Comparison between Letrozole and Tamoxifen Effects on the Lipid Profile in Women treated For Breast Cancer

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ABSTRACT

INTRODUCTION: Breast cancer is a heterogeneous and hormonally mediated disease and therapies that change hormonal levels are essential components to the treatment strategy. Tamoxifen has tissue- specific antagonist or agonist effects on oestrogen receptor, which is responsible for a promising effect on lipid metabolism in women. In postmenopausal oestrogen is synthesized in peripheral tissues by the enzyme complex aromatase. Inhibitors of aromatase suppress concentrations of oestrogen and thus several changes in parameters of lipid metabolism have been noted.

OBJECTIVE: This study compared the effect of tamoxifen on the serum lipid profile to that of letrozole.

METHODS: A prospective observation cohort study was conducted at Oncology Teaching Hospital, Medical City Directorate. Starting from October 2015 to October 2016. Sixty-six patients with breast cancer on hormonal therapy with tamoxifen or letrozole were included in this study. Data regarding the demographic and laboratory characteristics of the patients were reported. Patients were followed up for about three months by measuring total cholesterol (TC), triglyceride (TG), and high density lipoprotein (HDL) – cholesterol in both groups and the results are compared between them.

RESULTS: At the end of third month of hormonal therapy, tamoxifen showed a significant decrease in TG, TC, low density lipoprotein (LDL) and very low density lipoprotein (VLDL), (p=0.002,0.016,0.041, and 0.002) respectively. On the other side, letrozole showed significant increase over three months duration in TC and LDL, (p = 0.009 and 0.006) respectively.

CONCLUSION: Use of tamoxifen in post-menopausal breast cancer patients has a better effect on lipid profiles in comparison to letrozole after three months of use.

Key words: Breast cancer, Tamoxifen, Letrozole, Lipid profile, Menopause.

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INTRODUCTION

Breast cancer is a heterogeneous disease composed of several biologic subtypes that have dissimilar behaviour and response to therapy.[1] Hormone receptor-positive like oestrogen receptor (ER) and/or progesterone receptor (PR), breast cancers cover the common types of breast cancer; it represents 75 % of all cancer and regress on endocrine therapy (Tamoxifen or Letrozole). This hormonal therapy aims to diminish the exposure of breast cancer cells to oestrogen, either by inhibiting its synthesis or its receptor-mediated activity.[2]

Tamoxifen is a selective oestrogen receptor modulator (SERM), which works by blocking oestrogen from binding to the oestrogen receptor. It does not change oestrogen production.[3] Tamoxifen has both oestrogenic and anti-oestrogenic actions, depending on the objective tissue. It acts strongly as anti-oestrogenic on mammary epithelium; therefore, it is used in the management of breast cancer, and as pro-oestrogenic on uterine epithelium and increased incident of endometrial carcinoma.[4] Like definite oestrogens, tamoxifen lowers total serum cholesterol, low-density-lipoprotein cholesterol, and potentially reduces the risk of myocardial infarction.[5]

Letrozole is an aromatase inhibitors (AIs)

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that inhibits the formation of estradiol, a female hormone, by interfering with an aromatase enzyme.[6] These agents are highly selective for the aromatase enzyme and should only be used in post-menopausal women. If used in the premenopausal setting, initial streams of oestrogen occur due to the body's compensation mechanisms (hypothalamic-pituitary axis). Aromatase inhibitors do not possess the oestrogen-agonistic effects of tamoxifen, due to the high levels of oestrogen deprivation caused by AIs.[7]

A large population- created study conducted by Hernandez et al[8] has shown that there were no relations between tamoxifen and the incidence of atherosclerotic events. These outcomes are essential in risk/ benefit analyses as tamoxifen therapy in postmenopausal women is being replaced with aromatase inhibitors. On the other hand, Esteva and Hortobagyi[9] informed that tamoxifen has an overall favourable influence on lipid profiles. However, long-term data from tamoxifen clinical trials is unsuccessful to disclose a cardio-protective effect and patients treated with tamoxifen did not experience less cardiovascular events compared with those receiving a placebo.[9] Endocrine therapy represented a revolutionary advance in the treatment of breast cancer.[10]

Breast cancer is the leading cause of cancer among the Iraqi female population in general; accounting for 19.5% of all newly diagnosed malignancies and 34% of the registered female cancers, with an incidence resembling 22 per 100,000 female population.[11] Five years of tamoxifen decrease the annual recurrence rate by 41% and breast cancer mortality by 34%.[12] Recently, large randomized clinical trials with aromatase inhibitors (AIs) have demonstrated the superiority of AIs over tamoxifen in terms of disease-free survival as adjuvant treatment of postmenopausal patients with early breast cancer.[13]

Most of the reports concerning the effects of endocrine therapy on lipid profile originate from outside Iraq and there is lack of data concerning these effects in Iraq and the data whatsoever obtainable is controversial. Accordingly, in view of these contrary and varying reports it becomes even more important to estimate the effect of endocrine therapy on lipid profile in patients of breast cancer. Moreover, knowing its relationship with cardiovascular risk factors will lead to better clinical understanding.

This study aims to compare the effect of tamoxifen to that of letrozole on the serum lipid profile in woman treated for hormonal positive breast cancer.

METHODS

Settings and study design: A Prospective, observation cohort study, was conducted at Oncology Teaching Hospital, Medical City Directorate in Baghdad from October 2015 to October 2016. Sixty-six patients with hormonal positive breast cancer that diagnosed by histopathological biopsy enrolled in this study and divided into two groups (A and B) each has 33 participants.

Ethical consideration: The local ethical Committee of the Medical City Directorate has approved the study. In addition, all patients signed an informed consent form before participating in the study.

Definition of the cases, inclusion and exclusion criteria: Patients at any age who were diagnosed as breast cancer with positive hormonal receptors, oestrogen and/or progesterone, and were on adjuvant hormonal therapy with tamoxifen or letrozole continuously over the 3 month period of the study were included in this study. Patients with metastasis, using cholesterol reduction formula, having diabetes mellitus, thyroid dysfunction, hepatic or renal impairment, being smokers, pregnant, or having hypertension and treated with antihypertensive drugs that may effect lipid profile like Beta -blocker and thiazide were excluded from this study.

Outcomes: Total cholesterol, Triglyceride, and high density lipoprotein (HDL)–cholesterol were measured. While, low density lipoprotein (LDL)-cholesterol and very low density lipoprotein (VLDL)-cholesterol were calculated according to the following formulas:

VLDL = TG/ 5[14]

LDL = Total cholesterol – (HDL + VLDL)[14]

A blood sample was withdrawn initially to measure total cholesterol, triglyceride, HDL, LDL, and VLDL. Another sample of blood were withdrawn after three months of continuous use of the same type and dose of hormonal therapy. A similar measurements were done.

Sample collection and procedure: Blood samples were drawn from a peripheral vein after an overnight (at least 12 hours) fast under identical conditions from the study patients. The samples were transferred immediately to the laboratory, centrifuged (1,600 × g, 10 minutes, 16 °C) and the serum was separated and analysed immediately or frozen at –20 °C until analysis. All the measurements (Total cholesterol, Triglyceride, HDL – cholesterol) relative to an individual patient were made at the same laboratory (Bagdad Teaching Hospital Laboratory) by using a chemistry autoanalyzer (Hitachi 7600–110; Tokyo, Japan) with the same commercial kit. Repeated measurement of identical markers was obtained at 3 months intervals during the study period.

Patients were divided into two groups; group A, included postmenopausal patients who were prescribed tamoxifen in a dose of 20 mg once daily for 3 months. Group B has included postmenopausal patients who were prescribed letrozole in a dose of 2.5 mg once daily for 3 months. Group A and B included 33 participants in each group.

The normal range of serum TG level is defined as less than 150 mg/dl, Total cholesterol less than 200 mg/dl and HDL – cholesterol between (40-60) mg/dl

Statistical analysis: Each patient was assigned a serial identification number. The data were analysed using Statistical Package for Social Sciences (SPSS) version 23. Continuous data were represented by median and interquartile range (IQR). Categorical data presented as frequency and percentage tables. Wilcoxon and mann whitney U tests were used to compare values between study groups. Mean and standard deviation are not used because data were not normaly distributed. The level of significance was set at P<0.05.

Table 1: Baseline characteristics of studied groups

Variable			(%)
Family History		Yes	(23.6)
		No	(76.4)
Marital-Status:	Married	Yes	(89.6)
	Single	No	(10.4)
Parity		Yes	(84.9)
		No	(15.1)
Site of Cancer		Right	(44.3)
		Left	(55.7)
Stage		I	(5.7)
		IIa	(4.7)
		IIb	(70.8)
		IIIa	(15.1)
		IIIb	(3.8)
Type of Surgery		Lumpectomy	(18.9)
		Mastectomy	(76.4)
Medication		Tamoxifen	(50)
		Letrozole	(50)

RESULTS

Overall, 82 patients were initially included in the study, only 66 were included in analysis, the remaining 16 patients were excluded from the study for different reasons, women were excluded due to loss of follow up (n =9), use of lipid-altering medications (n = 6), and one patient passed away during study. The descriptive characteristics are shown in table 1.

Group A, included postmenopausal patients who were prescribed tamoxifen showed a statistically significant decrease in TG, TC, LDL and VLDL over time from baseline, (p= 0.002, 0.016, 0.041 and 0.002) respectively, as shown in table 2. Group B has included postmenopausal patients who were prescribed letrozole showed a statistically significant increase in TC and LDL,

Table 2 : Influence of adjuvant tamoxifen on the serum lipid profiles of post-menopausal breast cancer patients.

Parameters (Lipids)	Median (IQR)		p-value [a]
	Base Line	After three month	
TG (mg/d)	157.25 (121-202)	140(86-171)	0.002*
TC (mg/d)	204.35(180-236)	193(164-221)	0.016*
HDL (mg/d)	44(36-50)	47(36-52)	0.242
LDL (mg/d)	127.30(108-157)	127(91-146)	0.041*
VLDL (mg/d)	31.45(24-40)	28(17-34)	0.002*

a: p value was calculated by using Wilcoxon test, *: Statistical Significance when p value is < 0.05 level
IQR, interquartile range .TG, triglyceride ; TC, total cholesterol ; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL , very low density lipoprotein.

Table 3: Influence of adjuvant letrozole on the serum lipid profiles of post-menopausal breast cancer patients.

Parameters	Median (IQR)		p-value [a]
	Base Line	After 3 months	
TG (mg/d)	149(103-200)	143(111-200)	0.0575
TC (mg/d)	208(184-266)	213(200-263)	0.009*
HDL (mg/d)	40(37-52)	42.63(35-45)	0.228
LDL (mg/d)	131.4(115-175)	150(126-188)	0.006*
VLDL (mg/d)	29.8(20-40)	28.6(22-40)	0.575

a: p value was calculated by using Wilcoxon test, *: Statistical Significance when p value is < 0.05 level
IQR: interquartile range.

Table 4: The difference in medians of selected lipid parameters between tamoxifen and letrozole in post-menopausal women after three months of treatment from baseline.

Parameters	Tamoxifen		Letrozole		p-value [a]
	Median	Mean rank	Median	Mean rank	
TG (mg/d)	28	39.74	-5	27.26	0.08
TC (mg/d)	17	41.58	-12	25.42	0.001*
HDL (mg/d)	-4	29.83	3	37.17	0.12
LDL (mg/d)	9.76	41.09	-16.7	25.91	0.001*
VLDL (mg/d)	5.6	39.79	-1	27.21	0.008*

a: p value was calculated by using Mann whitney U tests.
*: Statistical Significance when p value is < 0.05 level

(p = 0.009 and 0.006) respectively, as shown in table 3.

There is a statistically significant increase in TC, LDL and VLDL in letrozole group compared to tamoxifen group in postmenopausal patients (p=0.001 , 0.001 and 0.008) respectively table 4.

DISCUSSION

Breast carcinoma is the principal cause of carcinoma death in women.[15] One third of all breast cancers are oestrogen dependent and regress on endocrine therapy (ET).[2] Two most commonly used endocrine treatment are either interfering with oestrogen signalling by a selective oestrogen-receptor modulator, such as tamoxifen, or inhibiting endogenous oestrogen production through an aromatase inhibitor (AI), such as letrozole.[16] The core effect of tamoxifen on breast tissue is anti-oestrogenic, whereas many of its other effects, such as those on the lipid metabolism, considered to be oestrogen-agonistic. Oestrogen agonist or antagonist effects are thus dependent on the organ-specific type and amount of ER available for ligand binding.[17-18]

In this study, tamoxifen was found to cause significant reduction in TC and LDL in postmenopausal patients (p= 0.016 and 0.041) respectively, similar observations on postmenopausal women have been made by Esteva et al[9] in 2006, Markopoulos et al[19] in 2005, and Gupta et al[20] in 2006 and was attributed to oestrogenic effect of tamoxifen. Nevertheless, the outcomes of this study are in contrast with Hozumi et al[21] who are reported in 2006 that the serum TC levels remained unchanged after tamoxifen treatment. Hozumi's population was composed of postmenopausal and lymph node-negative disease and their blood samples were collected before and at 2 months after the initiation of tamoxifen treatment.

We found that TG levels have decreased with a statistical significance (p= 0.002) in postmenopausal breast cancer women after tamoxifen treatment. These results has contradicted those found by Esteva[9] in 2006, Markopoulos[19] in 2005, and Liberopoulos[22] in 2002, who have reported that TG levels have increased by using tamoxifen. Increase in TG level is a pharmacological effect resulting from the hepatic first pass effect of oestrogens,[23] however, tamoxifen does not share this oestrogen agonist effect. The menopausal status modulates the effect of SERMs.[17-18] Atalay et al[24] in 2004 have reported that being oestrogenic, tamoxifen increases the levels of triglycerides.

Letrozole administration in the current study has been associated with a significant increase in TC and LDL cholesterol levels (p- value = 0.009 and 0.006) respectively. A similar observation was reported by Bell[25] in 2012, and Elisaf[26] in 2001. Wasan et al[27] in 2005 has also confirmed that letrozole therapy did not significantly change lipid parameters. Differences in study design, prior tamoxifen use, and inclusion/exclusion of patients on lipid-altering medications may explain the variability seen in AI-induced changes in lipid profiles. Letrozole inhibit the production of oestrogen by preventing the conversion of androstenedione and testosterone to oestrone and oestradiol[28] and letrozole lack of the beneficial oestrogenic effects on lipid Profile[29] these lead to increase TC and LDL in postmenopausal breast cancer women treated with letrozole in contrast to tamoxifen as in cur-

rent study .

CONCLUSION

Use of tamoxifen in post-menopausal breast cancer patients have shown to have an advantageous effect on TG, LDL, TC, and VLDL after three months of use. In contrary, use of letrozole was associated with a statistically significant increase in TG and LDL level.

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Abbreviation list: Aromatase inhibitors (**AIs**), Deciliter (**dl**), Endocrine therapy (**ET**), Estrogen receptor (**ER**), Gram (**g**), High density lipoprotein (**HDL**), Interquartile range (**IQR**), Low density lipoprotein (**LDL**), Milligram (**mg**), Number (**n**), Progesterone receptor (**PR**), Selective estrogen receptor modulator (**SERM**), Statistical Package for Social Sciences (**SPSS**), Total cholesterol (**TC**), Triglyceride (**TG**), Very low density lipoprotein (**VLDL**) .

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