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Evaluation of lipid profile in postmenopausal breast cancer patients and its association with serum level of thyroid hormones, vitamin D and estrogen

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Abstract

The aim of the present research is to evaluate the lipid profile in postmenopausal breast cancer patients and its association with serum level of thyroid hormones, vitamin D, and estrogen level. In this research, 45 postmenopausal women with breast cancer (BC group) and 45 postmenopausal healthy women (control group) were participated. Serum level of cholesterol, triglyceride, and HDL were measured using spectrophotometry. Serum level of LDL and VLDL was estimated by formula and serum level of TSH, T3, T4, fT4, 25 (OH) D3 and estrogen hormone were determined by the ELISA technique. The obtained results show that the concentrations of HDL-C in BC subgroup (P_{value} less than 0.05) were substantially lower than the healthy group. Although other lipid profile including TC, TG, LDL and VLDL in the BC group was higher than in the healthy group, however, this difference was not significant. Also, T3 level in the BC group was significantly higher than the healthy group (P< 0.05). Finally, the serum concentration of 25-OH- D3 was considerably lower in the BC group (P 0.05) than in the healthy group and the serum concentration of estrogen in the BC group was significantly higher than the healthy group (P < 0.05). A significant positive correlation was observed between T4 and HDL (r=0.33, P=0.02). Also T4 had a significant negative correlation with TG (r= -0.37, p=0.01) and VLDL (r= -0.37, P=0.01). Based on these findings, it can be concluded that thyroid dysfunction, vitamin D deficiency, lipid profile disorders, and high level of estrogen can be considered as risk factors for breast cancer in postmenopausal women. Therefore, routine screening of these parameters in the postmenopausal period is recommended to reduce the incidence of breast cancer.

Keywords: Thyroid hormones; Lipid profile; Estrogen; Breast cancer

1. Introduction

Breast cancer is one of the most frequent malignancies in females worldwide and is approximately up to ~70–80% of patients with early-stage, without metastatic disease (1). Breast cancer is extremely rare before the age of30, after which it becomes more common as you get older, peaking around the age of 50 (2). Breast cancer incidence rises steadily with age, but the slope of the age–incidence curve changes dramatically at about age 50, and this is unique for breast cancer. The apparent change in slope is probably associated with hormonal changes in menopause, which are accompanied by a decrease in circulating level of estrogen (4-6, 33). The most common breast cancer histology is invasive ductal carcinoma (50%-75% of patients), followed by invasive lobular carcinoma (5%-15% of patients), and with mixed ductal/lobular carcinomas and other rarer histologist making up the remainder of patients. The primary risk factors of cancer include age, high hormone level (7), race, economic status, and iodine deficiency in diet (8). Some of hormones like estrogen thought to affect the progression of starting mammary gland cells in the path to malignancy. Occupational, reproductive and hormonal factors, there is no evidence clinical risk factors for breast cancer (9, 34).

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The link between thyroid disease and the risk of breast cancer is supported by studies that demonstrate the role of thyroid hormones in regulating breast epithelial cell growth (10) Also, thyroid abnormalities are strongly related to lipids, in addition to a number of other cardiovascular risk factors. Hypothyroidism is relatively common and is associated with an unfavorable effect on lipids (11). A higher percentage of positive thyroid peroxidase antibodies are seen in women with B.C in comparing to healthy controls (12). High levels of thyroid hormones have estrogen like effects in several laboratory studies, and their association with the progression of breast cancer and other cancers has been studied in the past with inconsistent results. It has been recently reported that Vit-D and its receptor are managed in breast cancer pathogenesis (13, 14). Vitamin D activates by attaching to a protein called the vitamin D receptor (VDR), which is present in breast tissue cell proliferation, differentiation, and apoptosis. According to previous research, VDR regulation induces gene expression (15, 16, 35). Previous research has shown that activated *1,25-(OH)2D vitamin D influences cellular events that may be important not only for breast cancer pathogenesis but also for prognosis and survival (17-19). Therefore, the aim of the proposed paper is to evaluate the lipid profile in postmenopausal breast cancer patients and its association with serum level of thyroid hormones, vitamin D, and estrogen.

2. Material and methods

This is a case control study which was proceeding in 2020-2021. After informing all infected and healthy participants to allow samples to be taken for laboratory and clinical examinations. This study was approved by the ethics and research committees of Ferdowsi university of Mashhad (IR.UM.REC.1399.089). There are ninety female participants in this study. Samples were collected from Karama Teaching Hospital/Wasset and the Al Zahra Teaching Hospital/wasset, Iraq. Ninety studied women were divided in 2 groups including; 1-Post menopausal breast cancer (BC) group (n=45), 2-Post menopausal healthy women group (n=45). Inclusion criteria for post-menopausal women with breast cancer: Histological confirmation of breast cancer, Age (50-60) years, no radiotherapy, no chemotherapy, no anti-estrogens, no vitamin D supplementation, no liver or kidney disease, no ovariohysterectomy, no other cancers, no smoking and alcohol drinking. Inclusion criteria for control groups: Age (50-60) years, clinically healthy women, no family history of breast cancer, no vitamin D supplementation, no liver or kidney disease, no ovariohysterectomy, no other cancers, no smoking and alcohol drinking.

2.1. Blood sampling

Blood samples were collected after 12 hours of fasting. The venous blood sample was collected and placed in a gel tube for the serum separation (centrifugation at 3000 rpm for 10 minutes). Serum samples were stored in the freezer at -20 ° C.

2.2. Evaluation of serum biochemical parameters

Cholesterol, HDL-cholesterol and Triglyceride were measured using ELISA kit (Biolabo Company, France).VLDL–cholesterol was determined according to the following Equation 1.

$$\text{VLDL– Cholesterol concentration} = \frac{\text{Triglyceride concentration (mg/dl)}}{5} \qquad \text{Equation 1}$$

Also, LDL–cholesterol was estimated by applying Equation 2:

Equation 2= LDL-Cholesterol=Total cholesterol– (VLDL - cholesterol + HDL -cholesterol) (mg/dl)

Thyroid-Stimulating Hormone (TSH), Triiodothyronine (T3) hormone, Thyroxin (T4) hormone, and FT4 were measured by ELISA assay (Cell Biolabs, UAS; Abnova, Germany). Human D3 were measured by ELISA assay (Abnova, Germany). Human estrogen was measured by ELISA assay (Mybiosource, USA). The statistical tests were performed using the SPSS software (version 16, USA). The distribution of obtained data was assessed using Kolmogorov-Smirnov test. Regarding the normal distribution of the obtained data, two independent samples T test was applied for comparison of data between groups. The correlation between the studied variables was investigated by Pearson test and the findings have been significant (* $p<0.05$).

3. Results

According to the average level of BMI, breast cancer group as well as healthy women, are obese. Also, no significant difference in BMI was observed between breast cancer (30.2±8.1 kg/m^2) and control groups (30.7±7.5 kg/m^2) ($P>0.05$). The results of the level of lipid profile are presented in Table 1. The obtained results show that the concentration of HDL-C in the BC group was significantly lower than the healthy group ($P<0.05$). Also, although other lipid profiles

including TC, TG, LDL and VLDL in the BC group were higher than in the healthy group, however, this difference was not significant (P>0.05). Figs. S1-S5 show the average levels of triglycedide, cholesterol, HDL, LDL and VLDL in BC group and control subjects, respectively.

Table 1 Comparison of serum level of lipid profile fractions (Mean ± SD) between breast cancer and control groups

	Cholesterol in (mg/dl)	**Triglyceride In (mg/dl)**	**HDL In (mg/dl)**	**LDL In (mg/dl)**	**VLDL In (mg/dl)**
Control	173.1 ± 57.46	138.2 ± 125.7	48.6± 10.92*	96.84±40.48	27.6± 25.1
Breast cancer	178.9 ± 34.9	181.1± 82.4	42.2± 10.99	100.48±30.31	36.23 ± 16.49

*: refer to significant difference (p <0.05) between groups

Table 2 shows the level of thyroid hormones in BC and control groups. The obtained results indicated that, T3 level in the BC group was significantly higher than the healthy group (P< 0.05). However, there are no significant difference were observed in the serum level of TSH, T4 and FT4 between BC and control groups (P>0.05). Figs S6-S8 show the average levels of T3, T4, and FT4 in BC group and control subjects, respectively.

Table 2 Comparison of serum level of thyroid hormones (Mean ± SD) between breast cancer and control groups

Thyroid Hormone / Groups	**T3 (ng/dL)**	**T4 (µg/dL)**	**FT4 (ng/dL)**	**TSH (µIU/mL)**
Control	59±17.06 *	5.62±1.41	1.01±0.26	4.802±1.275
Breast cancer	70.63±19.8	5.31±1.30	1.04±0.32	4.75±1.26

* significant difference of (p <0.05) between groups

Serum level of 25-OH-D3 and estrogen in control and BC groups are presented in Table 3. According to the results, the serum concentration of 25-OH-D3 in the BC group was significantly lower than the healthy group (p < 0.05); however, the estrogen level in BC group was significantly higher than control subjects. Figs S9 and S10 show the average levels of 25-OH-D3 and estrogen in BC group and control subjects, respectively.

Table 3 Comparison of serum level of 25OH-D3 and Estrogen (Mean ± SD) between breast cancer and control groups

Groups / Parameter	**Control group (n=45)**	**Breast cancer group (n=45)**
25-OH- D3 (ng/mL)	45.7 ± 18.02 *	37.8 ± 17.4
Estrogen (pg/ml)	120.66 ±71.50*	344.5 ± 255.0

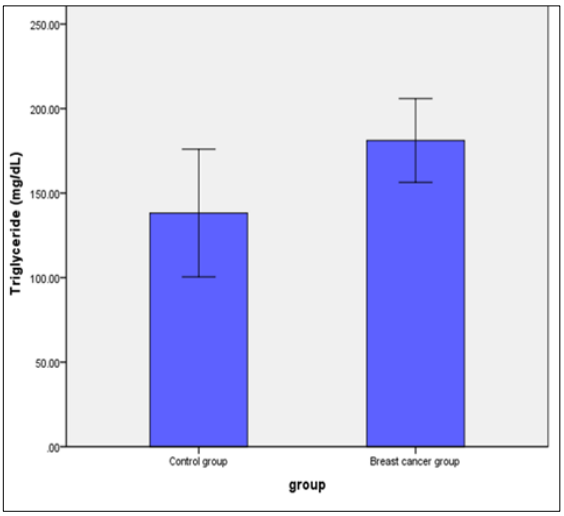

Figure 1 Triglyceride level in BC and control subjects (P>0.05)

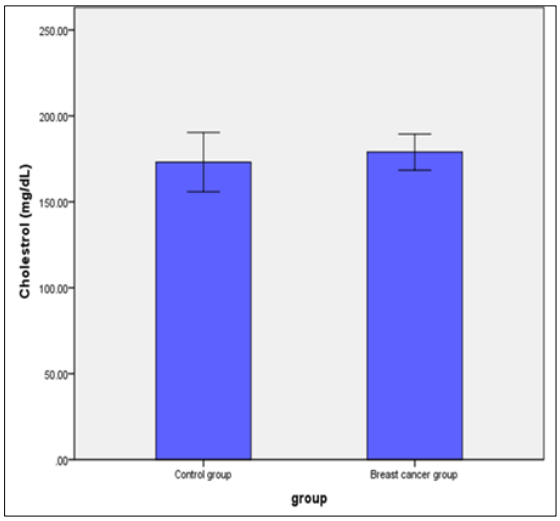

Figure 2 Cholesterole level in BC and control subjects (P>0.05)

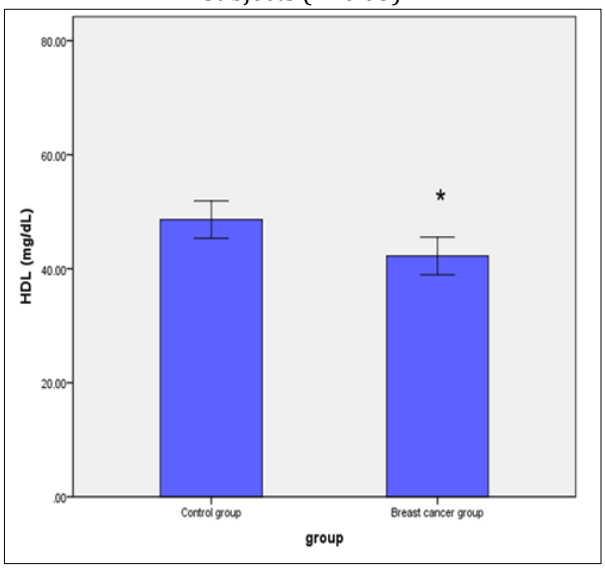

Figure 3 HDL level in BC and control subjects (P<0.05)

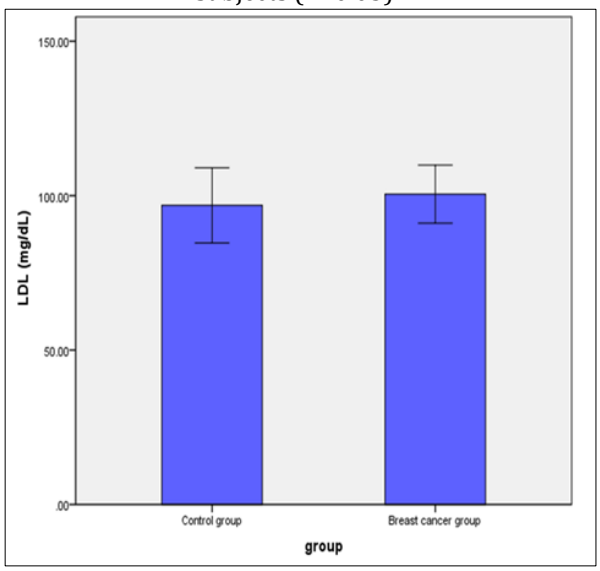

Figure 4 LDL level in BC and control subjects (P>0.05)

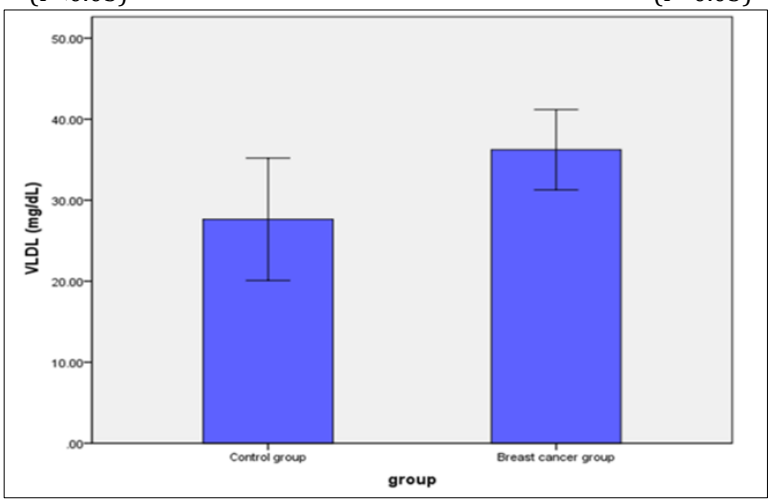

Figure 5 VLDL level in BC and control subjects (P>0.05)

3.1. Correlations between thyroid hormones *(T3,T4,TSH,FT4) and lipid profile parameters

Table 4 shows the relations between (thyroid hormones, lipid profile)eparameters. The obtained results show that: 1- In BC group, a significant positive correlation was observed between T4 and HDL (r=0.33, p=0.02). Also T4 had a significant negative correlation with TG (r= -0.37, p=0.01) and VLDL (r= -0.37, p=0.01). 2- In the control group, there is no significant correlation showed between thyroid hormones and lipid profile (p>0.05).

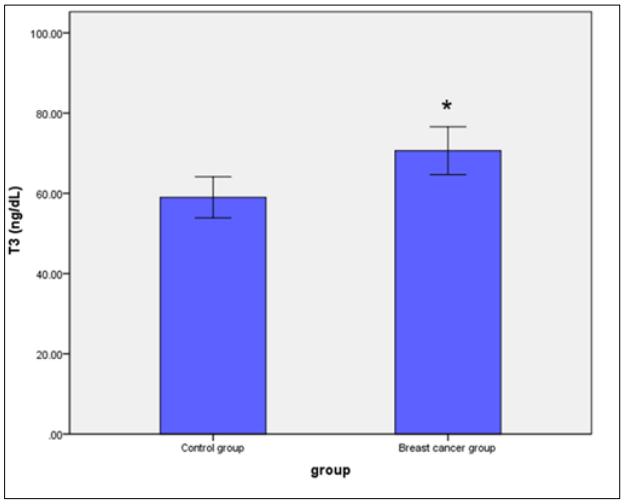

Figure 6 T3 level in BC and control subjects (P<0.05)

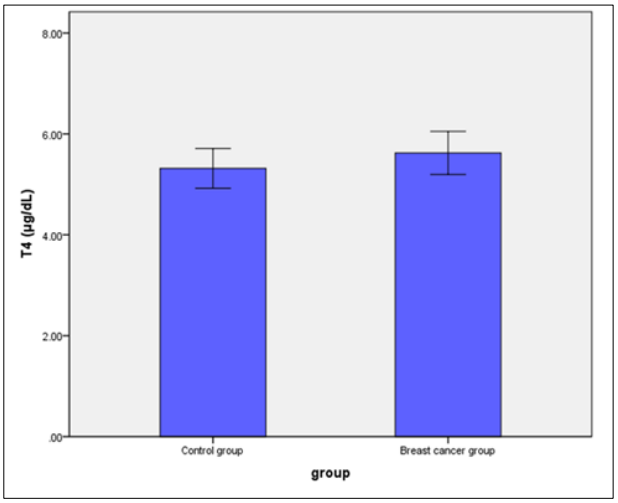

Figure 7 T4 level in BC and control subjects (P>0.05)

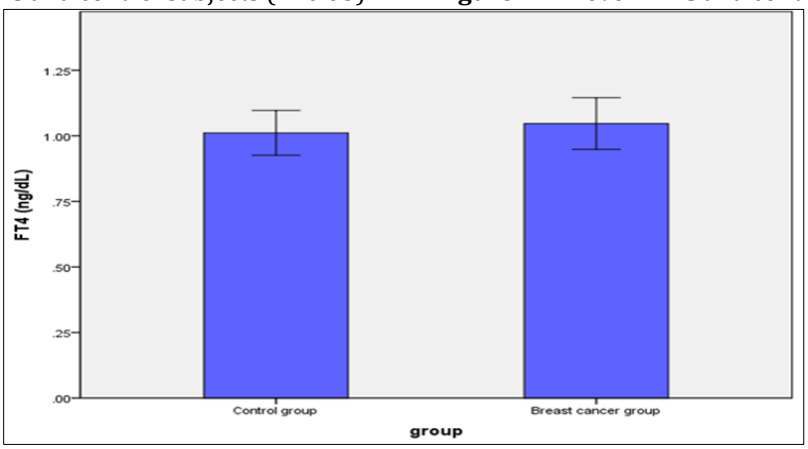

Figure 8 FT4 level in BC and control subjects (P>0.05)

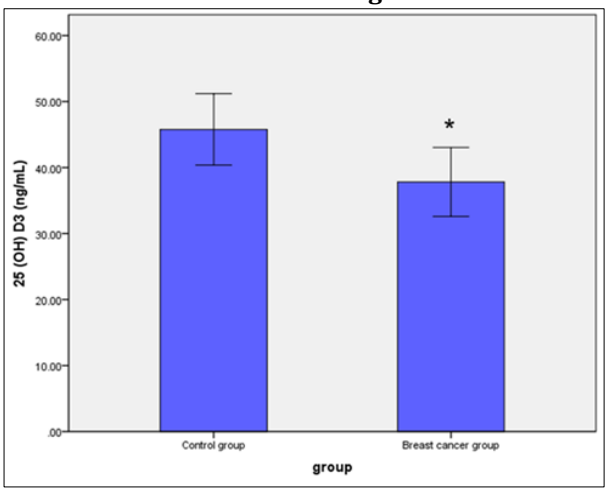

Figure 9 25(OH)D3 level in BC and control subjects (P<0.05)

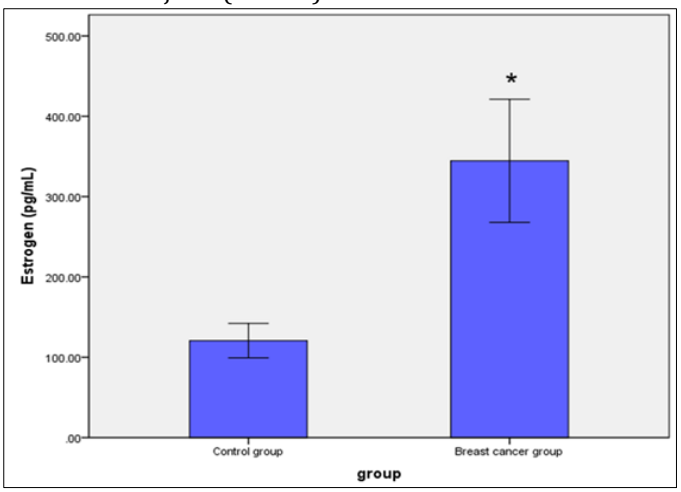

Figure 10 Estrogen level in BC and control subjects (P<0.05)

Table 4 Correlations between hormonal test and lipid profile fractions

Parameters		Breast cancer group (n=45)				Control group (n=45)			
		T3	T4	TSH	fT4	T3	T4	TSH	FT4
TC	r	0.52	-0.15	0.03	0.21	0.23	0.09	0.01	0.13
	p	0.09	0.31	0.82	0.16	0.11	0.52	0.96	0.36
TG	r	0.10	-0.37*	0.01	0.03	0.06	0.07	0.10	0.08
	p	0.49	0.01	0.95	0.84	0.66	0.63	0.50	0.58
HDL	r	0.17	0.33*	0.2	0.22	0.26	0.25	-0.29	-0.05
	p	0.24	0.02	0.18	0.13	0.08	0.10	0.051	0.72
LDL	r	0.00	-0.08	0.03	0.13	0.23	0.02	0.03	0.23
	p	0.99	0.56	0.80	0.36	0.13	0.86	0.87	0.12
VLDL	R	0.10	-0.37*	0.01	0.03	0.06	0.07	0.10	0.08
	P	0.49	0.01	0.95	0.84	0.60	0.63	0.50	0.57

* and ** indicate significant correlation with p value < .05 and < .01 respectively

Table 5 and 6 show the correlations between vitamin D3 (25-OH- D3) and estrogen level and lipid profile parameters. According to the results; 1- There is no correlation between vitamin D level and lipid disorder (P>0.05). 2- There is no significant correlation between estrogen and lipids and lipoproteins in both BC and control groups (P>0.05).

Table 5 Correlations between vitamin D3 (25-OH- D3) and lipid profile fractions

		25-OH- D3	
		Breast cancer (n=45)	Control (n=45)
T.C	r	0.03	0.11
	p	0.84	0.2
T.G	r	-0.02	0.3
	p	0.88	0.1
HDL	r	0.11	0.1
	p	0.46	0.4
LDL	r	0.01	0.1
	p	0.97	0.2
VLDL	r	-0.02	0.3
	p	0.88	0.1

* and ** indicate significant correlation with p value < .05 and < .01 respectively

Table 6 Correlations between vitamin Estrogen and lipid profile fractions

		Estrogen	
		Breast cancer (n=45)	**Control (n=45)**
T.C	r	0.029	0.07
	p	0.8	0.6
T.G	r	0.22	0.02
	p	0.1	0.8
HDL	r	0.03	0.1
	p	0.8	0.3
LDL	r	0.07	0.08
	p	0.6	0.5
VLDL	r	0.22	0.02
	p	0.1	0.8

* and ** indicate significant correlation with p value < .05 and < .01 respectively

4. Discussion

Most studies indicate that obesity and higher body mass index (BMI) may increase the risk of breast cancer in females (20). These abnormalities may expedite tumor development. by influencing the spectrum of cancer epithelial cells and indirectly or in anther languish called tumor microenvironment (21). In some types of cancer, blood cholesterol undergoes noticeable changes. It has been shown that there is direct association between the blood lipid profile and different tumors (22). In this research, the concentration of HDL-C The survival rate of breast cancer patients was significantly lower than in the healthy group ($P < 0.05$). Although other lipid profile fractions including TC, TG, LDL and VLDL in the BC group were higher than in the healthy group, this difference was not significant. Cholesterol plays an important role in steroid hormone formation so that endogenous steroid hormones are related with risk factors of breast cancer (23). Abu Bedair et al. showed a significant increase in the blood cholesterol levels in both postmenopausal and premenopausal women with breast cancer compared to the control group, reflecting the risk of high cholesterol in promote breast cancer (24). Different studies showed, serum particles of HDL have a single copy or multiple copies from apolipoprotein A-I (apoA-I), the most abundant HDL apolipoprotein. Apolipoprotein A-I considered a key role in promoting cholesterol produce from cells; It has anti-inflammatory, antioxidant, and anti-apoptotic characteristics, as well as an impact on innate immunity (25).

Our results indicated T3 concentration in the BC group showed significantly higher than the healthy group ($P<0.05$). However, no significant difference was observed in the serum level of TSH, T4 and FT4. Thyroid hormones are associated with growth, development, metabolism and physiological capacity for almost all mammalian tissues including the breast (26). T3 may be stimulated tumor proliferation and play key role in the growth and progression of breast cancer. The proliferative effect of T3 has been demonstrated in various types of cancer. Hall et al., in 2008, show that in BC cell lines, T3 may foster the conditions for tumor proliferation; thus, T3 may play a role in the development and progression of BC. Also, thyroid hormones are essential for lipid metabolism regulation, therefore, thyroid dysfunction is usually associated with dyslipidemia (27). Thyroid hormones activate 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, the first step in the production of cholesterol (28). The obtained results in this study show that, the serum concentration of 25-OH- D3 in the BC group was significantly lower than the healthy group ($P< 0.05$). Experimental studies showed that vitamin D inhibits the development of breast cancer and metastasis by inducing apoptosis, reducing cell growth and angiogenesis (29). Khosravi et al., in 2018 investigate the effect of Vitamin D supplementation on lipid profile in obese and fat women. Their results show that after using VitD supplement for 6 weeks, factors including TC, TG and (LDL , HDL)cholesterol , did not change significantly ($P > 0.05$) which consistent with the results obtained in our study (30).

The results in this study showed a higher level of estrogen in postmenopausal women with breast cancer risk compared to healthy women ($P<0.05$). It has been shown that higher levels of estrogen are associated with an increased risk of postmenopausal breast cancer (31). Estrogens are associated with an increased process of proliferation and

decreased apoptosis, and may promote proliferation of cells with genetic mutations. agree with Henderson and Feigelson (32).

5. Conclusion

In this research, the lipid pr0file in postmenopausal patients with breast cancer was analyzed and its association with serum level of thyroid hormones, vitamin D, and estrogen were evaluated. The obtained results in this research show that the concentration of HDL-C in the BC group was significantly lower than the healthy group ($P<0.05$). Also, T3 and estrogen level in the BC group was significantly higher than the healthy individuals ($P<0.05$) and 25-OH-D3 in the BC group was significantly lower than the healthy group ($P<0.05$). Likewise, A significant positive correlation was observed between T4 and HDL ($r=0.33$, $P=0.02$), however, T4 had a significant negative correlation with TG ($r= -0.37$, $P=0.01$) and VLDL ($r= -0.37$, $P=0.01$). Based on these findings, it can be concluded that thyroid dysfunction, vitamin D deficiency, lipid profile disorders, and high level of estrogen can be considered as risk factors for breast cancer in postmenopausal women. Therefore, routine screening of these parameters in the postmenopausal it is recommended to decrease the incidence of breast cancer during this period. Also, It suggests that since estrogen hormones can assist in the innovation of breast cancer, either anti-estrogens or aromatase inhibitors might be more effective in preventing breast cancer.

Compliance with ethical standards

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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