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The Relationship between Serum Concentration of Steroid and Thyroid Hormones with Breast Cancer in Iraqi Women

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Abstract

Breast cancer (BC) is the most common types of cancer among women. Based on international organizations, hundreds of women die from this disease each year around the world. Most common risk factors of BC in women are hormone-related pathway. Some cases of BC show an increase in the level of steroid-receptor protein in the breast tissue, these cases of cancers are called hormone dependent. In the other hand, a clear relationship between high level of thyroid hormone and BC has been reported in some studies. In this work, the relationship between steroid and thyroid hormones with BC was studied in Iraqi women who are diagnosed with BC and before starting any kind of therapy. Serum concentrations of steroid and thyroid hormones was measured using a fully automatic device. Blood samples were collected from 60 women affected with BC and 60 healthy women, those groups are dividing into two sub-groups; premenopausal and postmenopausal. The level of estrogen was increased significantly ($p < 0.05$) in pre-menopausal and post-menopausal patients compared to controls, while, the level of testosterone was increased significantly in pre-menopausal patients and the increase in its level was non-significant ($p > 0.05$) in postmenopausal patients compared with healthy. Furthermore, the increase in progesterone level was significant only in postmenopausal patient women. In addition, the differences in the T3 levels was non-significant between all women with BC and controls, while, the level of T4 was significantly increased in pre-menopausal and post-menopausal women who are affected with BC and the level of TSH was reduced significantly just in post-menopausal patients. It can be concluded that hormonal disorders in women, especially estrogen, can lead to activation of BC cells.

Keywords: Hormones, Thyroid hormones, Estrogen, Breast cancer.

1. Introduction

There are many terminologies in literature which are described the cancer, based on the American Cancer Society [1], it can be described as a disease that spread because of the disorderly growth of abnormal cells which they have not orthodox function within the human body. In contrast to normal, abnormal cells have no useful function, they only can harm the body. Breast cancer (BC) is the most type of cancer in women and it is the leading cause of death in women who are diagnosed with cancer. Based on the

French Public Health Agency, between 1980 and 2005 the incidence of BC has raised to 138% [2]. There are many factors can lead to occurrence of BC. Although it is a globally disease, its incidence and mortality or survival rates are vary frequently in different countries due to many factors like, lifestyle, genetic factors, population structure and environment. Several factors are known to increase the risks of breast cancer such as age, gender, family history, breast density, smoking and alcohol consumption and hormones factors. [3].

Most common risks factors of BC in women are hormone-related pathway. [4]. Normal tissue of breast contains a small quantities of estrogen and progesterone receptors proteins, and some cases of breast cancer show an increase in the level of those receptors in the breast tissue, these cases of cancers are called hormone dependent[5]. Experimental results support the relationship between estrogens and BC risk, and the androgens may also alter risk [6]. The studies has considered premenopausal and postmenopausal women in separately way due to the production of and exposure to endogenous estrogen varies considerably during a woman's lifespan [4]. A clear relationship between high thyroid hormone levels and BC has been reported in many studies [7][8][9]. In [8][9], Only postmenopausal individuals showed a connection with subclinical hyperthyroid hormonal patterns. It has been hypothesized that these women's elevated thyroid hormone/E2 ratios may encourage tumor growth. While oestrone predominates at menopause, E2 is the predominate estrogen during the female reproductive years. Therefore, it is not surprising that the thyroid hormone/E2 ratio was found to be increased since the level of E2 is low in postmenopausal women.

There are many studies that are focused on the role of serum concentration level of steroid and thyroid hormones in BC, Farhat *et al.* have reported that elevated estrogens were statistically significant in women who are newly diagnosed BC compared to the control of their study, they have concluded that hormone therapy that targets estrogens is risky for postmenopausal women with low estrogens level and therefore, the estimation of estrogens is necessary for predicting the appropriate approach of treatment, in addition, they have reported non-significant increase of testosterone level in postmenopausal women who are affected with BC [10]. In a study of Yousif *et al.*, the workers have reported a high level of steroid hormones in the serum of women with BC, including estradiol, they have suggested the performance of periodic check of steroid hormones in BC patients to obtain maximum accuracy in the prognosis of the patients, they are also reported a significant increase of serum testosterone level in women with BC compared to the control of their study. The authors have related this increasing of testosterone to the stress that associates with BC in women, furthermore, the authors has reported significant increase in the serum level of progesterone in women with BC diseases compared to the control of their study.[11]

Trabert *et al.* have stated that for every SD rise in circulating progesterone, women were at an increased risk for BC. They have also indicated that in postmenopausal women, high circulating progesterone levels were associated with a 16% rise in the risk of BC.[12] Ditsch *et al.* have reported significant higher levels of T3 and T4 in women with BC compared to the control of their study. Moreover, they have observed lower but non-significant level of TSH in BC patients.[13] In most recent study, Bach *et al.* have reported a significant link between the increased risk of BC with hyperthyroidism or hypothyroidism. Moreover, they have concluded that the link does not include TSH, but only thyroid hormones (T3 and T4).[14]

2. Materials and methods

This work was carried out in the Oncology Teaching Hospital (Baghdad-Iraq) between January and December 2021. Blood samples were collected from (60) women who are early diagnosed with breast cancer and before starting any kind of therapy (patients), in addition, blood samples were collected from (60) healthy women (controls), all patients and controls are aged between 35-60. Blood sampling was done by collected (5 ml) of blood from patients and (5 ml) from controls and immediately transferred to a gel tube. The blood samples allows clotting at room temperature and then centrifuged with 3000 rpm for 10 min. The resulting sera were separate and stored in (-20 C⁰) until subsequent analysis. Biochemical tests in order to estimate the steroid hormones in addition to thyroid hormones levels were carried out for all patients and controls groups, all these tests were done using the protocol of the electrochemiluminescence immunoassay (ECLIA) steroid and thyroid kits supplied by Cobas/Germany using fully automated device (Cobas e411/Germany).

3. Statistical analysis

The data was statistically processed for mean comparison between patients and control using the independent sample t-test. The correlation between parameters were analyzed using Pearson's correlation. Moreover, the sensitivity of using these parameters in the prognosis of breast cancer was analyzed by the received operating characteristics. The statistics were performed by SPSS software version 26.0.

4. Results and Dissection

In order to measure the serum concentration level of steroid hormones which are affected by the menstrual cycle, the patients and controls are divided into two sub-groups, pre-menopausal and post-menopausal women as following in the table 1:

Table 1: Main and sub-Groups of patients and controls

Main Group	Sub-Group	No.	Age
Patients	pre-menopausal	13	35-44
	post-menopausal	47	45-60
Controls	pre-menopausal	13	35-44
	post-menopausal	47	45-60

. In the table 2 below, the levels of the steroid and thyroid hormones are expressed in the form of mean ±SD.

Table 2: The levels of steroid and thyroid hormones in control and patients.

Parameters	Premenopausal			Postmenopausal		
	Control	Patients	P-value	Control	Patients	p-value
No.	13	13	-	47	47	-
Estrogen (pg/mL)	54.98±19.48	100.40±67.15	0.028	12.32±5.93	22.78±11.12	<0.0001

Testosterone (ng/mL)	0.38±0.23	0.67±0.32	0.015	0.52±0.24	0.54±0.28	0.661
Progesterone (ng/mL)	3.28±1.60	5.78±5.08	0.105	0.36±0.20	0.53±0.31	0.002
T3 (nmol/L)	1.23±0.51	1.50±0.47	0.175	1.51±0.43	1.57±0.47	0.512
T4 (nmol/L)	97.63±20.63	129.06±28.44	0.004	105.60±29.82	139.30±24.35	<0.0001
TSH (μIU/mL)	2.49±0.94	1.76±1.65	0.175	2.77±1.21	1.98±1.03	0.001

The level of estrogen was increased significantly ($p < 0.05$) in premenopausal women with BC (100.40 ± 67.15 pg/mL) compared to premenopausal control (54.98 ± 19.48 pg/mL). Moreover, the level of estrogen was increased significantly ($p < 0.05$) in postmenopausal women with BC (22.78 ± 11.12 pg/mL) compared to postmenopausal control (12.32 ± 5.93 pg/mL), as shown in Figure 1.

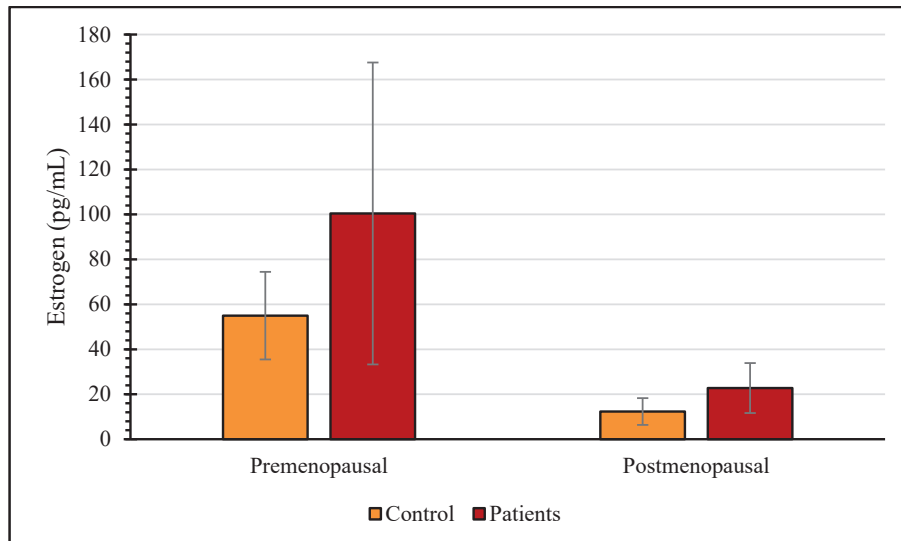


Figure 1: The level of estrogen in control and patients.

The level of testosterone was increased significantly ($p < 0.05$) in premenopausal women with BC (5.78 ± 5.08 ng/mL) compared to premenopausal control (0.38 ± 0.23 ng/mL). Nevertheless, the increase of testosterone level was non-significant ($p > 0.05$) in postmenopausal women with BC (0.54 ± 0.28 ng/mL) compared to postmenopausal control (0.52 ± 0.24 ng/mL), as shown in Figure 2.

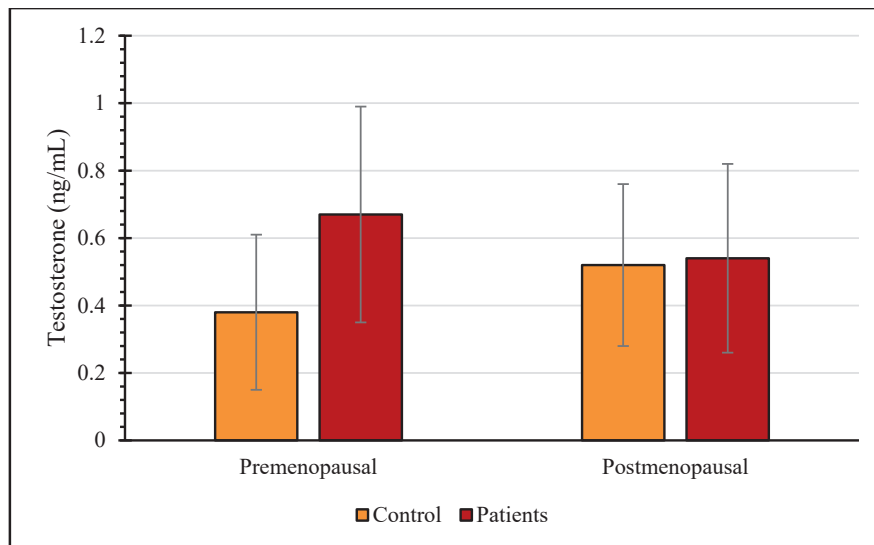


Figure 2: The level of testosterone in control and patients.

The level of progesterone was increased non-significantly ($p>0.05$) in premenopausal women with BC (0.81 ± 2.68 ng/mL) compared to premenopausal control (3.28 ± 1.60 ng/mL). Nevertheless, the increase of progesterone level was significant ($p<0.05$) in postmenopausal women with BC (0.53 ± 0.31 ng/mL) compared to postmenopausal control (0.36 ± 0.20 ng/mL), as shown in Figure 3.

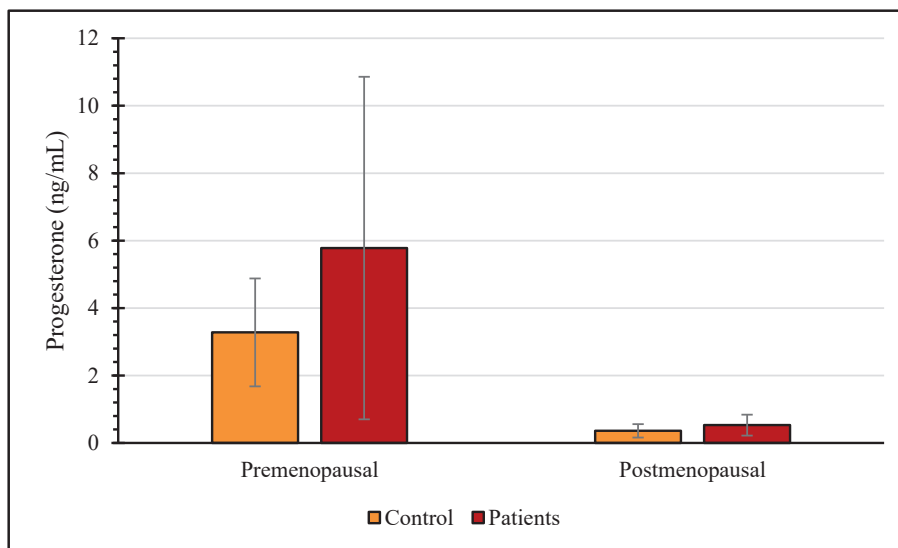


Figure 3: The level of progesterone in control and patients.

The differences in the levels of T3 hormone was non-significant ($p>0.05$) between premenopausal women with BC (1.50 ± 0.47 nmol/L) and premenopausal control (1.23 ± 0.51 nmol/L). Also, the differences of T3 hormone levels were non-significant ($p>0.05$) between postmenopausal women with BC (1.57 ± 0.47 nmol/L) and postmenopausal control (1.51 ± 0.43 nmol/L), as shown in Figure 4.

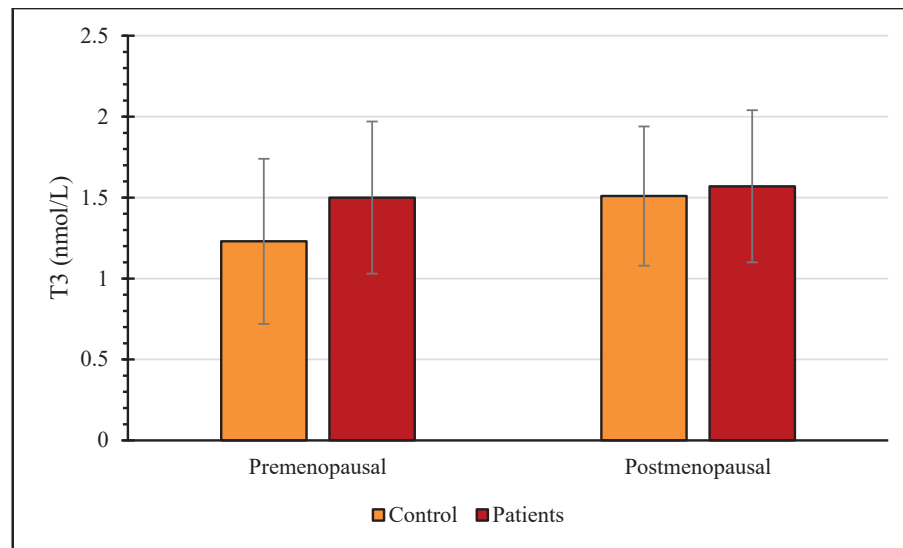


Figure 4: The level of T3 in control and patients.

The level of T4 hormone was increased significantly ($p < 0.05$) in premenopausal women with BC (129.06 ± 28.44 nmol/L), compared to premenopausal control (97.63 ± 20.63 nmol/L). Also, the increase of T4 hormone level was significant ($p < 0.05$) in postmenopausal women with BC (139.30 ± 24.35 nmol/L) compared to postmenopausal control (105.60 ± 29.82 nmol/L), as shown in Figure 5.

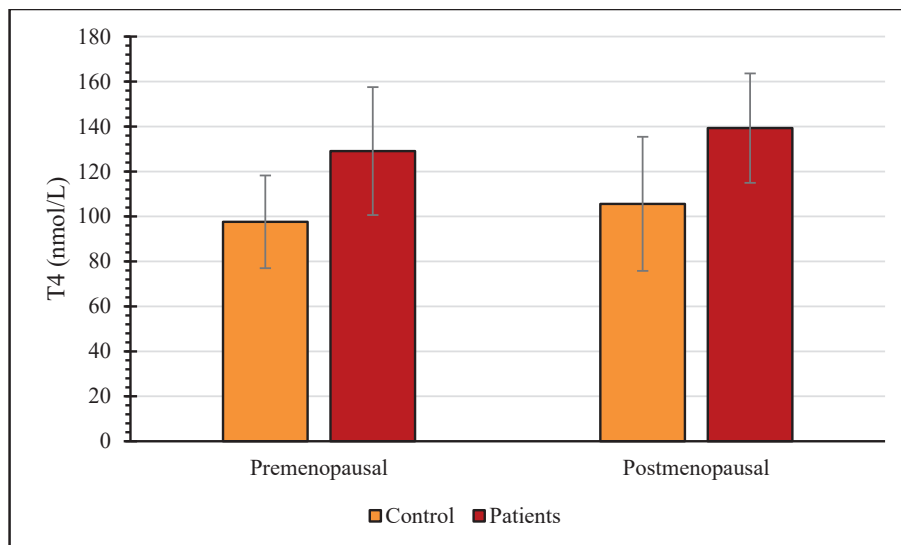


Figure 5: The level of T4 in control and patients.

The level of TSH was reduced non-significantly ($p > 0.05$) in premenopausal women with BC (1.76 ± 1.65 μ IU/mL) compared to premenopausal control (2.49 ± 0.94 μ IU/mL). Nevertheless, the reduction of TSH

was significant ($p < 0.05$) in postmenopausal women with BC ($1.98 \pm 1.03 \mu\text{U/mL}$) compared to postmenopausal control ($2.77 \pm 1.21 \mu\text{U/mL}$), as shown in Figure 6.

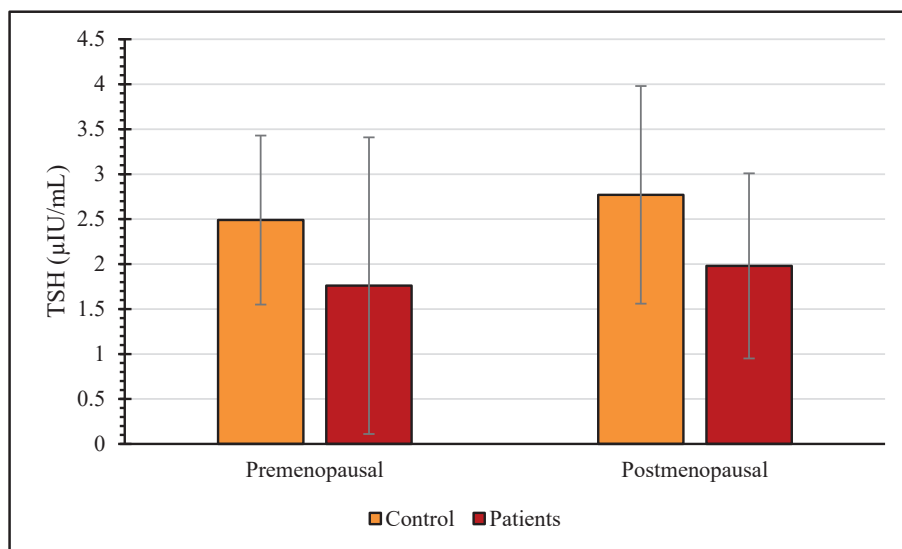


Figure 6: The level of TSH in control and patients.

5. ROC and AUC of Data to Prognosis Breast Cancer

5.1. Patients and Controls Premenopausal Status

Table 1 in the supportive documents illustrate the values of area under the ROC curve (AUC) of each parameter to predict the usefulness of using these parameters in the prognosis of BC in premenopausal women, from the table we can say the estrogen has shown good sensitivity in the prognosis of BC in premenopausal women (AUC=0.840). The cut-off value of estrogen was observed as 55.35 pg/mL with 76.9% sensitivity and 69.2% specificity. Testosterone has also shown a good sensitivity (AUC=0.837), the cut-off value is 0.45 ng/mL with 84.6% sensitivity and 84.6% specificity, while the progesterone has shown poor sensitivity in the prognosis of BC in premenopausal women (AUC=0.698).

When we are talking about thyroid hormones, T3 has shown poor sensitivity in the prognosis of BC in premenopausal women (AUC=0.654), while, the T4 has shown a good sensitivity (AUC=0.822) and the cut-off value of T4 is 116.8 nmol/L with 76.9% sensitivity and 76.9% specificity, furthermore, TSH has shown fair sensitivity with AUC=0.760, the cut-off value was 1.77 $\mu\text{U/mL}$ with 76.9% sensitivity and 69.2% specificity.

5.2. Patients and Controls Postmenopausal Status

Table 2 in the supportive documents illustrate the values of area under the ROC curve (AUC) of each parameter to predict the usefulness of using these parameters in the prognosis of BC in postmenopausal women, it is clear that estrogen has shown good sensitivity in the prognosis of breast cancer in postmenopausal women (AUC=0.808). The cut-off value of it observed as 13.15 pg/mL with 76.6% sensitivity and 68.1% specificity, in addition, the progesterone has shown a poor sensitivity with

AUC=0.698, the cut-off value was 0.39 ng/mL with 66% sensitivity and 66% specificity while the testosterone has failed in the prognosis of BC in postmenopausal women (AUC=0.500).

In the thyroid hormones, T3 has also failed in the prognosis of BC in postmenopausal women, its AUC=0.548, while T4 has shown good sensitivity with AUC=0.830, its cut-off value was 120.57 nmol/L with 85.1% sensitivity and 80.9% specificity, finally, The TSH has shown a fair sensitivity with AUC=0.702, the cut-off value was observed as 2.25 μ U/mL with 76.9% sensitivity and 69.2% specificity.

6. Conclusions

In this work, the relationship between steroid and thyroid hormones with BC was studied in Iraqi women who are affected with BC and before they took any kind of treatment, from the biochemical measurements and statistical analysis. It was found that there is a clear relationship between these hormones and BC, especially estrogen and T4. It can be concluded that hormonal disruption in women, especially estrogen, can lead to activation of BC cells. Therefore we recommend conducting on the physiological relationship between T4 hormone and BC.

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