Original Article

Effect Of Chemotherapy On Lipid Profile And Insulin Resistance Among Post Mastectomy Women

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Abstract

Background Breast cancer survival rates have been increased due to earlier detection and better care. Nevertheless, despite its effectiveness, adjuvant chemotherapy may have unintended adverse effects, because some women with breast cancer suffer from long-term metabolic effects. The lipid profiles and insulin resistance in patients of breast cancer may be affected by a different types of therapies. This study designed to estimate the influence of chemotherapy on lipid profile in serum and insulin resistance by homeostasis model assessment (HOMA-IR) among post mastectomy women. **Research design** This study is an interventional study which carried to determine how chemotherapy will affect the lipid profile and insulin resistance. The research involved 116 patients in total. **Results** Our results revealed that there were a statistically significant rise in total cholesterol, triglycerides, LDL, VLDL cholesterol, fasting blood glucose, HOM-IR, and fasting insulin compared to the baseline before chemotherapy, whereas there was a statistically significant decline in high-density lipoprotein cholesterol. **Conclusion** Given that the adjuvant chemotherapy used to treat female breast cancer might result in severe changes in the blood lipid and glycemic profiles, frequent evaluations of these variables are required for follow-up care during management of breast cancer.

Key words Breast cancer; Lipid profile; Chemotherapy; Insulin resistance.

INTRODUCTION

Breast cancer is now the second-leading cause of death globally in women and the most often diagnosed malignant tumors **(Siegel et al., 2019).** Screening and better medical care have improved survival rates. Adjuvant chemotherapy may have undesirable adverse effects despite its effectiveness, since some breast cancer patients suffer negative long-term metabolic effects. **(Buch et al., 2019).**

The survival rate for breast cancer has increased significantly as a result of the considerable improvements in treatment of breast cancer, especially (neo) adjuvant chemotherapy, over the earlier few years. However, cardiovascular diseases have replaced cancer as the primary cause of mortality for breast cancer survivors as a result of the harmful and adverse effects of (neo) adjuvant chemotherapy medications on the circulatory system and the fact that breast cancer and cardiovascular disease share several risk factors **(Hendrick et al., 2019)**.

Chemotherapy is a crucial treatment for people with early-stage breast cancer because it increases overall and disease-free survival. However, chemotherapies have long-term negative effects, such as cardiovascular diseases (CVD). Following chemotherapy, CVD as hypertension, heart failure and myocardial ischemia, have become the most common complications, owing to the direct cardiotoxicity of chemotherapeutic medications as well as the effect on serum lipid profile (**Guan et al., 2019).**

The prognosis of breast cancer survivors may be improved by well management of cardiac risk factors. The widely-used (neo) adjuvant chemotherapy medications Taxane and Anthracycline have been significantly increase the risk of dyslipidemia in patients of breast cancer following chemotherapy. In addition, emerging data indicates that dyslipidemia is detrimental to the survival rate of the patients **(Fichtali et al, 2020).**

Chemotherapy has been linked to altered lipid metabolism, cardiovascular risk, diabetes, and other metabolic abnormalities however underlying mechanism is not obvious. Consequently, regular evaluation of lipid profiles, cardiovascular indicators, and diabetes markers is needed for effective treatment of cancer. In order to reduce complications and improve survival rates, Breast cancer patients need to carry out diabetes and cardiovascular disease screening **(Basnyat, et al., 2016).**

According to recent research, chemotherapy can lead to altered lipid and glucose metabolism in breast cancer women. As a result, the effects of post-operative chemotherapy on blood lipid and glucose metabolism would have an influence on patients with invasive breast cancer. There is emergent data that cytotoxic therapy may produce significant changes in cancer survivors' metabolic state **(De Haas et al., 2010)**. Numerous studies have demonstrated that metabolic markers, including fasting blood glucose, blood pressure, triglycerides, and cholesterol levels, decrease following chemotherapy **(Dieli et al., 2016).**

Subjects and methods

This study is an interventional study which was be conducted to estimate the effect of chemotherapy on lipid profile and insulin resistance by homeostasis model calculation among post mastectomy women attending Clinical Oncology Outpatient Clinic at hospitals of Zagazig University.

Sample size

Assuming that mean ± SD of total cholesterol before chemotherapy (81.64 ± 18.9) versus after chemotherapy (91.8±19.83) based on the study by **Tian et al. (2019**), Sample was calculated to be 116 participants using Open Epi program with test power 80% , CI 95%.

Inclusion criteria

1. Age range from 20 to 60 years.
2. Post mastectomy women before receiving chemotherapy.
3. Stage I to III Breast Cancer
4. Patients who had one of the four usual chemotherapy protocols described below: epirubicin and cyclophosphamid followed by paclitaxel (EC-T); doxorubicin and cyclophosphamid followed by paclitaxel (AC-T), fluorouracil, cyclophosphamide, and epirubicin (FEC) or cyclophosphamide and paclitaxel (TC).

Exclusion criteria

1. Suffering from any chronic metabolic disorders e.g. DM, taking lipid lowering drugs.
2. Breast cancer women with additional malignancies
3. Patients who within the previous 12 months underwent chemotherapy.
4. Patients who did not finish the prescribed chemotherapy protocols.
5. Patients with inconsistent information.

Data Collection

The data were collected by the following

1) Anthropometric measurements comprising body mass index, waist-hip ratio and waist boundary
2) Metabolic parameters
   a) ***Detection of insulin resistance*** by homeostasis model assessment (HOMA-IR): (it is determined by multiplying the ratio of fasting plasma insulin to fasting plasma glucose and dividing the result by constant 22.5).

b) ***Lipid profile,*** baseline estimation before starting chemotherapy therapy and second estimation after completion of chemotherapy regimens. Comparing measurements before and after chemotherapy.

Operational design

Prior to beginning the real field study, a pilot study was conducted on 10% of the post-mastectomy women being examined to verify the study tools are clear, applicable, and feasible and that any required adjustments will be made. It also assisted in estimating the duration of the process of collecting data and identifying the study's challenges.

Anthropometric measurements include measurements of body weight, height, waist (WC), and hip circumference (HC). Body mass index (BMI) is calculated by dividing the body weight by the square of the height (kg/m2). These findings were interpreted in accordance with the global categorization suggested by the World Health Organization **(WHO, 2020).**

Plasma lipid measurements

On an empty stomach, blood samples were taken in the morning within a week of the start of the first chemotherapy cycle and within two weeks of the ending of the last chemotherapy cycle. The biochemical indicators of dyslipidemia, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDLC), and high density lipoprotein (HDL-C) were classified using the following cut-off values: TC 5.2 mmol/L, TG 1.7 mmol/L, LDL-C 3.1 mmol/L and HDL-C 1.0 mmol/L. The term "dyslipidemia" refers to fasting serum TG>1.7 mmol/L or TC>5.2 mmol/L or HDL-C<1.0 mmol/L or LDL-C>3.1 mmol/L **(Jacobson et al., 2014)**.

TC and TG levels were measured using enzymatic techniques, while HDL-C and LDL-C levels were determined using homogeneous enzyme colorimetry techniques.

Insulin resistance measurements

Before chemotherapy, in the morning after the patients had fasted for at least 8 hours, blood samples were obtained to assess fasting insulin levels and fasting blood glucose. Fasting insulin levels were measured using a radioimmunoassay technique, while fasting blood glucose levels were measured using a spectrophotometric technique. Normal values for fasting blood glucose were accepted as 70-100 mg/dL **(Danaei et al., 2011),** normal values for fasting insulin levels were 4-25 µIU/mL **(Manley et al.,2007)**, With the model: Fasting glucose (nmol/L) x fasting insulin (μ/L)/22.5, the HOMA-IR score was computed using fasting insulin levels and fasting blood glucose. The diagnosis of insulin resistance was achieved with a HOMA-IR score >2.6 **(Ascaso et al., 2003).**

Statistical analysis

The statistical package for social science (SPSS) version 20 analyses the collected data using the proper statistical techniques. To summarize the data, means and standard deviation were used. In order to compare categorical data, the chi square test was used. To compare matched pairings, an independent sample t test was applied. If a probability's P-value is 0.05 or below, it is deemed significant.

Results

Our results revealed that the studied women's ages varied from 27 to 60, with a mean of 46.89 years. 53.4% of patients from urban areas compared to 46.6% from rural areas. 72.4 % of patients are married and 76.7 % of them were unemployed, 64.7% of patients with middle socio-economic status as presented in Table (1).

Table (1) Demographic statistics of the patients (n=116)

Variables	**Mean ± SD**	**Range**
Age (year)	46.89 ± 8.37	27 – 60
	N=116 (%)	
Residence:		
Rural	54 (46.6%)	

Urban	62 (53.4%)
Education:	
Illiterate	17 (14.7%)
Literate	3 (2.6%)
Primary	8 (6.9%)
Prep	15 (12.9%)
Secondary	43 (37.1%)
University	26 (22.4%)
Postgraduate	4 (3.4%)
Marital status	
Single	14 (12.1%)
Married	84 (72.4%)
Divorced	8 (6.9%)
widow	10 (8.6%)
Job:	
Unemployed	89 (76.7%)
Employed	27 (23.3%)
socio-economic status: Low	35 (30.1%)
Middle	75 (64.7%)
High	6 (5.2%)

Regarding pathological type, most of patients were invasive ductal carcinoma (83.6 %), (81%) of them with modified radical mastectomy, (69%) of them with negative family history compared to (31%) with positive family history mainly first degree (56.7%) as depicted in Table (2).

Table (2) Disease-specific data of studied patients (n=116)

Variables	**N=116 (%)**
Pathology:	
IDC	97 (83.6%)
ILC	19 (16.4%)
Stage:	
I	46 (39.7%)
II	46 (39.7%)
III	24 (20.6%)
Surgery:	
Simple/total	22 (19%)
Modified	94 (81%)
Date of mastectomy	
One month	58 (50%)
Two months	36 (31%)
Three months	22 (19%)

Family history:	
Negative	86 (69%)
Positive	30(31%)
Family degree:	N=30
First	17 (56.7%)
Second	11 (36.7%)
Third	2 (6.6%)

IDC: invasive ductal carcinoma   ILC: invasive lobular carcinoma

As shown in Table (3), Body mass index was varied from 19 to 34 (kg/m^2) with a mean of 25.46 (kg/m^2). Hip circumference ranged from 96 to 129 cm with mean 109.95 cm. Waist circumference ranged from 70.3 to 102.5 cm with mean 84.36 cm. waist/hip ratio ranged from 0.7 to 0.92 with mean 0.77

Table (3) Anthropometric data of studied patients (n=116)

	Mean ± SD	**Range**
Body mass index(kg/m^2)	25.46 ± 3.96	19 – 34
Waist circumference (cm)	84.36 ± 9.17	70.3 – 102.5
Hip circumference	109.95 ± 8.38	96 – 129
Waist/hip ratio	0.76 ± 0.03	0.7 – 0.92

Our results revealed that there was a statistically significant elevation in total cholesterol, triglycerides, VLDL , LDL, cholesterol and significant decline in HDL cholesterol as depicted in Table (4).

Table (4) Lipid profile before and after chemotherapy

	Before chemotherapy	**After chemotherapy**	**t**	**p**
	Mean ± SD	**Mean ± SD**		
Total cholesterol	147.14 ± 22.58	184.5 ± 42.08	-11.835	<0.001**
Triglycerides	100.72 ± 18.61	146.09 ± 49.04	-11.979	<0.001**
HDL	45.68 ± 6.04	44.01 ± 5.67	7.303	<0.001**
LDL	90.81 ± 15.32	106.87 ± 28.64	-8.284	<0.001**
VLDL	27.31 ± 4.29	33.96 ± 6.6	-16.425	<0.001**

Table (5) Risk ratio before and after chemotherapy

	Before chemotherapy	**After chemotherapy**	**t**	**p**
	Mean ± SD	**Mean ± SD**		
Risk ratio 1*	3.27 ± 0.68	4.22 ± 1.08	-11.835	<0.001**
Risk ratio 2*	2.01 ± 0.38	2.47 ± 0.75	-11.979	<0.001**

Risk ratio 1* (cholesterol / HDL)   Risk ratio 2* (LDL / HDL)

Table (6) Glycemic profile before and after chemotherapy

	Before chemotherapy	After chemotherapy	t	p
	Mean ± SD	**Mean ± SD**		
FBG	84.93 ± 10.04	89.52 ± 13.67	-3.073	0.003*
	Median (IQR)	**Median (IQR)**	**Z**	**p**
HOMA-IR	1.6 (1.1 – 1.98)	2.33 (1.8 – 3.68)	-8.763	<0.001**
Fasting insulin	8.58(5.5 – 11.8)	12.15(8.56 – 17)	-8.068	<0.001**

IQR interquartile range Z Wilcoxon signed rank test

Discussion

Although the survival rates of breast cancer patients has been increased in the recent years, it was revealed that some of them eventually died due to problems not related to cancer. Recent statistics demonstrate that among early cancer survivors, the percentage of non-cancer related mortality has progressively increased and exceed cancer related mortality **(Fu et al., 2017)**. Cardiovascular diseases, not the tumour itself, are the main cause of death of breast cancer females **(Rasmussen-Torvik et al., 2013).**

Concerning serum lipid profile, dyslipidemia is the main and prominent risk factor for atherosclerotic cardiovascular disease (ASCVD) **(Rodrigues Dos Santos et al., 2014).** Adjuvant chemotherapy increases overall survival and disease-free in addition to increasing cardiac toxicity and lead to CVD, particularly in long-lived survivors **(Gernaat et al., 2017)**. It's important to remember that previous studies showed that serum lipid levels of breast cancer women might elevated following chemotherapy. Nonetheless, only limited studies have examined the adverse effects of various chemotherapy protocols on blood lipids **(Bicakli et al., 2016).**

In the current study, there was a statistically significant increase (p <0.001) in total cholesterol (184.5 ± 42.08 after chemotherapy), Triglycerides (146.09 ± 49.04 after chemotherapy), LDL (106.87 ± 28.64 after chemotherapy), VLDL cholesterol (33.96 ± 6.6 after chemotherapy) and significant decrease in HDL cholesterol (44.01 ± 5.67 after chemotherapy) in patients who received chemotherapy. Additionally, there was statistically significant increase (p <0.001) in risk ratio 1 (cholesterol / HDL) and risk ratio 2 (LDL / HDL) afterward chemotherapy**.** Chemotherapy may directly induce endothelial dysfunction and insulin resistance, which then results in cytokine changes, this is the probable reason for the elevated lipid profiles **(Finkelman et al., 2017).** *Li and his colleagues* carried out a retrospective study to evaluate the levels of lipoproteins and lipids before and after chemotherapy, and revealed significantly higher TC, TG, and LDL-C levels in patients after chemotherapy than before chemotherapy, while the HDL-C level showed the opposite results **(Li et al., 2018)**.

Dieli et al. (2016) revealed that whereas HDL-cholesterol reduced following chemotherapy for patients of breast cancer, TG, TC, and LDL-C dramatically elevated. Earlier research had found that patients receiving anthracycline medication for a prolonged period displayed a severe preclinical vasculopathy, defined by increased arterial stiffness and endothelial dysfunction resulting in a cardiovascular failure **(Finkelman et al., 2017).** Another possible explanation for the increase in serum lipids following chemotherapy is a potential increase in systemic oxidative stress caused by various chemotherapy protocols which in turn causes lipid peroxidation and damage to the liver, a crucial organ that controls lipid metabolism **(Chung et al., 2017)**.

Our results were consistent with the results of **Sharma et al. (2016); Tian et al. (2019); He et al. (2020)** and **Dong et al. (2022)**. Therefore, we advise rigorous cholesterol control for breast cancer patients receiving chemotherapy in order to avoid atherosclerotic disease.

Important components of metabolic syndrome include insulin resistance, hyperinsulinemia, or increased blood glucose levels, all of which can be induced by chemotherapy. The cause of this is assumed to the direct effect of different chemotherapeutic drugs on insulin sensitivity. For anthracyclines, alkylators, epipodophyllotoxins, camp-tothecins, and platinum-based treatments this might be due to increased production of reactive oxygen species (ROS) and mitochondrial dysfunction **(Rosen et al., 2013).** Only a limited number of research have examined how insulin resistance and chemotherapy interact using measuring techniques like the HOMA-IR score. The objective of this study was to evaluate how breast cancer patients' insulin resistance was affected by adjuvant chemotherapy.

In the current study, there was statistically significant increase in fasting blood glucose (p <0.003), HOM-IR {2.33 (1.8 – 3.68)} (p <0.001) and fasting insulin (p <0.001) after sixth months of chemotherapy**.** The most probable explanations appear to be a combination of exhaustion, altered appetite, physical inactivity, and sarcopenic obesity, which negatively affects insulin and glucose metabolism in particular **(Buch et al., 2019)**. Alterations in glucose metabolism may also be depend on the rise in circulating lipids. Various alternative mechanisms exist, such as a decreased basal metabolic rate and alterations in the circadian rhythm following chemotherapy **(Berger et al., 2012).**

Our results were in the same line with some researchers who revealed that chemotherapy-treated patients had elevated HOMA-IR, although these alterations tended to revert to baseline within 12 months **(Fredslund et al., 2019 and Dieli-Conwright et al., 2016).** Another study with 128 breast cancer patients who had no previous history of diabetes mellitus demonstrated that chemotherapy treatment resulted in B-cell malfunction and insulin resistance **(Lu et al., 2014).**

Godinho-Mota et al. (2021) with in the same line with our results who showed that the physical function, body composition, insulin resistance, and lipid markers were all negatively affected by chemotherapy. **Makari-Judson et al., (2022)** demonstrated that chemotherapy patients suffer from severe short-term metabolic deficits that are indicative of insulin resistance. Although the acute insulin resistance seems to lessen over time, the long-term effects are yet unknown. Recent study included 28 participants diagnosed with breast carcinoma, in the breast cancer group compared to the control group, fasting blood insulin and HOMA-IR values were statistically substantially higher (p 0.05). Only three individuals in the control group met the HOMA-IR criteria for insulin resistance **(Doruk & Kaya, 2022).**

Our results are inconsistent with **Doğan & Yüksel (2022)** study that showed a statistically insignificant rise in fasting blood glucose levels during and after the chemotherapy protocol, which is assumed to be due to the steroid impact. Nevertheless, the HOMA-IR score's declined. These reductions can be explained by the impact of chemotherapy on the insulin pathway or by paying more attention to nutrition condition. Also, **Chala et al., (2006)** observed a considerable drop in insulin levels at two hours during an oral glucose tolerance test as compared to before adjuvant chemotherapy.

Conclusion

We concluded that the adjuvant chemotherapy used to treat female breast cancer might result in severe changes in blood lipid and glycemic profiles, frequent evaluations of these variables are required for follow-up care during breast therapeutic interventions.

Ethics approval

The necessary official permissions were obtained: Approval from the ethical committee in faculty of Medicine, Zagazig University.

Declaration of Competing Interest

The authors declare no known competing interests.

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