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ORIGINAL ARTICLE

Comparative Effects of Tamoxifen and Anastrozole on Lipid Profile and Liver Enzymes in Patients with Breast Cancer

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ABSTRACT

Background: Breast cancer has emerged as one of the most common malignancies diagnosed among women worldwide. Hormone therapy with Tamoxifen or aromatase inhibitors is an essential part of the treatment for estrogen-receptor-positive breast cancer patients. This study evaluated the effect of Tamoxifen and anastrozole on the plasma lipid profile and liver enzymes.

Methods: A total of 93 pre- and postmenopausal breast cancer patients were divided into two groups: tamoxifen and anastrozole. All patients had undergone surgery and were randomized to receive tamoxifen 20 mg once daily (n=50) or anastrozole 1 mg once daily (n=43). Lipids and liver enzymes were measured at baseline and after six months of follow-up.

Results: Total cholesterol (TC) and low-density lipoprotein (LDL) levels significantly decreased in patients treated with tamoxifen at 6 months, while anastrozole caused a significant increase in TC and LDL. Moreover, TC and LDL levels were significantly decreased in pre-and postmenopausal patients of the tamoxifen group. High-density lipoprotein (HDL) levels increased significantly in premenopausal patients who received tamoxifen compared to postmenopausal patients. Tamoxifen group was associated with a significant elevation in both aspartate transaminase (AST) and alanine transaminase (ALT) levels compared to anastrozole group.

Conclusion: Tamoxifen treatment has a favorable effect on lipid profiles in both pre-and postmenopausal women compared to anastrozole. However, tamoxifen is associated with an increase in liver function tests.

Key words: Breast Cancer; Tamoxifen; Anastrozole.

INTRODUCTION

Breast cancer has emerged as one of the most common malignancies diagnosed among females worldwide. It represents 25% of all types of cancer. There were about 1.6 million new cases per year in the world [1].

In the United States, breast cancer accounts for nearly one in three cancers [2]. The incidence rate of breast cancer in developing countries (883,000 cases) slightly surpasses that in more developed countries (794,000 cases) [3]. Studies in Iraq indicate that one-third of female cancers are breast cancer, which causes one-quarter of female deaths from the disease [4].

Estrogen plays a significant role in the development and progression of hormone-sensitive breast cancer. The action of estrogen on breast cancer and other target sites throughout the body is mediated by estrogen receptors (ER) [5]. Treatment of breast cancer involves surgery, radiotherapy, chemotherapy, and hormonal therapy, depending on the stage and estrogen receptor status of the disease in the individual patient [6].

Hormonal therapy is a critical part of adjuvant endocrine therapy. The two most commonly used hormonal treatments in women with hormone-receptor-positive breast cancer are either the interference with estrogen signaling by a selective estrogen-receptor modulator, such as tamoxifen, or the inhibition of production of the endogenous estrogen by an aromatase inhibitor (AI) [7].

Tamoxifen has been classified as an anti-estrogenic agent, but subsequent experience has shown that it has agonistic activity on bone, liver, and endometrium, so it's now classified as a selective estrogen receptor modulator [8]. This agent has been a gold standard adjuvant treatment for many years after surgery for women with early breast cancer in pre-and postmenopausal women. However, the development of selective aromatase inhibitors provides an alternative hormonal treatment for postmenopausal breast cancer patients [9].

The oral aromatase inhibitor anastrozole, has shown to be more effective than tamoxifen in producing responses in all stages of breast cancer. Anastrozole works by lowering circulating plasma estrogen and intertumoral estrogen levels by inhibiting the aromatase enzyme which is responsible for the synthesis of estrogen from androgenic substrates [9].

In the Arimidex, Tamoxifen alone or Combination (ATAC) trial, anastrozole was associated with a favorable effect in terms of risk-benefit profile compared to tamoxifen in postmenopausal women [10]. Estrogen has been reported to have a favorable effect on lipid metabolism. Reduced estrogen levels following menopause have been found to cause an increase in the rate of hyperlipidemia and risks of hypo-estrogenic diseases like myocardial infarction and stroke [11]. Moreover, estrogen deprivation following treatment for breast cancer, particularly in the adjuvant setting or when used in the prevention of the disease, can affect lipid profile and the development of cardiovascular disease, especially considering the 5-year duration of the treatment period.

Despite evidence supporting the efficacy and safety of adjuvant endocrine therapy in breast cancer treatment, several studies have reported that tamoxifen increases the risk of developing fatty liver disease [12]. Potential adverse effects may reduce compliance when taking endocrine therapy, so such issues should be investigated.

This study aims to evaluate and compare the long-term effect of tamoxifen and anastrozole on serum lipid parameters and liver enzymes in women with breast cancer.

MATERIAL AND METHODS

A prospective study, conducted from November 2017 to November 2018, took place at the Oncology Department in Rizgary and Nanakaly hospitals, Erbil. 93 pre- and postmenopausal breast cancer patients (ages 29 to 66) participated in the study.

The choice of hormone therapy was based on physicians' decisions considering clinical data such as menopausal status, age, side effects, and tolerance. All patients were subjected to a detailed history. Inclusion criteria included:

- Histologically confirmed estrogen receptor-positive breast cancer patients.
- No evidence of recurrence or metastatic diseases.
- No history of any concomitant disease that could affect the lipid profile.
- No reports of cholesterol-lowering agent consumption.
- No history of alcohol consumption.

Adjuvant chemotherapy was administered as per specialist discretion. Tamoxifen and anastrozole, given 4 weeks post-chemotherapy, were prescribed based on the hormone status of breast cancer. Tamoxifen was dosed at 20 mg orally per day, and anastrozole at 1 mg daily, with patients monitored for six months.

Five milliliters of venous blood were collected from fasting patients, clotted at room temperature, centrifuged at 3,000 rpm for 15 min, and analyzed.

The serum lipid profile and liver enzymes were assessed in early-stage breast cancer patients starting tamoxifen or anas-

trozole therapy. Out of 97 participants, 93 completed the study, with 50 on tamoxifen and 43 on anastrozole over six months. Measurements were taken at baseline and after six months for TC, TG, HDL, LDL, AST, and ALT. Tests were conducted using the Reflaton Auto analyzer with commercial kits from Reflaton, Germany.

We analyzed patients who properly began the protocol treatment, assessing if tamoxifen and anastrozole differently impacted serum lipids and liver enzymes.

SPSS (version 18) was used for statistical analysis. Descriptive statistics (mean, standard deviation, ranges, percentages) characterized study participants. A paired t-test compared mean differences at baseline and after 6 months of tamoxifen and anastrozole treatment. The chi-square test assessed percentage changes. Results were statistically significant with P-values ≤ 0.05.

RESULTS

Ninety three breast cancer patients were enrolled in the study, with four excluded due to missed follow-up as shown in Figure 1. The mean age was 48.34 ± 9.5 years. Fifty patients (53.2%) received tamoxifen (Tamoxifen group) for six months, and forty-three (46.8%) received anastrozole (Anastrozole group) for six months. Baseline characteristics are in Table 1.

Means and standard deviations for the effect of tamoxifen and anastrozole on plasma lipid parameters, measured at the start of treatment and after 6 months, are presented in Table 2.

In the tamoxifen group, there was a significant decrease in total cholesterol levels (191.2 ± 40.7 vs. 179.3 ± 39.6, $P<0.001$) and LDL levels (141.3 ± 39.8 vs. 120.48 ± 33.9, $P<0.001$) after six months of treatment. TG levels did not differ significantly between baseline and the follow-up period (135.26 ± 43.4 vs. 138.7 ± 51.1, $P=0.111$). A slight increase in HDL levels from baseline was noted; however, this increase was statistically non-significant (39.6 ± 9.1 vs. 41.3 ± 11.8, $P=0.059$). In the anastrozole group, there was a small but significant rise in total cholesterol (202.8 ± 47.6 vs. 205.5 ± 49, $P=0.044$) and LDL-C levels (125.91 ± 24.8 vs. 127.1 ± 27.1, $P=0.040$) after six months of treatment. No significant change was observed in TG levels (166.51 ± 66.9 vs. 167.1 ± 63.2, $P=0.712$) and HDL-C levels (32.1 ± 9.9 vs. 33 ± 10.1, $P=0.221$) throughout the study period.

In the tamoxifen group, both premenopausal and postmenopausal patients showed significant reductions in TC (184.9 ± 40.4 vs. 174.85 ± 39.1, $P<0.001$; 215.7 ± 37.9 vs. 198.38 ± 40, $P<0.001$) and LDL (132.4 ± 37.3 vs. 114.24 ± 35.1, $P<0.001$; 169.77 ± 38.7 vs. 139.7 ± 26.7, $P<0.001$). HDL levels significantly increased in premenopausal patients (40.2 ± 9.2 vs. 43 ± 11.1, $P=0.042$) but showed a small, insignificant decrease in postmenopausal patients (34.7 ± 7.1 vs. 33.2 ± 10.4, $P=0.431$). TG levels increased in both groups, more so in the postmenopausal group, yet these changes were statistically insignificant (139.4 ± 50.4 vs. 141.6 ± 58.3, $P=0.323$; 133 ± 34.7 vs. 136.8 ± 33.7, $P=0.442$).

The liver enzymes were elevated in both groups after six months of tamoxifen and anastrozole treatment, as illustrated in Table 2.

Tamoxifen significantly increased AST and ALT levels at follow-up compared to baseline, AST (24.90 ± 16.24 vs 20.90 ± 7.3, $P=0.032$) and ALT (24.82 ± 15.68 vs 21.22 ± 9.927, $P=0.012$). Anastrozole also increased AST and ALT levels at follow-up, AST (25.47 ± 15.8 vs 23.32 ± 10.9, $P=0.063$) and ALT (23.49 ± 18.7 vs 22.6 ± 14.49, $P=0.434$), but the rise was not significant. The increase was notably higher in the tamoxifen group as shown in Table 2.

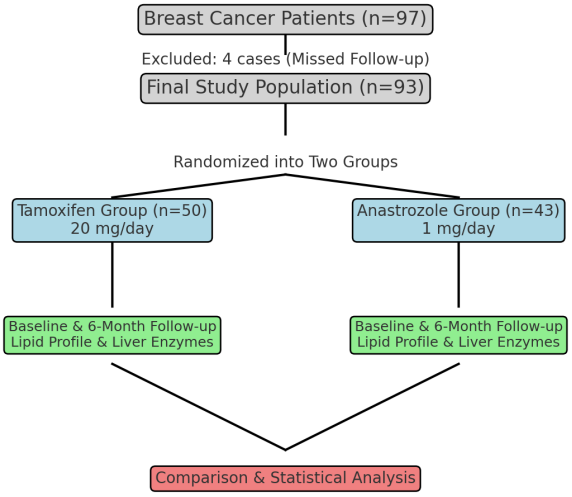

Figure 1. Study design flowchart illustrating patient selection, randomization, follow-up, and statistical analysis.

Table 1. Baseline characteristics of the study participants

Baseline Characteristics	Overall (n=93)	Tamoxifen (n=50)	Anastrozole (n=43)
Age (years)			
Mean	48	42	56
Range	(29 – 76)	(29-55)	(48-76)
BMI			
Mean	28.01	27.54	29
Range	(20 – 36)	(22-36)	(20-36)
Menstrual Status			
Pre-menopausal	33 (35.5%)	33 (66%)	-
Post-menopausal	56 (60.2%)	13 (26%)	43 (100%)
Peri-menopausal	4 (4.3%)	4 (8%)	-
Stage			
I	18 (19.6%)	9 (18%)	9 (21.4%)
II	15 (16.3%)	5 (10%)	10 (23.8%)
III	36 (39.1%)	26 (52%)	10 (23.8%)
IV	13 (14.1%)	5 (10%)	8 (19%)
Unknown	10 (10.9%)	5 (10%)	5 (11.9%)
Stage IV Metastasis			
Liver	8 (16.7%)	3 (6%)	5 (11.6%)
Bone	6 (12.5%)	-	6 (14%)
Liver and Bone	2 (4.2%)	2 (2.1%)	-
T Stage			
T1	8 (8.7%)	2 (4%)	6 (14.3%)
T2	70 (76.1%)	41 (82%)	29 (67.4%)
T3	9 (9.8%)	6 (12%)	3 (7%)
T4	-	-	-
Unknown	5 (5.4%)	1 (2%)	4 (9.3%)
Nodal Status			
0	19 (20.4%)	7 (14%)	12 (27.9%)
1-3	21 (22.6%)	10 (20%)	11 (25.6%)
4-7	15 (16.1%)	6 (12%)	9 (20.9%)
>8	36 (38.7%)	26 (52%)	10 (23.3%)
X	2 (2.2%)	1 (2%)	1 (2.3%)
Metastasis			
0	70 (75.3%)	40 (80%)	30 (69.8%)
1	17 (18.3%)	5 (10%)	12 (27.9%)
Unknown	6 (6.5%)	5 (10%)	1 (2.3%)
Type of Breast Cancer			
Invasive Ductal	82 (89.1%)	47 (94%)	35 (83.3%)
Invasive Lobular	6 (6.4%)	3 (6%)	3 (7.1%)
Medullary	2 (2.1%)	-	2 (4.8%)
Mucinous	2 (2.1%)	-	2 (4.8%)
Others	1 (1.1%)	-	-
Grade			
I	16 (17.2%)	8 (16%)	8 (18.6%)
II	60 (64.5%)	30 (60%)	30 (69.8%)
III	17 (18.3%)	12 (24%)	5 (11.6%)
Hormonal Status			
ER+ PR+ HER2-	60 (64.5%)	35 (70%)	25 (58.1%)
ER+ PR- HER2-	21 (22.6%)	10 (20%)	11 (25.6%)
ER+ PR+/- HER2+	12 (12.9%)	5 (10%)	7 (16.3%)
History of Surgery			
Yes	93 (100%)	50 (100%)	43 (100%)
No	-	-	-
Type of Surgery			
Mastectomy	87 (93.5%)	47 (94%)	40 (93%)
Quadrantectomy	3 (3.2%)	1 (2%)	2 (4.7%)
Lumpectomy	3 (3.2%)	2 (4%)	1 (2.3%)
History of Liver Disease			
Yes	4 (4.3%)	-	4 (9.3%)
No	89 (94.7%)	50 (100%)	39 (90.7%)
History of Hypertension			
Yes	23 (24.7%)	8 (16%)	15 (34.9%)
No	70 (75.3%)	42 (84%)	28 (65.1%)
History of Diabetes Mellitus			
Yes	7 (7.5%)	4 (8%)	3 (7%)
No	86 (92.5%)	46 (92%)	40 (93%)
History of Osteoporosis			
Yes	12 (12.8%)	1 (2%)	10 (23.3%)
No	81 (86.2%)	49 (98%)	33 (76.7%)

Table 2. Effect of Tamoxifen and Anastrozole on Lipid Profile and Liver Function Tests in Women with Breast Cancer

Laboratory Tests	Tamoxifen		*P* value*	Anastrozole		*P* value*
	0 week	24 weeks		0 week	24 weeks	
Lipid Profile (mg/dl)						
TC	191.2 ± 40.7	179.3 ± 39.6	**< 0.001**	202.8 ± 47.6	205.5 ± 49	**0.044**
LDL	141.3 ± 39.8	120.48 ± 33.9	**< 0.001**	125.91 ± 24.8	127.1 ± 27.1	**0.040**
HDL	39.6 ± 9.1	41.3 ± 11.8	0.059	32.1 ± 9.9	33 ± 10.1	0.221
TG	135.26 ± 43.4	138.7 ± 51.1	0.111	166.51 ± 66.9	167.1 ± 63.2	0.712
Lipid Profile in Premenopausal and Postmenopausal Women (mg/dl) - Tamoxifen Group						
Laboratory Tests	**Premenopausal (n = 33)**		***P* value***	**Postmenopausal (n = 13)**		***P* value***
	0 week	**24 weeks**		**0 week**	**24 weeks**	
TC	184.9 ± 40.4	174.85 ± 39.1	**< 0.001**	215.7 ± 37.9	198.38 ± 40	**< 0.001**
LDL	132.4 ± 37.3	114.24 ± 35.1	**< 0.001**	169.77 ± 38.7	139.7 ± 26.7	**< 0.001**
HDL	40.2 ± 9.2	43 ± 11.1	**0.042**	34.7 ± 7.1	33.2 ± 10.4	0.431
TG	139.4 ± 50.4	141.6 ± 58.3	0.323	133 ± 34.7	136.8 ± 33.7	0.442
Liver Function Tests (IU/L)						
Laboratory Tests	**Tamoxifen**		***P* value***	**Anastrozole**		***P* value***
	0 week	**24 weeks**		**0 week**	**24 weeks**	
AST	20.9 ± 7.3	24.9 ± 16.24	**0.032**	23.32 ± 10.9	25.47 ± 15.8	0.063
ALT	21.22 ± 9.92	24.82 ± 15.68	**0.012**	22.6 ± 14.49	23.49 ± 18.7	0.434

TC = Total cholesterol; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TG = Triglycerides; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase. *Two-sample *t*-test.

DISCUSSION

Breast cancer is one of the most common cancers affecting women worldwide. Early detection and treatment are crucial for improving patient outcomes and survival rates. Adjuvant therapy which is used for the treatment of early-stage breast cancer is preferred to be administrated over several years. Prolonged use of adjuvant treatment is preferable to ensure disease-free survival and overall survival. So, the advantages of these treatments should be weighed against possible long-term adverse effects. Development of side effects may be associated with a decrease in drug adherence [13].

The effect of changes in serum lipid levels on the development of cardiovascular disease has been reported in several epidemiological studies. Cholesterol and triglyceride concentrations are commonly used as an alternate indicator for long-term cardiovascular risk, therefore drugs that affect lipid profiles may increase the risk of developing cardiovascular disease. Studies showed that lipid-lowering medications could not protect women from changes in lipid profile that resulted from other drugs [14]. According to studies, a 10 mg/dl increase in LDL increases the risk of cardiovascular disease by 12%, while a 1mg/dl increase in HDL-C decreases the risk of coronary heart disease by 2-3% [15, 16].

Tamoxifen and anastrozole are both used as adjuvant therapy for breast cancer treatment; however, they possess different chemical structures and mechanisms of action. Tamoxifen acts as a selective receptor modulator with partial estrogenic activity. Estrogen has been shown to enhance LDL receptor upregulation, resulting in increased LDL particle clearance. This effect may explain why tamoxifen reduces total cholesterol and LDL levels in the current study involving both premenopausal and postmenopausal women. Three previous studies have demonstrated a reduction in total cholesterol and LDL levels induced by tamoxifen treatment, consistent with the findings of the present study [11, 17, 18].

In a conflicting report, a neutral effect of tamoxifen in both TC and LDL was observed in premenopausal patients [19]. Inclusion and exclusion of patients with or without vascular disease is likely to contribute to the differences in the results. In contrast, anastrozole showed a significant increase in total cholesterol and LDL levels, which was consistent with a previous study that evaluated 38 postmenopausal breast cancer patients [20]. This result may be related to the mode of action of anastrozole, which act by inhibition of estrogen synthesis. Moreover, a fall in the estrogen concentration, particularly in the postmenopausal period, is responsible for the elevation of LDL and TC levels [11].

However, our findings regarding the effect of anastrozole on

TC and LDL levels differ from those of the Sawada et al. study, which failed to demonstrate any change in these parameters after 12 weeks of treatment [11]. This discrepancy may be related to the longer follow-up period in the present study compared to the other study.

Tamoxifen causes a small insignificant increase in TG levels, which was higher in the postmenopausal patients compared to the premenopausal patients. This effect may also be related to the partial estrogenic activity of tamoxifen which induces hypertriglyceridemia through increasing triglyceride synthesis [21]. A significant increase in TG level by 22% was observed in a previous study [11]. Differences in study design may contribute to the variety seen in tamoxifen-induced changes on the TG level.

The beneficial estrogenic effect of tamoxifen on HDL levels was more obvious in the premenopausal compared to the postmenopausal patients. An increase in HDL level in this study may be correlated with the ability of tamoxifen, like estrogen, to increase the liver apolipoprotein A-I (apo A-I) production rate, with the same rate of apo A-I clearance. Hepatic apolipoprotein A-I is the major protein component of HDL and it is essential for HDL synthesis which is mediated by the membrane signal transduction pathway [22]. Another study reported an increase in HDL levels in both pre-and postmenopausal patients treated with tamoxifen [22]. However, the other two studies showed a neutral effect of tamoxifen on HDL level [11, 23]. Again, this variety may be related to the differences in the study design.

In the anastrozole group, a numerical non-significant increase in TG level has been reported. Additionally, no change in HDL level was observed during the study period. However, our findings on TG and HDL levels are contrary to the findings of a Chinese trial, which reported a significant decrease in TG level with an increase in HDL level that is explained by the effect of anastrozole on enhancing lipase enzyme activity. This disparity may be related to the extended follow-up period in the Chinese trial [24]. In the present study, liver function test after 6 months of treatment was higher with tamoxifen and anastrozole groups compared to baseline. These results are consistent with the results of Pan et al. which reported elevated AST and ALT levels at follow-up time compared to baseline [25].

CONCLUSION

Tamoxifen improves lipid profiles in both pre-and postmenopausal women compared to anastrozole by lowering TC and LDL levels over six months, while anastrozole increases them. Tamoxifen also affects liver function tests, whereas anastrozole does not cause significant changes. The study highlights the importance of baseline lipid and metabolic profiling for personalized treatment and reducing liver-related complications. Future long-term studies are needed to assess the tolerability of these drugs.

ETHICAL DECLARATIONS

- **Ethics Approval and Consent to Participate**

  The study was approved by the Ethical Committee of Howler Medical University, College of Medicine, Department of Pharmacology. All patients gave informed signed consent after receiving an explanation of the study's nature and purpose.

- **Consent for Publication**

  Non.

- **Availability of Data and Material**

  The datasets are available from the corresponding author upon reasonable request.

- **Competing Interests**

  The authors declare that there is no conflict of interest.

- **Funding**

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- **Authors' Contributions**

  All authors contributed significantly, directly, and intellectually to the work and consented to its publication.

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