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Lipid Disturbances in Breast Cancer Patients during Chemotherapy

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Abstract: Breast cancer is the most common cancer in women. Cardiovascular diseases are common complications after chemotherapy due to the effect of the drug on lipid levels. This study aimed to explore the changes in lipid profiles in patients with breast cancer under chemotherapy. Methods: In this prospective study, 50 patients with breast cancer participated. Three biochemical-lipid hematological tests were performed: total cholesterol (TC), triglycerides (TG), High-Density Lipoprotein (HDL-C), and Low-Density Lipoprotein (LDL-C) before initiation (pre-chemotherapy), at the start (1st follow-up), and at the completion (2nd follow-up) of the first cycle of chemotherapy. Statistical significance was set at $p < 0.05$. Analyses were conducted using SPSS Statistical Software (version 22.0). Results: Mean TC values increased significantly at 2nd follow-up. TG values decreased significantly from 1st to 2nd follow-up. HDL-C was significantly lower at 1st follow-up compared to pre-chemotherapy and 2nd follow-up reaching similar to the initial levels. LDL-C values were significantly higher at 2nd follow-up compared to pre-chemotherapy measurement. Significantly positive correlations of BMI with pre-chemotherapy LDL-C, 1st follow-up TC, 1st follow-up LDL-C, 2nd follow-up TC, and 2nd follow-up LDL-C were found. Conclusions: There is a statistically significant increase in the levels of TC and LDL-C in breast cancer patients during chemotherapy. This study was not registered.

Keywords: breast cancer; chemotherapy; lipids; triglycerides; HDL; LDL; cholesterol

1. Introduction

Breast cancer is the second leading contributor to cancer-related mortality, after lung cancer (23%), accounting for 15% of cancer deaths [1]. An estimated 2.3 million new cases are expected to be diagnosed each year. Lung cancer accounts for 11.8% of all new cases, colorectal cancer accounts for 12.9%, prostate cancer for 11.7%, and gastric cancer for 5.6%. As with other diseases, it is caused by a complex interaction between genetic and environmental factors [2]. Until now, a few rare mutations in genes, such as Breast Cancer 1 and Breast Cancer 2, which significantly increase the risk of the disease, have been discovered, as well as many other much more common genes, each of which individually contributes to an increased risk of developing the disease [3].

Several studies have shown that malignancies and especially their worsening are related to disturbances in the levels of lipids and lipoproteins [4,5]. Metabolic syndrome and accompanying lipid disorders are epidemiologically linked to many neoplasms (hepatocellular carcinoma, colorectal, endometrial, prostate), either due to their effect on hormonal changes, or because they are associated with common determinants (diet or inflammation) [6]. The lipid profile and its disturbances in patients with early-stage cancer are not only related to the disease but also to predisposing risk factors that affect lipids, such as polycystic ovary disease (for endometrial cancer)

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and obesity (for breast cancer) [7]. Researchers emphasize that low cholesterol levels are an important indicator of cancerous conditions but not necessarily a causative factor. Therefore, this finding usually concerns rapidly evolving malignancies, raising the suspicion of pre-existing preclinical malignancy [8]. In prostate malignancies, the results are inconsistent [9] since studies found weak or no correlation between cancer and high blood cholesterol levels [9] while lung cancer patients with lower HDL-C levels had an increased risk of lung cancer development [10]. Regarding the association of breast cancer with the levels of lipids, data are controversial [11]. A recent study [12] found a positive correlation of breast cancer rates with elevated lipid levels while an earlier study [13] showed lower cholesterol levels in breast cancer patients compared to a group of healthy individuals.

It has been reported that chemotherapy induces disturbances in lipid metabolism among breast cancer patients, and increases lipid levels [14]. Doxorubicin decreases ABCA1 gene and apoA1 expression in HepG2 cells, and ABCA1 expression in hepatocytes significantly contributes to HDL-C levels [13]. Taxanes and specifically paclitaxel treatment significantly reduce HDL-C levels and increase hydroperoxide levels compared to breast cancer patients who did not receive chemotherapy [15]. Chemotherapy itself can cause endothelial dysfunction increasing insulin resistance. This leads to a decrease in cytokines, increasing the patients' lipid profile [16]. Triglycerides (TG) are a sensitive measure to explore the impact of adjuvant chemotherapy in patients with breast cancer. High TG levels are linked to an increased risk of cardiovascular complications in patients with breast cancer, making them significant predictors of coronary heart disease [17]. Additionally, it has been observed that patients with breast cancer and high levels of High-Density Lipoprotein-Cholesterol (HDL-C) are more likely to develop coronary heart disease [18].

Another element that should be emphasized at this point is the lipid status in patients with metastases. Breast cancer patients with metastases were found to have lower total cholesterol and Low-Density Lipoprotein-Cholesterol (LDL-C) than non-metastatic breast cancer patients. Hypocholesterolemia in breast cancer patients has been attributed to disease progression since the neoplastic cells consume a significantly greater amount of cholesterol, resulting in lower LDL-C levels [19,20].

An area that has not been investigated, especially in tumors with long survival, is the changes in lipids during chemotherapy. Based on the above, the aim of this study was to explore the status and the changes of serum lipids among patients with breast cancer during chemotherapy.

2. Materials and Methods

This is a prospective study carried out with the participation of women hospitalized in an oncology clinic of a tertiary hospital in Athens.

Fifty women with independent stage of breast cancer with normal values of blood lipids participated in this study. Inclusion criteria were: women aged >18 years with diagnosis of primary breast cancer of any stage who had undergone chemotherapy after total or partial mastectomy. The chemotherapy drugs used in these women were either Doxorubicin-Cyclophosphamide for six cycles every three weeks or Docetaxel for eight cycles every three weeks. Exclusion criteria were: women diagnosed with metastases, history of other cancers, and presence of any cognitive or psychiatric difficulties. Women who had undergone or were currently undergoing any other therapeutic intervention other than chemotherapy (radiotherapy, hormone therapy), were, also, excluded.

When the patients entered the hospital, their age and Body Mass Index (BMI) were recorded. This record was noted because increasing age and body weight are associated with insulin resistance, which in turn affects lipid levels. The study was conducted in three phases: The first phase took place before the initiation of the first cycle of chemotherapy. The second phase took place at the start of the aforementioned treatment and the third phase at the completion of the first cycle of chemotherapy. In all three phases, a blood sample was obtained for biochemical control of lipids. The chemotherapy regimen consisted of six chemotherapy cycles. To perform the biochemical hematological control of lipids, the participants were informed that they must remain fasting and not smoke for 12 hours before the control. The study was conducted from March 2018 until August 2020.

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To conduct the study, licenses were obtained by the Scientific Committee of the Hospital (approval number 31/23.02.2018) Throughout the study, the principles of anonymity, voluntary patient participation, and data confidentiality were respected. Each participant was provided with information regarding the purposes of the study, the voluntary nature of their participation in it as well as their right to discontinue participation and withdraw at any time. The procedures respected the ethical principles of the Declaration of Helsinki.

The quantitative variables were described using mean and standard deviations. The qualitative variables were described in terms of absolute (N) and relative (%) frequencies. ANOVA with repeated measurements was utilized to examine any variations in the measurements over time. To detect type I error caused by multiple comparisons, a significance level ($\mu = 0.05/Kc$) was applied to the analysis based on the Bonferroni correction (K = number of comparisons). The percentages of individuals who had abnormal results in any of the three measurements were compared using the McNemar test. Pearson's correlation coefficient (r) was used to correlate BMI with lipid levels. Statistical significance was set at 0,05, and significance values are two-sided. The statistical analysis of the data was done through the statistical program SPSS 22.0.

3. Results

The mean age of the sample was 60.3 years (±11.4) while the mean value of BMI of women was 29.6 kg/m^2 (±5.4 kg/m^2), 46.0% (n = 23) of the participants were overweight, 38.0% (n = 19) were obese and 16% (n = 8) were of normal weight.

Total Cholesterol (TC) values increased significantly from the first measurement to the 2nd follow-up. Pre-chemotherapy triglycerides (TG) values were similar to the values of the 1st and 2nd follow-ups. However, the 2nd follow-up TG values were statistically significantly lower than the 1st follow-up values.

A statistically significant decrease in HDL-C levels was observed at the 1st follow-up compared to the pre-chemotherapy measurement, while at the 2nd follow-up, it was increased significantly compared to the 1st follow-up, reaching similar baseline levels.

Pre-chemotherapy LDL-C levels were similar to levels at the 1st follow-up. However, the values at the 2nd follow-up were significantly higher compared to baseline values. The changes in participants' lipid values during the three stages are given in the table below (Table 1).

Table 1. The changes in lipid values during the three stages of the study (N = 50).

				P- value		
	Pre-chemotherapy	**1st follow-up**	**2nd follow-up**	**Pre-chemotherapy vs 1st follow-up**	**Pre-chemotherapy vs 2nd follow-up**	**1st follow-up vs 2nd follow-up**
	Mean (SD) [1]	**Mean (SD) [1]**	**Mean (SD) [1]**			
TC (mg/dL)	214.9 (35.6)	218.2 (40.6)	232.2 (51.7)	> 0.999	**0.015**	0.085
TG (mg/dL)	139 (57.1)	151.7 (51.8)	123 (56.1)	0.392	0.368	**0.003**
HDL-C (mg/dL)	57.1 (15.5)	52.7 (14.4)	56.9 (13)	**0.005**	> 0.999	**0.026**
LDL-C (mg/dL)	130.1 (34)	134.8 (41.1)	146.1 (57.1)	0.743	**0.035**	0.127

[1] SD: Standard Deviation.

The percentages of participants with normal and abnormal lipid values during the three stages of the study are given in the table below (Table 2). The percentages of participants with abnormal lipid values were similar throughout the follow-up period.

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Table 2. The percentages of participants with normal and abnormal lipid values during the three stages of the study.

	Values	Pre-chemotherapy N (%)	1st follow-up N (%)	2nd follow-up N (%)	P-Value: Pre-chemotherapy vs 1st follow-up	P-Value: Pre-chemotherapy vs 2nd follow-up	P-Value: 1st follow-up vs 2nd follow-up
TC (mg/dL)	Normal	14 (28.0)	12 (24.0)	11 (22.0)	0.564	0.405	0.796
	Abnormal	36 (72.0)	38 (76.0)	39 (78.0)			
TG (mg/dL)	Normal	35 (70.0)	29 (58.0)	34 (68.0)	0.109	0.796	0.197
	Abnormal	15 (30.0)	21 (42.0)	16 (32.0)			
HDL-C (mg/dL)	Normal	36 (72.0)	35 (70.0)	41 (82.0)	0.705	0.096	0.058
	Abnormal	14 (28.0)	15 (30.0)	9 (18.0)			
LDL-C (mg/dL)	Normal	13 (26.0)	16 (32.0)	11 (22.0)	0.405	0.564	0.225
	Abnormal	37 (74.0)	34 (68.0)	39 (78.0)	0.405	0.564	0.225

3.1. Correlations

Statistically positive correlations were found between BMI Index and pre-chemotherapy LDL-C, 1st follow-up TC, 1st follow-up LDL-C, 2nd follow-up TC, and 2nd follow-up LDL-C. Correlations are shown in Table 3.

Table 3. Correlations between BMI Index and lipids.

		BMI
Pre-chemotherapy TC	r	0.224
	p	0.118
Pre-chemotherapy TG	r	−0.051
	p	0.727
Pre-chemotherapy HDL-C	r	−0.097
	p	0.501
Pre-chemotherapy LDL-C	r	0.294 *
	p	**0.038**
1st follow-up TC	r	0.330 *
	p	**0.019**
1st follow-up TG	r	0.122
	p	0.397
1st follow-up HDL-C	r	−0.219
	p	0.127
1st follow-up LDL-C	r	0.376 **
	p	**0.007**
2nd follow-up TC	r	0.543 **
	p	**<0.001**
2nd follow-up TG	r	0.112
	p	0.438
2nd follow-up HDL-C	r	−0.2
	p	0.165
2nd follow-up LDL-C	r	0.499 **
	p	**<0.001**

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

4. Discussion

The purpose of this prospective study was to look at serum lipids during the first cycle of chemotherapy in breast cancer patients. This study is significant because cancer and especially its progression is related to disturbances in lipid levels [21].

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This study showed that during chemotherapy in women with breast cancer, a significant increase in the levels of TC, LDL-C, and TG disturbance can be noted while HDL-C remained at the same levels at the end of chemotherapy. Several studies [22,23] highlight the importance of monitoring lipid levels during chemotherapy in women with breast cancer.

In the present study, TC values were increased significantly from the baseline to the last chemotherapy of the first regimen. Furthermore, pre-chemotherapy TG values were similar to values at baseline and the last chemotherapy of the first regimen. However, TG values at the last chemotherapy of the first regimen were significantly lower than the values at the start of chemotherapy.

In the current study, HDL-C decreased significantly at the 1st follow-up compared to the pre-chemotherapy measurement, while at the 2nd follow-up, it increased significantly compared to the 1st follow-up of chemotherapy, reaching similar baseline levels. Also, pre-chemotherapy LDL-C levels and 1st follow-up levels were similar. However, the values at the 2nd follow-up were significantly higher compared to the baseline values. These results are in contrast to those of a retrospective study in China among 141 invasive breast cancer patients in which no significant difference was found between TC, TG, and LDL-C before and after chemotherapy [24]. The different results are probably due to the fact that the measurement of the lipid profile in the above study was performed after six cycles of chemotherapy and not immediately after the first chemotherapy. Another retrospective study conducted in China in breast cancer patients undergoing various chemotherapy regimens found significantly increased levels of TG, TC, and LDL-C [25]. Li et al. (2018) [19] also revealed increased post-chemotherapy TG, TC, and LDL-C levels but lower HDL-C levels [22]. In the Study of Xu et al. (2020) [23], cholesterol, LDL-C, and TG levels were found to be significantly elevated at the end of one month after completion of chemotherapy, while 12 months after completion of chemotherapy only TG and LDL-C levels continued to be not at normal levels. The rate of dyslipidemia in breast cancer patients increased from 41.5% at the start of chemotherapy to 54.1% at 12 months after the end of chemotherapy [23]. In contrast, a meta-analysis found no significant difference between total cholesterol and LDL-C levels before and after chemotherapy in breast cancer patients [26]. Qu et al. (2020) [27], also, reported lower levels of TG, TC HDL-C και LDL-C among female patients with breast cancer compared to healthy women. After neoadjuvant chemotherapy, TG and LDL-C levels increased significantly, while HDL-C levels decreased significantly [27]. Changes in the lipid profile induced by chemotherapy may have implications for the patient's response to chemotherapy.

Regarding the correlations between BMI Index and lipids, this study revealed statistically positive correlations of BMI Index with pre-chemotherapy LDL-C, 1st follow-up TC, 1st follow-up LDL-C, 2nd follow-up TC, and 2nd follow-up LDL-C. This positive correlation was also highlighted by Okekunle et al. (2022) [28] in their study among premenopausal women. The correlation between these variables is a less explored area and the mechanism behind this correlation is still unclear. It is hypothesized that obesity may alter drug metabolism and pharmacokinetics, leading to reduced efficacy and increased toxicity of chemotherapy [29,30]. The relationship between BMI, lipids, and chemotherapy outcomes varies depending on the specific chemotherapy regimen used, the stage of breast cancer, and individualized factors related to the patient's clinical characteristics [15].

One of the limitations of this study is the non-stratification of patients into premenopausal and postmenopausal, as the levels of sex hormones affect lipid metabolism. Also, the type of chemotherapy the patients received was not recorded. Additionally, the study sample does not allow generalization of the results.

5. Conclusions

Women with breast cancer had a statistically significant increase in TC and LDL-C levels during the first cycle of chemotherapy while a lipid disorder was also revealed. BMI was positively correlated with TC and LDL-C levels. The above findings reinforce the need to further investigate the lipid profiles of patients with breast cancer in order to mitigate the risk for cardiovascular disease and to ensure the optimal therapeutic outcome of chemotherapy. To facilitate the continuous evaluation of metabolic profiles during the diagnosis and treatment of breast cancer, interdisciplinary

cooperation should be enhanced. Nurses are an integral part of the multidisciplinary team and play a prominent role in cancer screening and diagnosis, monitoring for potential chemotherapy-related disorders such as lipid disorders. Early detection of lipid disorders and quick referrals by nurses to their team members lead to improved therapeutic outcomes in terms of reducing cardiovascular risk and the possibility of metastases. Health education, nutritional counseling stemming from evidence-based nursing and provided by nurses, as well as placing patients in the context of the therapeutic alliance help patients understand the necessity of cooperation in treatment. Therefore, high-quality nursing care favors the improvement of clinical outcomes of chemotherapy.

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