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## Chemotherapy and Dyslipidemia (Doxorubicin and Cyclophosphamide Regimen versus Taxane) in Iraqi Women with Breast Cancer: A Comparative Study

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### ABSTRACT

Lipids are a major component of the cell membrane, essential for the growth and division of both the normal and malignant cell. This study aimed to study the effect of different chemotherapy regimens in the induction of dyslipidemia in Iraqi women with breast cancer. This cross-sectional study was conducted at the Department of Biochemistry, Medical College, University of Baghdad and at the Oncology Hospital, Medical City Hospital, Baghdad, Iraq, during the period from May 2018 to October 2018. It involved 56 regularly menstruated women (25-45 years) categorized into: group 1 [G1] included 29 women with primary breast carcinoma, group 2 [G2] consisted of the same 29 women of G1 but after finishing the first course of treatment [4 cycles of anthracycline chemotherapy], and group 3 [G3] which involved 27 women who completed full regimen of chemotherapy treatment [course 1 and 4 cycles of taxanes; the course 2]. Serum cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and TG were measured using colorimetric methods. The mean ( $\pm$  SEM) of serum cholesterol was significantly increased in G1 ( $p < 0.05$ ) and G2 ( $p < 0.01$ ) compared to G3. Also, the mean values of serum LDL-C were significantly elevated in G2 than G1 and G3 ( $p < 0.05$ ). Serum TG level showed no significant differences among the three groups. While that of serum HDL-C levels was significantly decreased in G3 compared to G1 ( $p < 0.05$ ), this study showed that breast cancer chemotherapy-associated dyslipidemia is transient, and anthracycline course has a significant effect than Taxane one.



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### INTRODUCTION

Carcinoma of the breast is a widely common neoplasm among women around the industrialized world. It was increased steadily over the past 40 years. It is considered the second cause of mortality among women aged between 20-59 (Jemal *et al.*, 2003). In Iraq, it is the first in ranking among cancers (Arkan *et al.*, 2016). The cause of the disease is unknown, but it could be hormonal, environmental, genetic, radiation, oncogenic viruses and dietary factors (Owiredu *et al.*, 2009). Many factors affect the relation of lipid changes with breast cancer, and this relationship is still a subject of controversy. Lipids are the major component of membranes of biological cells, integrity of cell

growth and development; both normal and malignant ones. Lipids are richly present in the mammary tissue. Some studies had found that changes in plasma lipids and lipoproteins are associated with the proliferation of malignant cells in the breast tissue. Recently, they had studied the role of both the endogenous and dietary lipids in the etiology and prognosis of cancer (Seema, 2015). The unbalanced lipid parameters including raised total cholesterol [TCh], low-density lipoprotein-cholesterol (LDL-C) and triglycerides [TG] along with decreased high-density lipoprotein-cholesterol [HDL-C] could be a risk factor of cardiovascular diseases (Xin *et al.*, 2018).

### Subjects and Methods

This cross-sectional study was conducted at the Department of Biochemistry, Medical College, University of Baghdad and at the Oncology Hospital, Medical City Hospital, Baghdad, Iraq, during the period from May 2018 to October 2018. It involved 56 Iraqi women diagnosed by Consultant Clinical Oncologist to have had primary carcinoma of the breast; their ages range was 25-45 years. The included women were categorized into groups according to their status of treatment: group 1 [G1] included 29 women with primary breast carcinoma who never subjected to chemotherapy treatment, group 2 [G2] consisted of the same 29 women of G1 but after finishing the first course of treatment [4 cycles of anthracycline chemotherapy including Doxorubicin 60mg/m<sup>2</sup> and Cyclophosphamide 600mg/m<sup>2</sup> chemotherapy], and group 3 [G3] which involved different 27 women who completed full regimen of chemotherapy treatment [(course 1) and 4 cycles of Taxane including (Docetaxel) 100mg/m<sup>2</sup>; (course 2)]. Exclusion criteria included pregnant woman, chronic diseases (diabetes mellitus, hypertension), alcoholics, smokers, and women used anti-inflammatory drugs. Formal consent was taken from each woman. Authors obtained ethical approval from the Scientific Committee of the Department of Biochemistry, Medical College, University of Baghdad, Iraq. Serum cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and TG were measured using colorimetric methods. Five millilitres of the blood sample was collected by venipuncture of the peripheral vein from each included woman, transferred into the plain tube, allow to clot and the serum was separated immediately by centrifugation at 2500–3000 rpm for a period of 10 min. Investigations included serum measurements of cholesterol, HDL, LDL and TG by colourimetric methods. All material kits for the measured parameters were provided from Human GmbH.65205 Wiesbaden, Germany. The statistical analysis, including ANOVA and Student's t-tests, were applied to test for significant differences among the studied

groups with respect to lipid parameters. Correlation among different studied parameters in each studied group was investigated by linear regression test [r], and the significance of the r-value was examined by related t-test. P-values of less than 0.05 were considered significant.

### RESULTS

**Table 1: Mean ( $\pm$ SEM) Values of Age and Body Mass Index (BMI) in G1 and G3**

Parameters	G1 (n=29)	G3 (n=27)
Age <sup>NS</sup> (years)	38.79 $\pm$ 0.91	39.59 $\pm$ 0.95
BMI <sup>NS</sup> (kg/m <sup>2</sup> )	30.04 $\pm$ 0.94	31.78 $\pm$ 1.24

BMI: body mass index; ANOVA test revealed a non-significant difference between groups (NS)

The demographic data in Table 1 depicts that there was no significant difference in mean values of age between G1 (38.79  $\pm$  0.91 years) and G3 (39.59  $\pm$  0.95 years). Similarly, mean values of BMI were comparable and did not differ significantly between G1 (30.04  $\pm$  0.94 Kg·m<sup>2</sup>) and G3 (31.78  $\pm$  1.24 Kg·m<sup>2</sup>).

Table 2 reveals the mean values of the serum measured lipid parameters. Serum levels of cholesterol were found to be increased in women who finished the first course of chemotherapy treatment [G2; 208.37  $\pm$  8.62 mg/dl] when compared to their levels before treatment [G1; 193.75  $\pm$  6.83 mg/dl] but did not reach the significant level. However, the level of serum cholesterol was then significantly declined in women who had complete finish courses of treatment [G3; 168.30  $\pm$  8.14 mg/dl] when compared to that of G1 [P < 0.05] and G2 [p < 0.01]. Similarly, serum LDL-C was significantly elevated in G2 [125.89  $\pm$  8.88 mg/dl] in comparison with each of G1 [104.24  $\pm$  7.17 mg/dl, p<0.05] and G3 [91.02  $\pm$  7.64 mg/dl, p<0.05]. Regarding serum HDL-C level, it was decreased in post-treatment groups compared to that before treatment, but with an only significant difference between G3 and G1 [p < 0.05]. Serum TG level showed no significant differences among all groups.

The present study showed that women of G1 exhibited a significant direct relationship between serum levels of cholesterol and LDL-C in G1 (r=0.95, p<0.01). Also, serum levels of TG and HDL-C showed a significant inverse correlation (r=-0.394, p< 0.05). Furthermore, a significant negative correlation was observed between serum LDL-C and serum HDL-C (r=-0.44, p<0.05) in G1. With respect to G2, there was a significant inverse relationship between age values and serum HDL-C levels (r= -0.376, p< 0.05) with a significant positive relationship between serum levels of cholesterol and LDL-C (r= 0.912, p<0.01). Regarding G3; there was a significant direct relationship between BMI

**Table 2: Values of Serum Cholesterol, HDL-C, LDL-C and TG in G1, G2 and G3**

Parameter	G1 (n=29)	G2 (n=29)	G3 (n=27)
Cholesterol mg/dl	193.75 ± 6.83 <sup>•</sup>	208.37 ± 8.62 <sup>•</sup>	168.30 ± 8.14
LDL-C mg/dl	104.24 ± 7.17	125.89 ± 8.88 <sup>••</sup>	91.02 ± 7.64
HDL-C mg/dl	58.60 ± 2.34	52.94 ± 3.71	47.61 ± 1.47 <sup>•••</sup>
TG mg/dl <sup>NS</sup>	154.37 ± 7.80	147.68 ± 7.16	148.33 ± 9.55

LDL: low-density lipoprotein-cholesterol, HDL: high-density lipoprotein-cholesterol, TG: triglycerides. Data are expressed as mean (±SEM). ANOVA and t-test revealed <sup>•</sup> significant increase of total cholesterol in G1 [p < 0.05] and G2 [p < 0.01] than in G3, <sup>••</sup> significant increase of LDL-C in G2 than in G1 [p < 0.05] and G3 [P < 0.05], <sup>•••</sup> significant decrease of HDL-C in G3 compared to G1 [p < 0.05], NS: non-significant differences.

and serum TG (r= 0.437, p<0.05) and between serum levels of cholesterol and LDL-C (r=0.964, p<0.01).

## DISCUSSION

Iso *et al.* (2009) reported that malignancy was associated with decreased plasma cholesterol levels, and certain types of cancer had a significant effect. The enhanced utilization of cholesterol by carcinoma tissues was the culprit in reducing plasma cholesterol (Iso *et al.*, 2009). One of the important causes in the development of breast cancer is increased exposure to estrogen hormone which plays a vital role in the metabolism of cholesterol and may reflect the association of breast cancer and increased HDL-C (Llaverias *et al.*, 2011). Although adjuvant chemotherapy may improve the survival of breast cancer patients, they had suggested that chemotherapy cause significant changes in the metabolism of lipids in cancer survivors (De Haas *et al.*, 2010).

Alexopoulos *et al.* (1992); found that breast cancer patients undergoing chemotherapy had a non-significant decrease in both total serum cholesterol and serum LDL. Serum HDL did not show any significance, while serum TG showed a significant increase. They had attributed these results to the low number of patients involved in the study, and they had indicated that these lipid disorders could be reversed with the effective treatment of the tumor (Alexopoulos *et al.*, 1992).

Rzymowska *et al.* (1999) studied 70 women with breast cancer and observed that both types of carrier cholesterol, HDL and LDL levels were declined after treatment of chemotherapy accompanied by significant elevation of triglycerides in women with malignant breast irrespective of being menstruated or menopause. They had stated that the mechanisms interpreting chemotherapy-associated dyslipidemia could be related to the type of therapy used (Rzymowska *et al.*, 1999).

Alacacioglu *et al.* (2010) had observed that breast cancer patients treated with a taxane, epirubicin and cyclophosphamide showed no significant changes in blood cholesterol, HDL, LDL and TG at

baseline and after six cycles of the treatment (Alacacioglu *et al.*, 2010). In a study done by Simin *et al.* (2016) who found that patients treated with adriamycin, cyclophosphamide and taxane showed no significant changes in the serum lipid profile although slight changes were recorded in each item (Simin *et al.*, 2016).

Xin *et al.* (2018) reported certain metabolic abnormalities during adjuvant chemotherapy treatment of women with breast cancer including hypercholesterolemia, hypertriglyceridemia; elevated LDL-C and Apo B along with a decrease in HDL-C and Apo A1. They suggested that carcinoma of the breast is accompanied by overt dyslipidemia, which worsens after chemotherapy (Xin *et al.*, 2018). These differences in the results may be due to the progression of cancer and side effects of the chemotherapeutic agents in addition to genetic, environmental and behavioral differences (Peela *et al.*, 2010).

The decrease in LDL-C in carcinoma could be attributed to increased uptake of cholesterol by these cells, with consequent elevation in LDL removal through the enhancement of LDL receptor activity. These derangements in lipid metabolism and parameters may be due to release of pro-inflammatory cytokines from the inflammatory cells which could be part of an acute-phase reactant against tumor or which may be itself participate in tumor development and also from the tumor itself (Xin *et al.*, 2018). The significant decrease in the serum HDL in this study was in agreement with that observed by Monika *et al.* (2016) who concluded that lipid changes that happened with chemotherapy are specific to the chemotherapeutic type used. Doxorubicin lowered HDL-C while paclitaxel increased apoB. In opposite, cyclophosphamide appears to have no significant effect on HDL or apoB metabolism (Monika *et al.*, 2016). Some hypotheses indicate that chemotherapy may cause dysfunction of the endothelial cells, which leads to cytokine alterations, and hence, lipids abnormalities (Vehmanen *et al.*, 2004; JA *et al.*, 2006). Other stated that adipocytes associated with cancer

would modify the phenotype of the cancer cells (Dirat *et al.*, 2011).

Owiredu *et al.* (2009); had observed that there was a significant positive correlation between the BMI and both serum total cholesterol and LDL- cholesterol, which is more susceptible to lipid peroxidation. They had attributed this to the oxidative stress leading to an increase in cell proliferation of the malignant cells. Also, they had noticed that there was a significant negative correlation between age and serum HDL. All these results were in concordance with the results of the present study (Owiredu *et al.*, 2009).

## CONCLUSION

Iraqi women with breast cancer had mildly increased in LDL-C, which exacerbated during chemotherapy treatment and resolved then after finishing the complete courses of treatment. These women showed a gradual decrease of HDL-C after treatment, even its value still within the expected level.

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