Tamoxifen Effects on the lipid profile in premenopausal women with Breast cancer: A follow up study

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Abstract:

Background: Breast cancer composed of several biologic subtypes that have response to hormonal therapy. Tamoxifen is hormonal therapy with tissue- pecific antagonistic or agonist effects, the latter being responsible for multiple effects on lipid metabolism in women .

Objective: This study was designed to determine the impact of Tamoxifen on the serum lipid profile in breast cancer women.

Patients and methods: Prospective observation cohort study conducted at Oncology Teaching Hospital, Medical city complx.starting from October 2015 to October 2016. A total number of 40 premenopausal women with breast cancer were enrolled in this study according to inclusion criteria . Patients were followed for three months by the measurements TC, TG, HDL – cholesterol and BMI .

Results: At the end of third months of hormonal therapy, Tamoxifen showed a significant decrease in TG, VLDL ($p < 0.001$ for both). On the other side HDL and BMI showed significant increase over three months duration , ($p = 0.001$ and 0.006, respectively) **.**

Conclusion: Beneficial alterations of lipid profiles were seen in pre-menopausal breast cancer patients treated with Tamoxifen.

Keywords: Breast cancer, Tamoxifen, the lipid profile, premenopausal women.

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Introduction:

Practically two-thirds of females with breast cancer have overexpression of estrogen (ER) and/or progesterone receptors, and will get advantage from anti-estrogen remedy (1, 2). Tamoxifen is a selective estrogen receptor modulator (SERM). Tamoxifen works by blocking estrogen from binding to the estrogen receptor. It does not change estrogen production. (3) It has strongly anti-estrogenic on mammary epithelium, hence use in the treatment of breast cancer, it is pro-estrogenic on uterine epithelium and increased occurrence of endometrial carcinoma. (4) Like definite estrogens, tamoxifen lowers total serum cholesterol, low-density-lipoprotein cholesterol due to estrogenic effect , and potentially reducing the risk of myocardial infarction. It is therefore inappropriate to refer to tamoxifen simply as an anti-estrogen. The term selective estrogen receptor modulator is more appropriate (5) .

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This study targets to determine the change in serum lipid profile in women treated with Tamoxifen for hormonal positive breast cancer.

Patients and methods:

Study design: A Prospective, observation cohort study, conducted at Oncology Teaching Hospital, Medical city complex in Baghdad. Starting from October 2015 to October 2016.

Definition of the case and inclusion criteria: Breast cancer women on adjuvant hormonal therapy with tamoxifen (in a dose 20 mg once daily), who start on tamoxifen with the start of the study were the target of this study. It included premenopausal women without metastasis disease.

Exclusion criteria : Patients with cholesterol reduction formula, with diabetes mellitus, thyroid dysfunction, hepatic or renal impairment , smoker patients, pregnant patients, and hypertensive patients on treatment which have effect lipid profile like beta -blocker and thiazide were excluded . For this long exclusion criteria the sample size is small, and bigger sample needs to be studied in the future .

Sampling: This study enrolled all patients who have followed for three months by the measurements of lipid profile (Total cholesterol, Triglyceride, HDL – cholesterol)

And calculated: LDL, VLDL and BMI by following formulas:

VLDL(mg/dl) = TG/ 5(6)
LDL (mg/dl) = Total cholesterol – (HDL + VLDL) (6)
BMI = Weight (Kg)/Height (m)2 (6)

Procedure: Blood sample from each women after an overnight fasting state (12- 14)hrs. Was aspirated from peripheral vein and collected in clean and sterile test tube. The samples were transferred immediately to the laboratory, centrifuged (1,600 × g, 10 minutes, 16.C) and the serum was separated and analyzed immediately or frozen at –20.C until analysis. Serum lipid concentration was measured before starting tamoxifen treatment, and three months thereafter. All the measurements (Total cholesterol, Triglyceride, HDL – cholesterol) relative to an individual patient were analyzed at the same clinical laboratory (Bagdad Teaching Hospital Laboratory) by using a chemistry autoanalyzer (Hitachi 7600–110; Tokyo, Japan) and with the same commercial kit. The questionnaire forms have been filled in by researchers themselves based on the data taken from the patients .

Statistical analysis: Each patient assigned a serial identification number. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 23. Basic descriptive statistics, including means, and percentages, were used to characterize the study participants. The Wilcoxon test was used to compare values among study group. The level of significance was set at P<0.05.

Results:
Overall, 47 patients were initially included in the study, only 40 were included in analysis, the remaining 7 patients were excluded from the study due to loss of follow up. The descriptive characteristics are shown in table 1 and 2. Studied group showed statistically significant decrease in TG , and VLDL, over time from baseline, percent of decrease (20.9% for both) (p< 0.001 for both). While HDL and BMI showed statistically significant increase by (10% and 2.6%)respectively and (p = 0.001 and 0.006) respectively , as show in table 3 and 4 .

Table 1: Baseline characteristics of studied groups (N=40).

Variablevava		%
Family History	Yes	13.6
	No	86.4
Married	Yes	94.6
	No	5.4
Parity	Yes	90.9
	No	9.1
Site of cancer	Right	35.3
	Left	64.7
Stage	I	8.7
	IIA	7.8
	IIB	66.5
	IIIA	13.3
	IIIB	3.7
Type of surgery	Lumpectomy	25.9
	Mastectomy	74.1

Table 2: Statistical characteristics of all studied patients.(N=40) .

Properties	Mean(Range) (N=40)
Age(year)	39.32(26-47)
Weight (Kg)	81.35(58-138)
Length(M)	1.61(1.45-1.75)
BMI(kg/m2)	29.71(26-34)

Table 3 : Change in lipid parameters and body mass index (BMI) after 3 months of adjuvant tamoxifen remedy in pre-menopausal breast cancer patients,(N=40).

Parameters	Median(IQR)		p-value [a]
	Base Line	After three month	
Lipid			
TG (mg/d)	120.8(98-153)	95.5(67-137)	<0.001*
TC (mg/d)	187.78(167-219)	190(152-212)	0.150
HDL (mg/d)	45(37-50)	49.5(43-59)	0.001*
LDL (mg/d)	120.14(106-140)	119.7(88-135)	0.067
VLDL (mg/d)	24.16(19-30)	19.1(13-27)	<0.001*
BMI			
BMI (Kg/m2)	29.71(26-34)	30.51(25-35)	0.006*

Wilcoxon test a, * Significant < 0.05 level .
IQR, interquartile range . TG, triglyceride ; TC, total cholesterol ; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL , very low density lipoprotein ; BMI , body mass index .

Table 4: Total percent change in lipid profile and body mass index after three month of treatment with tamoxifen in studied group(N=40).

Variable	Total % of Change
TG(mg/dl)	-20.9
TC(mg/dl)	NS
HDL(mg/dl)	10
LDL(mg/dl)	NS
VLDL(mg/dl)	-20.9
BMI (Kg/m2)	2.6

NS = Nor significant .

Discussion:
Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women.(7) Tamoxifen is the most universally endocrine treatment used in females with hormone-

positive breast cancers , which interfering with estrogen waving by a selective estrogen-receptor modulator, and exerts a beneficial effect on lipid profiles. (8)The main influence of tamoxifen on breast is anti-estrogenic, although several of its further properties, such as those on the lipid metabolism, considered to be estrogen-agonistic . (9) In the present study tamoxifen was found to cause significant reduction in TC ($P< 0.001$)
in premenopausal patients, but the outcomes of this study are in contrast to Liberopoulos et al, (10) (2002) who state that tamoxifen increased the TG levels, this difference may be due to difference in diet , duration of follow up and others. Increase in TG is a pharmacological effect resulting from the hepatic first pass effect of estrogens however, tamoxifen does not share this estrogen agonist effect. Also in current study, tamoxifen cause no important decline in TC and LDL which is different from observations have been made on breast cancer women in Gupta et al(11) (2006) ,but the results of this study are similar to Hozumi et al. (12) (2006) reported that the serum TC levels remained unchanged after tamoxifen treatment.
The estrogen agonist/antagonist properties of SERMs can be partly described through the two activation domains AF1 and AF2 of ER that mediate the transcriptional control of the receptor. Tamoxifen blocks the effect of estrogen by inhibiting AF2 but it does not inhibit AF1.
Therefore, tamoxifen has largely antagonist activity in breast tissue where AF2 is dominant but more agonistic activity in other tissues where AF1 is dominant. Estrogen agonist or antagonist effects are thus dependent on the organ-specific type and amount of ER available for ligand binding. Also the menopausal status modulates the effect of SERMs. Tamoxifen look like more estrogen antagonist than agonist in premenopausal women . (13-14) . More ever in this study there is statistically significant increase in HDL($p= 0.001$) was detected in pre-menopausal patients, due to estrogenic outcome of tamoxifen, this result in contrast to Singhai et al (2011)(15) did not find change in HDL level ,but similar to Bruning et al(16). The change in body weight is similar to Hoskin et al(17) (1992) , which due to great concentration of estrogen and other gonadotropins (17)

Conclusıon:

Beneficial changes of lipid profiles were seen in women treated with Tamoxifen in pre-menopausal breast cancer women. Triglyceride, and very low density lipoprotein, show statistically significant decrease. While there is statistically significant increase high density lipoprotein over time from baseline.

Authors' contribution:

Zainab A. Mohammed Ali*: Study design, sample collection and manuscripts writing.
Wasan K. Jasim : Selection of sample , collection and analysis of data .
Dilan Z. Hussein :Support in writing the theses and statistical analysis .
Manwar Abdulelah Alnaqash : Support in writing the theses and sample collection .

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تأثير التاموكسفين على مستوى الدهون في النساء ما قبل سن الياس المصابات بسرطان الثدي

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خلاصة البحث

المقدمة:

سرطان الثدي هو الورم الخبيث الأكثر شيوعا بين النساء في جميع أنحاء العالم , بل هو أيضا السبب الرئيسي للوفيات المرتبطة بالسرطان في الإناث . عقار التاموكسفين هو العلاج الهرموني الشائع للمرضى الذين يعانون من سرطان الثدي .حيث يعمل بانتقائية عالية عن طريق منع تأثير هرمون الأستروجين بواسطة منع ايصال الأستروجين للمستقبلات الضرورية لفعاليته في اجزاء معينه من الجسم وبنفس الوقت يقوم بفعاليته الاستروجين في اجزاء اخرى. لعقار التاموكسيفين تأثير ايجابي على مستوى الدهون في الجسم.

هدف البحث:

تم تصميم هذه الدراسة لتحديد تأثير التاموكسفين على مستوى الدهون في الدم لمريضات سرطان الثدي وتحديد تأثيرهما على مستويات الكوليسترول في الدم، وما لهو من تأثير على امراض القلب والشرايين .

المرضى والطرق:

دراسة مستقبلية، أجريت في المستشفى الأورام التعليمي في المدينة الطبية .بدءا من أكتوبر 2015 إلى أكتوبر 2016. شملت(40)مريضة بسرطان الثدي ممن تلقوا عقار التاموكسيفين في جرعة 20 ملغم مرة واحدة يوميا، مع متابعة المريضات لمدة ثلاث اشهر .

النتائج :

ما مجموعه(40) مريضة يعانون من سرطان الثدي تم ادراجهن في هذه الدراسة. وقد أظهرت الدراسة انخفاضا ملحوظا إحصائيا على مر ثلاثة اشهر في الدهون الثلاثية و الدهن المنخفض الكثافة الضار جدا. وعلاوة على ذلك هناك زيادة ملحوظة احصائيا في نسبة الدهن العالي الكثافة .وايضا هناك زياده في الوزن ذات دلالة إحصائية عند نهاية الدراسة .

الاستنتاجات: التغيرات الحاصلة في مستوى الدهون في المريضات ممن تلقين عقار التاموكسيفين في مرحلة ما قبل سن الياس لمريضات سرطان الثدي هي تغييرات مفيدة وذات دلالة مهمة إحصائيا .

مفتاح الكلمات:سرطان الثدي ،عقار التاموكسفين، مستوى الدهون في الدم، قبل سن الياس.