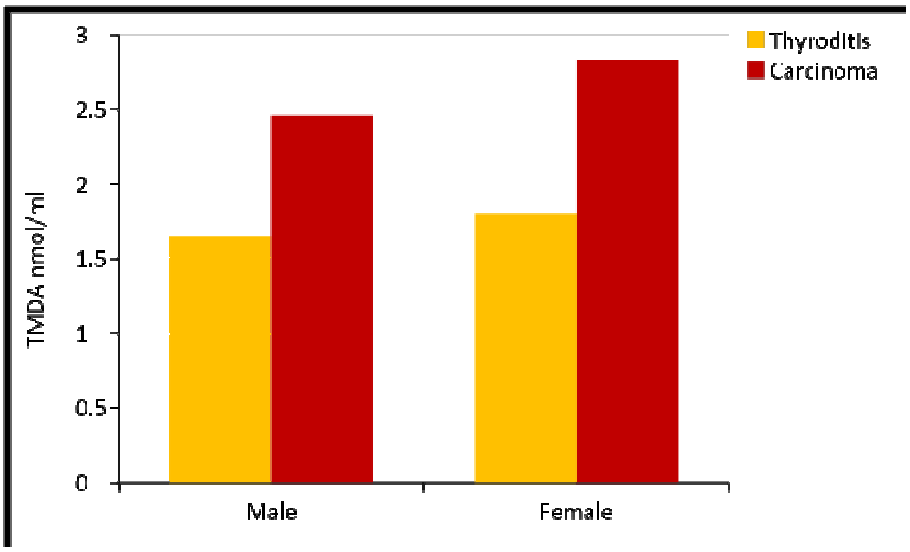

Figure 6: Effect of gender on TMDA level in different studied groups.

DISCUSSION

Thyroid cancer is the most common type of endocrine malignancy, and its incidence has been continuously growing over the last several decades (6). However, most of these approaches still have not reached the highest possible accuracy for the detection of all the main types of thyroid cancer, and they may have limited performance in the populations with a high pretest probability of cancer (7).

This study included (174) subjects, divided into (108) thyroid patients (22 male, and 86 female) and 66 matched healthy controls in age and sex (18male, and 48 female). The patients divided into two subgroups into thyroiditis (56) and thyroid Carcinoma patients (52). Cases and controls did not differ with regard to age and sex. Women comprised the majority of subjects in both case and control groups (79.5% and 72.7% respectively).

In the current study, there was a highly significant increase in serum TSH obtained from thyroiditis and thyroid cancer groups as compared to control group (*P*=0.001&0.001) respectively. Moreover, the level of Thyroid-stimulating hormone (TSH) obtained from the thyroiditis group was significantly reduced as compared with thyroid cancer.

This finding was in agreement with those of (8), (9) .The later demonstrated that Higher TSH levels were associated with Thyroid malignancy and the risk of malignancy rises in parallel with serum TSH within normal range, and high levels of serum TSH concentrations was associated with advanced stage of thyroid cancer.

In the current study, there was a highly significant increase in FT4 obtained from thyroiditis and thyroid cancer groups as compared to control group (*P*=0.001&0.001) respectively. Also, there was a highly significant increase in FT4 obtained from thyroiditis group as compared to thyroid cancer group (p=0.04). This result was confirmed by data obtained by (10), (11).

The finding result was not compatible with the data obtained from **Lin-zheng He** Who reported that FT4 were also compared between patients with thyroid cancer and patients with thyroiditis, but neither of them showed a significant difference, with or without the inclusion of the values out of the normal range (12).

In this study, there was no significant increase in FT4 from male thyroiditis as compared to male thyroid cancer group (*P*=0.33). While, there was significant increase in mean FT4 from female thyroiditis as compared to female thyroid cancer group (*P*=0.04). There was significant decrease in TSH from male thyroiditis as compared to male thyroid cancer group (*P*=0.001). Moreover, there was significant increase in mean TSH from female thyroiditis as compared to female thyroid cancer group (*P*=0.001).This result was in agreement with **Suzuki** (13).In **Melville** study, thyroid-stimulating hormone (TSH) levels show a significant association with the risk of papillary thyroid cancer (PTC) that appears gender-based, with lower than normal serum TSH levels years before a cancer diagnosis linked to an increased risk of PTC in women, while in contrast a higher than normal pre diagnostic level is linked to a greater risk in men(14).

In this study, highly significant decrease in TAC obtained from thyroiditis and thyroid cancer groups as compared to control group (*P*=0.001&0.001) respectively. This was in harmony with **Lassoued S**. who found that increased oxidative stress in thyroid cancer and thyroiditis has been revealed (15), and **Wang D.** who showed that TAC values were decreased in thyroid disease patients. Thus, TAC levels were lower in patients with thyroid cancer than in those with thyroiditis disease, which were in turn lower than those in healthy subjects (16). Our findings showed that MDA levels were increased, while serum TAC was decreased in thyroid cancer and thyroiditis patients as compared with control. These preliminary findings indicate that an oxidant/antioxidant imbalance associated with thyroid cancer and thyroiditis. Free radicals and ROS participate in physiological and pathological process in the thyroid gland. This result was in agreement with **SM Hosseini-Zijoud** who detected that that MDA levels were increased, while serum TAC was decreased in thyroid cancer and thyroiditis patients. These preliminary findings suggest that oxidant/antioxidant imbalance may be associated with or possibly indicate an increased risk to medullary thyroid carcinoma (17).

In this current study, there was no significant difference in TTAC from thyroiditis as compared to thyroid cancer groups (*P*=0.35), while, there was significant decrease in TMDA from thyroiditis as compared to thyroid cancer groups (*P*=0.001).

According to **Sagharchian** Oxidative stress has been shown to be the most significant influential factor in cancer pathogenesis. Follicular cells are affected in papillary thyroid carcinoma (PTC), which is the most prevalent thyroid cancer associated with oxidative stress. Thyroid cancer patients had oxidant/antioxidant imbalance, which could increase the risk of thyroid cancer. Thyroid hormones exert a key role in the modulation of antioxidant systems and oxidative stress is demonstrated both in hyper- and hypothyroidism. In the field of hypothyroidism (18).

To the best of our knowledge, this is the first study to evaluate MDA and TAC in association with thyroiditis and TC. In this study, the most important findings are the patients with thyroiditis and TC have elevated

E-mail address: Mohammed.memco@gmail.com

MDA levels and low TAC levels which when compared to healthy ones. These two parameters are playing a role on **OS** .No reports are available in the literature to comment on the simultaneous measurement of these parameters in TC. Thyroid hormones are associated with the oxidant and antioxidant status of the human organism. The findings obtained from in vitro and in vivo studies show that thyroid hormones have a strong impact on **OS** (19).Thyroiditis or TC is associated with an increase of parameters of **OS** in either tissue /plasma compared with control subjects including lipid peroxides. In conclusion, we found some important differences in the **OS** parameters and lipids profile between the patients and healthy controls. Increased MDA levels in both patients groups represent increased lipid peroxidation which might play an important role in the pathogenesis of the TC patients .also, MDA can be used as a reliable marker of **OS** and oxidative damage in studied groups.

As **OS** plays a role in the pathogenesis of many chronic diseases including thyroid diseases .previous studies indicate that patients with either hyperthyroidism or hypothyroidism have increased risk for the presence of oxidative stress(19),(2) **.** In this study, oxidative stress was found to be increased in both patients

CONCLUSIONS

This study found that gender of TC patients may effects on biochemical investigations of the thyroid. Thus additional studies are required to examine the possible relation between gender effects with environmental epidemiology, genetic mutations, diet, hobbits and other hormones involved in the development of thyroid cancer are warranted.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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E-mail address: Mohammed.memco@gmail.com

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E-mail address: Mohammed.memco@gmail.com

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E-mail address: Mohammed.memco@gmail.com