Evaluation of Serum Lipid Profile after Different Chemotherapeutic Regimens in Iraqi Patients with Breast Cancer

Zainab Nazar Hasan Anber

Lecturer (Ph.D. Clinical Biochemistry), Department of Therapeutics and Clinical pharmacy, Baghdad College of Medical Sciences, Baghdad, Iraq

Abstract

Objective: To investigate the effect of doxorubicin, cyclophosphamide and taxane chemotherapy on the lipid profile in Iraqi patients with breast cancer.

Method: This cohort prospective study was carried out at the Biochemistry Department, Baghdad College of Medical Sciences, and at the Oncology Clinic, Oncology Teaching Hospital, Baghdad, Iraq, during the period from May 2019 to October 2019. It included 56 women with regular menstrual cycle (25-45 years) classified into 3 groups: GI: 29 women with primary breast cancer (before starting chemotherapy), GII: the same 29 women of GI who were finished 4 cycles of anthracycline chemotherapy (course 1) and GIII: which involved another 27 women who had finished both courses of chemotherapy, (course 1) and 4 cycles of taxanes (course 2). Serum cholesterol, LDL, HDL and TG were measured using colorimetric method.

Results: The results of the present study showed that the (mean±SEM) of the serum cholesterol was decreased significantly ($p<0.05$) in GIII compared to GI and highly significantly ($p<0.01$) compared to GII. While, the serum HDL level was significantly ($p<0.05$) lower in GIII compared to GI. Concerning the serum LDL level, it was increased significantly ($p<0.05$) in GII compared to both GI and GIII. While; the serum TG level shows no significant difference between all groups.

Conclusion: Iraqi women with breast cancer had an abnormal state of dyslipidemia that become worsened after chemotherapy.

Keywords: *Breast cancer, chemotherapy, cholesterol, HDL, LDL, TG.*

Introduction

Carcinoma of 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 ages between 20-59[(1)]. In Iraq, it is the first in ranking among cancers[(2)]. The cause of the disease is unknown but it could be hormonal, environmental, genetic, radiation, oncogenic viruses and dietary factors[(3)]. 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 integrity in the biological cells, it plays roles in cell growth and development; both for normal and malignant ones. Lipids are richly present in the mammary tissue. Some studies had found that changes of 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[(4)]. The

Corresponding Author:
Dr. Zainab N.H. Anber
PhD. Clinical Biochemistry, University of Baghdad,
Lecturer at Baghdad College of Medical Sciences.
Baghdad-Iraq
e-mail: zainab.anber@yahoo.com

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[5].

Subjects and Method

This cross sectional study was conducted at the Department of Biochemistry, Baghdad College of Medical sciences and at the Oncology Hospital, Medical City Hospital, Baghdad, Iraq, during the period from May 2019 to October 2019. It involved 56 Iraqi women diagnosed by Consultant Clinical Oncologist to have had primary carcinoma of 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^2 and Cyclophosphamide 600mg/m^2 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^2; (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 of Baghdad College of Medical sciences. Serum cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and TG were measured using colorimetric method. Five milliliters of blood sample was collected by venipuncture of the peripheral vein from each included woman, transferred into 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 colorimetric method. 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 significance 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

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

Table 1: Mean (±SEM) Values of Age and Body Mass Index (BMI) in G1 and G3

Parameters	G1 (n=29)	G3 (n=27)
Age^{NS} (Years)	38.79±0.91	39.59±0.95
BMI^{NS} (kg/m2)	30.04±0.94	31.78±1.24

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

Table 2 reveals the mean values of the serum measured lipid parameters. It shows that the serum levels of cholesterol was found to be increased in women who finished the first course of chemotherapy treatment [G2; 208.37±8.62 mg/dl] when compared to their levels before treatment [G1; 193.75±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 finished complete courses of treatment [G3; 168.30±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±8.88 mg/dl] in comparison with each of G1 [104.24±7.17 mg/dl, $p<0.05$] and G3 [91.02±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 only significant difference between G3 and G1 [$p < 0.05$]. Serum TG level showed no significant differences among all groups.

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•	208.37±8.62•	168.30±8.14
LDL-C mg/dl	104.24±7.17	125.89±8.88••	91.02±7.64
HDL-C mg/dl	58.60±2.34	52.94±3.71	47.61±1.47•••
TG mg/dl NS	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 • significant increase of total cholesterol in G1 [p < 0.05] and G2 [p <0.01] than in G3, ••significant increase of LDL-C in G2 than in G1 [p<0.05] and G3 [P<0.05], •••significant decrease of HDL-C in G3 compared to G1 [p < 0.05], NS: non- significant differences.

The present study showed that women of G1 exhibited 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 significant inverse correlation (r= -0.394, p< 0.05). Furthermore 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 significant positive relationship between serum levels of cholesterol and LDL-C (r= 0.912, p<0.01). Regarding G3; there were a significant direct relationship between BMI 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 decrease plasma cholesterol levels, and certain types of cancer had a significant effect. The enhanced utilization of cholesterol by carcinoma tissues was culprit in reducing plasma cholesterol [(6)]. One of the important causes in development of breast cancer is increased exposure to estrogen hormone which plays a vital role in metabolism of cholesterol and may reflect the association of breast cancer and increased HDL-C [(7)]. 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 [(8)].

Alexopoulos et al. (1992); found that breast cancer patients undergoing chemotherapy had a non- significant decrease in both serum total 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[(9)].

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 menopaused. They had stated that the mechanisms interpreting the chemotherapy associated dyslipidemia could be related to the type of therapy used[(10)].

Other previous studies reported that HDL-C levels were significantly reduced after chemotherapy and they had found that doxorubicin downregulates the expression PPARγ (peroxisomal proliferator-activated receptor γ), liver X receptor α (LXRα), and ATP binding cassette transporter A1 (ABCA1). While, cyclophosphamide or paclitaxel did not affect the ABCA1 level[(11,12)]

Recent studies reported that taxane-containing chemotherapy has been proven to induce dyslipidemia, which reduces the plasma HDL-C level and increases the plasma hydroperoxide level[(13,14)].

Alacacioglu et al. (2010) had observed that breast cancer patients treated with taxane, epirubicin and cyclophosphamide showed no significant changes in blood cholesterol, HDL, LDL and TG at baseline and after six cycles of the treatment[(15).]

Another study examined the metabolic changes in breast cancer patients who received chemotherapy and they had shown significant increases in TC, TG and LDL-C levels[(16)].

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 [17].

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 decrease in HDL-C and Apo A1. They suggested that carcinoma of breast is accompanied by overt dyslipidemia which worsen after chemotherapy [5]. These differences in the results may be due to progression of cancer and side effects of the chemotherapeutic agents in addition to genetic, environmental and behavioral differences [18].

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 derangement 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 [5] . 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 [19]. Some hypotheses indicate that chemotherapy may cause dysfunction of the endothelial cells which leads to cytokine alterations, and hence lipids abnormalities[20,21]. Other stated that adipocytes associated with cancer will modify the phenotype of the cancer cells [22].

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 [3].

On the other hand; Delgobo et al 2019 found that Chemotherapy appeared to exert a greater effect on younger breast cancer patients and that lipid metabolism is associated with sex hormones [23].

They had explained that changes in lipid levels after chemotherapy correlate with changes in menstruation. they had concluded that plasma lipid levels are more sensitive to chemotherapy agents since young patients have higher levels of sex hormones and a better lipid metabolism status[20] .

Conclusion

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

Ethical Clearance: Authors obtained ethical approval from the Scientific Committee of the Department of Biochemistry of Baghdad College of Medical sciences.

Source of Funding: Authors had no source of funding (self).

Conflict of Interest: Nil.

References

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ: cancer statistics 2003.CA Cancer J Clin . 2003; 53: 5-26.
2. Arkan O J .Breast cancer in Western Iraq: Clinicopathological single institution study. Advances in breast cancer research.2016; 5: 83-89.
3. Owiredu WK, Donkar S, Addai BW, Amidu N. Serum lipid profile of breast cancer patients. Pak J Biol Sci. 2009; 12: 332-8.
4. Seema M. lipid profile in breast cancer. International journal of pharmaceutical and medical research.2015; 3:1.
5. Xin L, Zi-Li L, Yu-tuan W, He W, Wei D, Bilal A, Zhou X, Hao L, Kai-nan W and Ling-quan K. Status of lipid and lipoproteins in female breast cancer patients at initial diagnosis and during chemotherapy. Lipids in health and disease. 2018; 17:91.
6. Iso H., Ikeda A., Inoue M., Sato S., Tsugane S. Serum cholesterol levels in relation to the incidence

of cancer: the JPHC study cohorts. Int J Cancer. 2009; 125:2679–86.

7. Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, Sotgia F, Lisanti MP, Frank PG. Role of cholesterol in the development and progression of breast cancer. Am J Pathol. 2011; 178(1):402-12.
8. De Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT, Gietema JA. The metabolic syndrome in cancer survivors. Lancet Oncol. 2010; 11:193–203.
9. Alexopoulos CG, Pournaras S, Vaslamatzis M, Avgerinos A, Raptis S. Changes in serum lipids and lipoproteins in cancer patients during chemotherapy. Cancer Chemother Pharmacol. 1992; 30(5):412-16.
10. Rzymowska J. Effect of cytotoxic chemotherapy on serum lipid levels in breast cancer patients. Pathobiology. 1999; 67(3):129-32.
11. Sharma M, Tuaine J, McLaren B, Waters DL, Black K, Jones LM, et al. Chemotherapy Agents Alter Plasma Lipids in Breast Cancer Patients and Show Differential Effects on Lipid Metabolism Genes in Liver Cells. PloS one. 2016;11(1):
12. Basso F, Freeman L, Knapper CL, Remaley A, Stonik J, Neufeld EB, et al. Role of the hepatic ABCA1 transporter in modulating intrahepatic cholesterol and plasma HDL cholesterol concentrations. Journal of lipid research. 2003;44(2):296–302
13. Yeo W, Mo FKF, Pang E, Suen JJS, Koh J, Loong HHF, et al. Profiles of lipids, blood pressure and weight changes among premenopausal Chinese breast cancer patients after adjuvant chemotherapy. BMC women's health. 2017;17(1):55.
14. Panis C, Binato R, Correa S, Victorino VJ, Dias-Alves V, Herrera A, et al. Short infusion of paclitaxel imbalances plasmatic lipid metabolism and correlates with cardiac markers of acute damage in patients with breast cancer. Cancer chemotherapy and pharmacology. 2017;80(3):469-78.
15. Alacacioglu A., Kebapcilar L., Sari I., Gokgoz Z., Tarhan O., Somali I., Yuksel A., Bozkaya G., Sop G.. Taxane-based adjuvant chemotherapy reduces endothelin-1 and symmetric di- methylarginine levels in patients with breast cancer. Journal of BUON.2010; 15: 572-76.
16. Arpino G, De Angelis C, Buono G, Colao A, Giuliano M, Malgieri S, et al. Metabolic and anthropometric changes in early breast cancer patients receiving adjuvant therapy. Breast cancer research and treatment. 2015;154(1):127–32.
17. Simin H., Mansour S. D. and Minu J. Does Adriamycine, Cytoxan with Taxol Treatment Affect FBS and Lipid Profile in Breast Cancer Patients? Archives of Medicine. 2016; 8(5): 1-8.
18. Peela JR, Jarari AM, El Saiety SO, El Busaifi S, El Awamy H. The relationship between serum Lipids and Breast cancer in Libya. Clin Chem. 2010; 56 (Supl-6).
19. Monika S., Jo T., Blair M., Debra LW., Katherine B., Lynnette M J., Sally PA. Chemotherapy Agents Alter Plasma Lipids in Breast Cancer Patients and Show Differential Effects on Lipid Metabolism Genes in Liver Cells. PLOS One .2016; 11(1):
20. Vehmanen L, Saarto T, Blomqvist C, Taskinen MR, Elomaa I. Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids. Br J Cancer.2004; 91(3): 476–81.
21. JA K. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation.2006; 113(15): 1888–1904.
22. Dirat B, Bochet L, Dabek M, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res.2011; 71(7): 2455–65.
23. Delgobo M, Agnes JP, Goncalves RM, Dos Santos VW, Parisotto EB, Zamoner A, et al. N-acetylcysteine and alpha-lipoic acid improve antioxidant defenses and decrease oxidative stress, inflammation and serum lipid levels in ovariectomized rats via estrogen-independent mechanisms. The Journal of nutritional biochemistry. 2019;67:190–200.
24. De Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT, Gietema JA. The metabolic syndrome in cancer survivors. Lancet Oncol. 2010; 11: 193–203.