Correlation Between Lipid Profile Biomarkers and Pre- and Postmenopausal Breast Cancer Patients in Iraqi Women.

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Abstract
The current study aims to evaluate the relationship between Iraqi women subjected to breast cancer (BC) and their serum levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and very low density lipoprotein cholesterol (VLDL-C). The study was conducted on one hundred women's, sixty women's with BC and fourty women healthy. The samples were divided in to two groups (pre-menopausal and post-menopausal). Concentration of serum TC, TG, HDL-C were determined by enzymatic colorimetric method using Semi-Auto Analyzer instrument (spectrophotometry) and serum level of LDL-C and VLDL-C was estimated by Friedewald's equation. All the biochemical values showed significant differences between the BC patients and healthy controls. The obtained results showed that the concentrations of HDL-C in pre-menopausal and post-menopausal BC were substantially lower than the healthy groups (P≤0.05), while the concentrations of serum TC, TG, LDL-C and VLDL-C levels was significantly higher than the healthy groups (P≤0.05). In addition, BMI (Body Mass Index) in pre and post-menopausal was statistically associated with high lipid profile level. Based on these findings, it can be concluded that lipid profile can be considered as risk factors for women's with BC. Therefore, routine screening of these parameters in women's with BC is recommended to reduce the incidence of disease.

Keywords: Lipid profile; Postmenopausal; Premenopausal; Breast cancer; BMI.

1- Introduction

Breast cancer (BC) 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]. BC is a complex, heterogeneous disease with various biological characteristics, therefore, each breast cancer patient may have different responses to treatment [2]. The incidence of all cancer types is still increasing. In 2020, there were 2.3 million women diagnosed with BC and 685,000 deaths globally occurring in the world in women at any age after puberty [3]. In Iraq it represents more than 24% of overall cancer cases making it a great problem to the health system in our country [4].

One modifiable risk factor that may raise a women risk of BC is obesity [5,6]. Tissue lipid metabolism and circulating lipid levels may have a role in the biological relationship , between obesity and illness risk [7]. Furthermore, obesity and overweight are increasingly thought to be risk factors for the onset and spread of BC.

Numerous population studies have shown that obesity and the excess adipose tissue accumulation it causes are independent unfavorable prognostic markers for mammary tumors and are linked to an increased risk of BC, particularly in postmenopausal women [8,9,10,11,12,13,14]. Evidence that connects plasma lipid levels to the development and worse outcomes of BC has surfaced in the last few decades [15]. This has to do with reprogramming tumor cells to increase their ability to absorb lipids for cell division [16]. Some studies found a significant correlation between high total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), or triglycerides (TG) and the risk of BC [17,18], while others studies indicated negative [19,20] or inverse relationships [21].

Regardless of temperature fluctuations, cholesterol stabilizes and preserves the permeability and fluidity of cell membranes. Together with phospholipids, sphingolipids, and glycosylphosphatidylinositol-anchored proteins, cholesterol is also essential for the formation and maintenance of lipid microdomains, or lipid rafts [22]. There exist various mechanisms by which hypercholesterolemia is connected with an increased risk of developing BC [23, 24, 25, 26]. The development and metastasis of malignancies have been favorably connected with a number of cholesterol metabolites [8].

High density lipoprotein cholesterol (HDL-C) may help to reduce intracellular sterol accumulation and its detrimental effects on BC because it extracts cholesterol and oxysterols from cells [27]. HDL-C carries cholesterol to the liver, where it is partially stored as cholesterol esters and discharged as bile [28]. There is a negative link between HDL-C and BC; according to certain previous studies, Touvier et al. found a negative correlation between premenopausal women HDL-C levels and their risk of BC [29]. Additionally, Kucharska et al. [30] found a correlation between premenopausal women low HDL-C and a higher incidence of BC. Patients with low serum HDL-C levels are reported to have an increased risk of death from triple negative breast cancer (TNBC) [31]. The meta-analysis done by Zhao et al. [32] has proven that HDL-C levels are a protective factor for overall survival in cancer patients.

Since LDL-C and HDL-C are primarily responsible for transporting cholesterol, numerous research studies have linked them to BC. A research study evaluating the lipid profile in women diagnosed with BC revealed that LDL-C levels at diagnosis were a predictor of the advancement of the tumor. Furthermore, lymph node metastasis was more common in patients whose LDL-C level was higher than 144 mg/dL [33]. More significantly, a Mendelian randomization study discovered that a higher risk of BC was linked to genetically elevated LDL-C [28, 34].

According to previous research, the LDL-C fraction is strongly linked to the development of BC and may even be helpful in identifying and tracking high-risk individuals. As a result, LDL-C levels upon diagnosis became a predictive factor for BC patients [35, 36].

3- Materials and Methods

3-1- Collection of Blood Sample

A cases and controls study was conducted in 2022 after informing all sick and healthy individuals to allow samples to be taken for laboratory and clinical exam. The samples were collected from Anbar Cancer Center in Anbar, Iraq. Participating in this study were women and divided into two groups: 1- premenopausal (patients n = 25 and healthy women n = 23); 2- postmenopausal (patients n = 35); and (healthy women n = 17).

3-2- Blood Sampling

The venous blood sample was collected and placed in a gel tube for the serum separation (centrifugation at 3000 rpm. for 10 min.). Serum samples were stored in the freezer at -20°C until use.

3-3- Evaluation of Serum Biochemical Parameters

Serum TC, TG, and HDL-C were measured using a Semi-Auto Analyzer kit (AGAPPE, Switzerland). LDL-C was calculated using Friedewald's equation (LDL-C = TC - HDL-C – VLDL-C), and VLDL-C was calculated using the equation (VLDL-C = TG/5).

3-4- Statistical Analysis Used

To estimate the relationship between lipid profiles and BC, we categorize lipid profiles such as TC, HDL-C, LDL-C, and TG based on clinically abnormal values or cutoff points. The proportion and mean differences between cases and controls were analyzed using Statistical Package (SPSS for Windows version 16.0 (2018)). At a p-value <0.05 and p-value <0.01, all statistical tests in this study are considered significant.

4- Ethics approval

To carry out the study, ethical permission was obtained from the Anbar cancer center of the Iraq Ministry of Health and the Scientific Research Ethics Committee of Anbar University. In addition, each participant in the case and control groups signed a consent form as an agreement to participate in this study.

5- Results

The results of the measured lipid profile parameters in the research were listed in tables below for women with BC and healthy.

(Table 1) showed comparison of lipid profile parameters in women with BC at premenopausal statue and control groups .The results showed significantly higher (p≤0.01) in Serum TC, Serum TG, Serum LDL-C and Serum VLDL-C camper with healthy women. There was no significant difference observed in Serum HDL-C and Age in premenopausal BC patients compared with healthy women.

Table 1: Changes in lipid profile levels (mean ± SE) in premenopausal BC patients compared with control groups.

Variables	Cases (n=25) (Mean ± SE)	Control (n=23) (Mean ± SE)	P-Value
Age	38.42 ± 5.20	37.80 ± 5.12	0.11
TC	197.462± 8.818	110.304 ± 3.464	0.0027
TG	177.615±13.542	90.333± 2.874	0.0032
HDL	39.654±0.899	43.278± 1.419	0.09
LDL	127.115 ± 7.137	49.348 ± 3.869	0.0018
VLDL	35.269 ± 2.712	18.222± 0.586	0.0045

P≤0.05= significant, p≤0.01= high significant

(Table 2) showed comparison of lipid profile parameters in women with BC in post-menopausal and the healthy women. The results showed significantly higher (p≤0.01) in Serum TC , Serum LDL-C and Serum VLDL-C and significant difference (p≤0.05) in Serum TG and Serum HDL-C comparison with healthy women, while no found significant difference (p>0.05) in Age in post-menopausal BC patients and control group.

Table 2: Changes in lipid profile levels (mean ± SE) in postmenopausal BC patients compared with control groups.

Variables	Case (n=35) (Mean ± SE)	Control (n=17) (Mean ± SE)	P-Value
Age	57.50 ± 8.18	56.12 ± 7.33	0.244
TC	172.94 ± 5.059	115.278 ± 3.737	0.008
TG	210.086 ± 18.887	90.333 ± 2.874	0.002
HDL	32.886 ± 0.668	43.278 ± 1.419	0.01
LDL	98.00 ± 5.071	53.611 ± 3.625	0.009
VLDL	42.029 ± 3.783	18.222 ± 0.586	0.002

P≤0.05= significant, p≤0.01= high significant

A statistically significant difference (p≤0.05) was observed in blood lipid values between premenopausal and postmenopausal groups, as in (table 3).

Table 3: Comparison of lipid profile parameters (mean ± SE) between premenopausal and postmenopausal women with BC.

Variables	premenopausal (n=25) (Mean ± SE)	postmenopausal (n=35) (Mean ± SE)	P-Value
Age	38.42 ± 5.21	57.50 ± 8.18	0.043
TC	197.462± 8.818	172.94 ± 5.059	0.046
TG	177.615±13.542	210.086 ± 18.887	0.031
HDL-C	39.654±0.899	32.886 ± 0.668	0.048
LDL-C	127.115 ± 7.137	98.00 ± 5.071	0.011
VLDL-C	35.269 ± 2.712	42.029 ± 3.783	0.049

P≤0.05= significant, p≤0.01= high significant

(Table 4 and 5) illustrates the impact of body mass index (BMI) on the serum lipid profile level in women with BC in premenopausal statue. The cases and control groups were divided according to BMI from (18-24) kg/m², (25-29) kg/m², and (30-40) kg/m².
(**Table 4**) showed the effect of BMI on serum lipid profile level in woman with BC in pre-menopausal statue and control group. Our results showed at BMI (18-24) kg/m2 a high significantly deference (p≤0.01) in Serum TC and a significantly (p≤0.05) in Serum TG, LDL-C and VLDL-C , while no observed significantly deferent in serum HDL-C level (p>0.05) compared with healthy women's. At BMI (25-29) kg/m2, our results showed a significantly deference (p≤0.05) in Serum TC, TG, HDL-C, and VLDL-C, while showed a significantly higher at (p≤0.01) in Serum LDL-C and at BMI (30-40) kg/m2, our findings showed a significantly higher (p≤0.01) in Serum TC, TG and LDL-C, while showed a significantly deference at (p≤0.05) in Serum HDL-C and VLDL-C compere with control.

Table 4: Effect of BMI in premenopausal women with BC on serum lipid profile values (mean ± SE)

BMI (kg/m²)	Groups	Mean ± SE				
		T.C mg/dl	TG mg/Dl	HDL-C mg/Dl	LDL-C mg/dL	VLDL-C mg/dL
18 – 24	Control (no.7)	93.286±4.779	91.857±4.228	45.000±0.488	30.143±5.166	18.286±0.865
	Case (no.7)	169.875±6.509	110.500±5.729	41.000±0.455	107.500±7.495	21.750±1.146
	P-Value	0.008	0.049	0.06	0.01	0.05
25 – 29	Control (no.7)	114.714±6.305	124.286±2.495	40.000±0.690	33.556±2.973	24.857±0.553
	Case (no.9)	168.222±14.874	138.778±11.108	35.444±1.784	156.000±10.471	31.556±2.512
	P-Value	0.037	0.05	0.033	0.005	0.049
30 – 40	Control (no.9)	120.111±2.395	147.444±3.452	40.444±1.159	59.111±2.233	29.556±0.603
	Case (no.9)	211.889±6.746	246.667±17.353	31.111±0.772	132.889±4.254	49.000±3.504
	P-Value	0.007	0.004	0.044	0.006	0.021

P≤0.05= significant, p≤0.01= high significant

(**Table 5**) showed the effect of BMI on serum lipid profile level in woman with BC in post-menopausal state. The mean BMI (18-24) kg/m² showed a significantly deference (p≤0.05) in all parameters, except HDL-C no showed a significantly deference (p>0.05) compared with healthy women. At BMI (25-29) kg/m², our results showed a significantly deference (p≤0.05) in Serum TC, TG, HDL-C, and VLDL-C, while showed a high significantly deference (p≤0.01) in Serum LDL-C. At BMI (30-40) kg/m², our findings showed a significantly higher (p≤0.01) in Serum TC, TG and LDL-C, while showed a significantly deference (p≤0.05) in Serum HDL-C and VLDL-C.

Table 5: Effect of BMI in postmenopausal women with BC on serum lipid profile values (mean ± SE)

BMI (kg/m²)	Groups	Mean ± SE				
		T.C mg/dl	TG mg/Dl	HDL mg/Dl	LDL mg/dL	VLDL mg/dL
18 – 24	Control (no.6)	111.167±8.807	88.833±5.510	42.333±1.760	51.000±8.173	17.833±1.138
	Case (no.11)	131.909±11.308	134.000±13.812	37.091±1.601	68.000±12.143	26.818±2.763
	P-Value	0.042	0.031	0.05	0.048	0.049
25 – 29	Control (no.6)	118.000±6.050	99.667±2.499	43.333±0.615	54.000±4.234	20.167±0.543
	Case (no.12)	183.000±10.278	274.417±4.767	31.083±0.435	97.083±6.408	54.833±1.884
	P-Value	0.042	0.0079	0.015	0.038	0.046
30 – 40	Control (no.5)	116.667±4.800	82.500±4.185	44.167±0.703	55.833±5.095	16.667±0.803
	Case (no.12)	200.500±7.738	215.500±17.435	30.833±0.604	126.417±8.194	43.167±3.492
	P-Value	0.006	0.002	0.033	0.0081	0.0095

P≤0.05= significant, p≤0.01= high significant

4- Discussion

The association between BC women in premenopausal and postmenopausal status and their lipid profiles (TC, TG, HDL-C, LDL-C, and VLDL-C) was the main focus of this study. Our study results showed that lipid profile levels in women with BC were higher than in healthy women in both status pre- and post-menopausal, but the lipid profile level in both status was different.

In this study the TC level of premenopausal women were lower (197.462± 8.818) compared with postmenopausal statue (172.94 ± 5.059) and showed significantly difference at probability level (p<0.05). The findings were consistent with those of Gupta et al. [37] and Belbraouet et al. [3]. Serum lipid levels might potentially be impacted by menstruation. According to our findings, premenopausal women had lower levels of VLDL-C (35.269 ± 2.712) and TG (177.615±13.542) than postmenopausal women (VLDL-C = 42.029 ± 3.783 and TG = 210.086 ± 18.887), whereas HDL-C levels in premenopausal (39.654±0.899) and in postmenopausal (32.886 ± 0.668) show the opposite trend. These findings agree with previous studies [38, 39]. Consequently, different menopausal statuses may have different roles for lipoproteins in BC risk, a finding that is supported by multiple research [40, 41]. These findings correspond with earlier studies [38, 39]. Consequently, different menopausal statuses may have different roles for lipoproteins in BC risk, a finding that has been confirmed by multiple research [40, 41]. It has been demonstrated that cholesterol production is

elevated in cancer cells. This may have aided in the carcinogenesis of BC because of the availability of precursors or elevated transcription [42]. Statins inhibit the enzyme hydroxy-3-methyl-glutaryl-coA reductase, which reduces the proliferation of cells in vitro and suggests that cholesterol production plays a role in tumor formation. Furthermore, acyl-CoA: cholesterol acyl transferase inhibition, an enzyme implicated in cholesteryl esterification, reduces proliferation and invasion rate, and high cholesterol content is a hallmark of breast cancers [43]. Though intracellular cholesterol production is increased in cancer cells, this action is not anticipated to result in hypercholesterolemia and explain the observed relationships [44]. Thus, cancer cells may exploit plasma LDL-C. It has also been shown through in vitro investigations that cancer cells can ingest HDL-C via exogenous triglycerides [47] and the scavenger receptor class B [45,46,47]. Though our results do not rule out the possibility of consuming cancer cells, HDL-C or triglyceride tests in our clinical scenario did not show abnormal alterations. Laboratory results demonstrating that exogenous HDL-C and LDL-C can both stimulate proliferation and migration, characteristics of aggressive cancers, support this theory [48,45,46]. Studies on animals also shown that hypercholesterolemic mice had a greater tumor and metastatic load as well as a faster rate of disease progression when compared to nonhypercholesterolemic controls. Exogenous cholesterol may be released from body reserves by HDL-C or from food by hepatic metabolism and LDL-C [49].

Growth of oestrogen receptor-positive BC cells can be stimulated by the cholesterol metabolite 27-hydroxycholesterol, which can function as an oestrogen. Researchers have found that the metabolic syndrome, which has dyslipidemia as one of its symptoms, may increase the risk of BC by increasing blood levels of leptin and decreasing levels of adiponectin. Additionally, studies have demonstrated that these two hormones raise the risk of developing BC [50].

It is important to recognize that lipid metabolism plays a part in obesity and the symptoms of cancer. Various processes [51, 52, 53, 54] elucidate the advantageous inverse correlation of HDL-C changes related to obesity. First, a link between fractional rate cholesterol esterification (FER-HDL) and HDL-C particle subfractions-2b (HDL-2b) is a plausible explanation. FER-HDL has a positive correlation with BMI [54] and is a useful metric for determining HDL ability to esterify free cholesterol [55]. Traditionally, unesterified free VLDL and LDL are deposited as extra fat in the fatty tissues [56]. FER-HDL and HDL-2b, however, have an inverse correlation [54]. Secondly, the potential correlation between HDL-C and obesity may stem from the release of big HDL particles via ATP-binding cassette transporters, which prevent cellular lipid accretion in hepatic cells and macrophages [57.58,59]. Third, among metabolically unhealthy obese individuals, HDL particle subfractions 2b have been shown to have anti-inflammatory potential by adversely influencing lymphocyte activation and showing an inverse relationship with inflammation markers (e.g., high-sensitivity C-reactive protein, interleukin-6) [52].

Our study revealed that the obesity and a higher BMI may raise a women risk of BC in addition to her chance of developing more aggressive tumors and a worse prognosis [60, 61]. Obese women adipose microenvironments have numerous characteristics in common with tumor microenvironments, including cellular composition, low-grade inflammation, and elevated reactive oxygen species [62].

The results also shown an important association between BMI and elevated levels of (TC, TG, LDL-C, VLDL-C), and decreased HDL-C in women with BC, both in pre- and post-menopausal groups. The findings demonstrated that, in comparison to the control groups, patients' levels of lipid profile increased with increasing BMI. Comparing our results to the control at BMI (18 - 24, 25 - 29, and 30 - 40) kg/m^2, it found a significant rise in the level of lipid profile at the probability level (P value <0.05 and P value <0.01), as shown in (Tables 4 and 5). These results were in agreement with earlier research conducted by Dhakad et al. [63], Kumar K et al., Laisupasin et al. [64, 65], and Okekunleet al. [66]. Studied risk factors (cholesterol, BMI, and central obesity) significantly correlated with BC. BMI has a positive significant correlation with BC, and central obesity has a low but positive significant correlation with BC. Moreover, the binary logistic regression model also showed a significant association between biochemical factors and BC occurrence. Regression analysis depicted a linear relationship between a dependent variable (BC occurrence) and independent variables (central obesity, cholesterol, BMI) [67].

Additionally, our research revealed a significant difference in serum lipid levels associated with obesity between BC before and after menopause. This could be because pre- and post-menopausal BC variations in the etiology of plasma lipid metabolism occur [68]. Nonetheless, age- and hormone-related (menopausal) functional impairments in lipid metabolism could provide a reasonable explanation, as suggested by several reviews [69, 70]. A number of detrimental metabolic changes, such as dysregulated lipid metabolism [70] and potentially changes in the production of pancreatic enzymes essential for lipid metabolism [50], have been associated with post-menopausal estrogen insufficiency. For instance, compared to premenopausal women, healthy postmenopausal women have been shown to have lower paraoxonase-1 activity [72]. Paraoxonase-1 is a hydrolytic enzyme with multiple roles in preventing lipid oxidation [71].

5- Conclusion
The study examined the relationship between lipid profile levels and women with BC in pre- and postmenopausal women. Results showed increased levels of TC, TG, LDL-C, and VLDL-C in pre- and postmenopausal women, while HDL-C values decreased compared with control group. The results also showed a difference in the levels of lipid profile between women before and after menopause, as the levels of TC, LDL, and HDL in women before menopause was higher than

after menopause, while the levels of TG and VLDL were the opposite. The study also found differences in lipid profile level based on BMI.

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