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Fatty Liver Formation in Patients with Breast Cancer on Tamoxifen Therapy in Iraqi Female

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***Abstract*---** This is a prospective, hospital based, case-control study conducted at Oncology and Nuclear medicine specialist Hospital, in Nineveh province in Iraq during the period from February 2018 to November 2018, to determine the prevalence of fatty liver formation in tamoxifen treatments by ultrasonographic examinations. Fifty-patients receiving tamoxifen were involved in this study, 11 of these were premenopausal from the premenopausal subgroup patients14 (28%) their age (25-44) years in which 10 of them were Grade I fatty liver & 1 case was Grade II fatty liver, no cases seen had Grade III , and 32 patients were postmenopausal were from post menopausal subgroup patients 36 (72%) range their age (45-78) years, in which 16 of them had fatty liver Grade I, & 16 of them had fatty liver Grade II, no cases seen had Grade III, The duration of tamoxifen was range (6<–72) months, with 33control case, which were 24 case premenopause and 9 case postmenopause which had 3 of them were grade II in premenopausal age group , while 3 cases were postmenopausal patients age group in which 1 case was Grade I fatty liver & 2 cases were Grade II, In present study 43 (86%) of them had fatty liver , with significant relation between fatty liver formation and duration of tamoxifen with P. Value = .020.,also had relation with age group which 11of these were premenopausal , while 32 patients were postmenopausal with P.V =.043, in this study also shows relation with fatty liver formation and increase body weight during tamoxifen therapy with P.V =.001**.** The present study result suggests that tamoxifen is associated with increased risk of fatty liver development, that tamoxifen has a strong influence on hepatic fat content and is

strongly associated with the frequent development of hepatic steatosis in patients with breast cancer.

***Keywords*---**tamoxifen, fatty liver formation, breast cancer.

Introduction

Tamoxifen is a selective estrogen receptor modulator treatment, which has a complex mechanism of action including anti-estrogenic action in the breast and tissues like those in the breast. And estrogenic effects in other tissues has been widely used to treat ER-positive breast cancer for chemoprevention in high risk pre- and postmenopausal women [(1)]. Tamoxifen treatment for 5 years can decrease the annual mortality rate by 31% and prevent cancer over the next 20 years [(2)]. Tamoxifen acts as an estrogen agonist in the endometrium, the bones, the coagulation system, and lipoprotein metabolism and exerts beneficial effects by maintaining the bone density and lowering the cholesterol level[(3)], Several studies showed that taking tamoxifen may incur a 30-40% risk of developing nonalcoholic fatty liver disease (NAFLD), according to different diagnosis instruments [(4)]. In general, fatty liver is more likely to be associated with obesity and unhealthy diet habits [(5,6)]. A number of case reports have shown hepatic steatosis associated with adjuvant tamoxifen [(7)]. Menopause occurs during the aging process in female and is characterized by a steady decline in ovarian functions. multiple pathologies associated with the onset of menopause, such as metabolic syndrome and fatty liver disease [(8),] Although the molecular events giving rise to menopause-associated pathologies are largely unknown, loss of ovarian function is suggest to be the underlying mechanism. This idea has led to hormone replacement treatment being the central component of clinical treatment for menopausal symptoms [(9)]. Estrogens can mediate their biologic effects in the liver through a number of mechanisms. The classic mechanism of E2 action involves E2 binding to the steroid nuclear hormone receptors, estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ). ERα and ERβ have the classic features of steroid hormone receptors – an activation function 1 (AF1) domain, a ligand-binding domain, a DNA-binding domain, and an activation function 2 (AF2) domain [(10)]. Estrogen increasing expression levels of the hepatic estrogen receptors (ER) α, but not β. Furthermore, the ERα-selective agonist propylpyrazole, but not the ERβ-selective agonist diarylpropionitrile, augments hepatic cholesterol output.[(12)] . Similar to estrogen treatment, tamoxifen action [(12)], the hepatic ERα acts a crucial role in exposure to high levels of estrogen [(12)]. High doses of estrogen significantly increase intestinal cholesterol absorption, mostly due to an up regulated expression of intestinal sterol influx transporter Niemann-Pick C1 like 1 protein (NPC1L1) by the intestinal ERα pathway [(13)]. Tamoxifen also induced acute pancreatitis with severe hypertriglyceridemia and one event of death [(14)]. The aim of study is due to tamoxifen has both antiestrogen and estrogen-like activity, a possible relation between long-term tamoxifen administration and fatty liver formation was assessed in premenopausal and postmenopausal breast cancer patients in this study.

Method

The subjects for our study were recruited from the Cancer Follow-Up of the Oncology and Nuclear medicine specialist Hospital, Mosul/Iraq , after obtaining an informed consent were 50 cases This was a case control study in hospital based study carried out during the period of February 2018 through November 2018, There were 14 premenopausal and 36 postmenopausal patients. All of them had undergone surgical treatment, chemotherapy, and radiotherapy for the malignancy and were on a regular follow-up. Demographic details including the age, weight, age at menopause, and so on, were collected. As a part of the routine workup during the follow-up visits, each patient underwent Trans abdominal ultrasonography (TAU) with a 1-6 MHz convex transducer (Alpinion Portable Color Doppler E-CUBE). All these examinations were performed by the same physician and the grading of fatty liver were noted. 33 number of age- and gender-matched control cases were recruited from the partner of Inpatient Department of pediatrician in Ibn Alatheer teaching hospital, after obtaining informed consent. A daily dose range from 10-40 mg tamoxifen was prescribed for each of the study patients. The data obtained were analyzed with appropriate statistical tests.

Inclusion criteria:
1. Premenopausal & Postmenopausal breast cancer patients who have undergone mastectomy and are taking Tamoxifen
2. Those who satisfy the above criterion and have completed their course of Tamoxifen

Exclusion criteria:
1. Those who are on Hormone Replacement Therapy
2. Those who have taken Oral Contraceptives in the past.
3. Patient with history of alcoholic consumption.
4. Patients with stage IV of breast cancer (liver metastasis) at diagnosis.
5. Evidence of liver disease on physical examination

Statistical analysis: Descriptive statistics are expressed as , Pearson Chi-square was used in case of discrete variables All the findings of the cases studied were tabulated using Microsoft Excel hence statistical analysis was done by using Statistical packages SPSS18 (Statistical Package for Social Sciences version 18) . Paired t-test was used to compare intergroup data. For the evaluation of statistical significance, Chi-square test was employed. Probability values less than 0.05 were considered significant.

Results

In present study we had a Fifty- female patients receiving tamoxifen therapy were enrolled in this study, 14 (28%) of them were premenopausal range their age was between (25-44) years, and 36 (72%) postmenopausal range their age was between (45-78) years, at the time when they were monitored for fatty liver assessment, the control group were 33 cases in which 24 case were premenopausal & 9 of them were postmenopausal. The duration of tamoxifen therapy was (range < 6–72) months, in present study we found there's relation between the duration of tamoxifen therapy taken and incidence of fatty liver,

which 43 (86%)of cases had found formation of fatty liver, while 6 (18.2%) control cases shown had fatty liver & 27 (81.8%) of control cases had normal liver echo texture examined by trans abdominal ultrasound. The P-Value shown significant relation between incidence of fatty liver and duration of tamoxifen therapy were = .020, as shown in tables (1) below

Table (1): Relation between the duration of tamoxifen and formation of fatty liver

Duration-Group	FATTY LIVER				Total	P.V
	normal	Grade I	Grade II	Grade III		
<6	4	1	1	0	6	**0.020**
6-12	2	9	5	0	16	
13-24	1	3	3	0	7	
25-36	0	4	2	0	6	
37-48	0	5	2	0	7	
49-60	0	2	2	0	4	
61-72	0	2	2	0	4	
Total	7	26	17	0	50	

The present study shows there's correlation between age group of patients and formation of fatty liver that measured by ultrasonography study, in which fatty liver were diagnosed in 43 (86%) patients, 11 of these were premenopausal from the premenopausal subgroup patients14 (28%), in which 10 of them were Grade I fatty liver & 1 case was Grade II fatty liver , no cases seen had Grade III. 32 patients were postmenopausal were from post menopausal subgroup patients 36 (72%), in which 16 of them had fatty liver Grade I, & 16 of them had fatty liver Grade II , no cases seen had Grade III. The present study shows relation between age group and formation of fatty liver in which increase incidence in postmenopausal patients more than premenopausal patients with P-value =0.043, as table (2) shown below, while in control cases we found 6 cases had fatty liver in different grade from 33 total cases 3 of them were grade II in premenopausal age group , while 3 cases were postmenopausal patients age group in which 1 case was Grade I fatty liver & 2 cases were Grade II , as table (3) below.

Table (2): Relation between the age group of patients on tamoxifen therapy and formation of fatty liver

age-group	Fatty liver on patient with tamoxifen therapy				Total	P-V
	normal	Grade I	Grade II	Grade III		
Premenopausal	3	10	1	0	14	0.043
Post menopause	4	16	16	0	36	
Total	7	26	17	0	50	

Table (3): Relation between the age group of control cases and incidence of fatty liver

age-group	Fatty liver in control cases				Total
	normal	Grade I	Grade II	Grade III	
Premenopausal	21	0	3	0	24(72.7)
Post menopause	6	1	2	0	9(27.2)
Total	27	1	5	0	33

The 50 cases that enrolled in this study, shows the patients had body weight range from (45 – 105 kg), in this study shows a highly significant relation with incidence of fatty liver and increase body weight during tamoxifen therapy with P.V =0.001, as tables (4) shown below and in control cases shows also some relation with weight age group in comparison with incidence with fatty liver were founded in this study as table (5) below.

Table (4): Relation between the incidence of fatty liver formation and body weight of patients with tamoxifen treatment

Weight group in K.G	**Fatty liver in patients with tamoxifen therapy**				**Total**	**P.V**
	Normal	Grade I	Grade II	Grade III		
45-55	0	5	0	0	5(10%)	
56-65	4	4	0	0	8(16%)	0.001
66-75	3	8	4	0	15(30%)	
76-85	0	2	9	0	11(22%)	
86-95	0	2	2	0	4(8%)	
96-105	0	5	2	0	7(14%)	
Total	**7**	**26**	**17**	**0**	**50**	

Table (5): Relation between the incidence of fatty liver formation and body weight of control cases:

Weight group in K.G	**Fatty liver in control cases**				**Total**
	normal	Grade I	Grade II	Grade III	
45-55	6	0	0	0	6(18.2)%
56-65	16	0	0	0	16(48.5)%
66-75	4	0	1	0	5(15.2)%

76-85	0	1	1	0	2(6)%
86-95	0	0	2	0	2(6)%
96-105	1	0	1	0	2(6)%
Total	**27**	**1**	**5**	**0**	**33**

Discussion

The effect of tamoxifen on hepatic fat content has not been precisely investigated**,** Tamoxifen is one of the most effective anti neoplastic treatment. More than 67% breast cancer patients have been reported to be sensitive to tamoxifen therapy [18], It has been shown that 43% breast cancer patients treated with tamoxifen develop steatosis within the first two years of treatment [19], tamoxifen is associated with various complications, including hypoglycemia, hypertriglyceridemia, changes in plasma cholesterol levels and liver diseases, such as NAFLD [20]. Tamoxifen was shown to increase hepatic fat content, through blocking the role of estrogen in maintaining hepatic lipid homeostasis by supporting the expression of genes involved in lipid β-oxidation, albeit the exact mechanism is not known. In addition, tamoxifen has been shown to increase serum triglyceride and lower low-density lipoprotein and cholesterol levels. It is possible that tamoxifen increases serum triglyceride levels and reduces hepatic lipid β-oxidation, and ultimately this may enhance hepatic fat content [21,22]. Some data showed that hepatic sinusoidal endothelial cell and Kupffer cell in the livers of female rats contained ER, and they were decreased by ovariectomy. Long-term treatment of 17b-estradiol elevated the level of ER in hepatic sinusoidal endothelial cell and Kupffer cell in ovariectomized rats [11]. Tamoxifen exhibits antiestrogen, estrogenic or mixed activity depending upon the target organ assessed. In this study we found the postoperative tamoxifen treatment for breast cancer led to significant fatty liver, which noticed that 43 (86%)of 50 tamoxifen-treated female patients found had fatty liver formation, The time of tamoxifen treatment of these women was range (< 6–72) months, With regard to Tamoxifen therapy among our investigated women the daily dose ranged from 10- 40 mg. the present study shows there's relation between the duration of tamoxifen therapy taken and formation of fatty liver , which 43 (86%)of cases from 50 cases involved in this study had found formation of fatty liver, The duration of Tamoxifen use was categorized as < 6, 6-12, 13-24, 25-36, 37-48, 49-60 and 61-72 months respectively , which shows only 7 cases normal liver appearance by ultra-sonographic examination, & 26 cases had fatty liver formation with grade I & 17 cases had fatty liver formation with grade II. the P. Value shown significant relation between incidence of fatty liver and duration of tamoxifen therapy were = .020, while 6 (18.2%) control cases shown had fatty liver & 27 (81.8%) of control cases had normal liver echo texture examined by trans abdominal ultrasound, while 1(3%) case had a fatty liver formation with grade I & 5 (15.2%) cases had a fatty liver formation with grade II. This agree with Taiwan study (Pan H-J. et al 2015) [17] , which were 406 breast cancer cases were eligible in this study, 266 (64%) of the cases were in the tamoxifen group and 140 (36%) were in the control group, in which this study had revealed that the tamoxifen group tended to exhibit more prominent fatty liver changes which higher moderate and severe degrees and less normal and mild degrees of fatty liver were found in the tamoxifen group which proved that

postoperative adjuvant tamoxifen therapy for breast carcinoma led to significant increase incidence of fatty liver formation. In this study shows there's correlation between age group of patients and formation of fatty liver, which fatty liver were diagnosed in 43 (86%) patients, 11 of these were premenopausal from the premenopausal subgroup patients14 (28%), in which 10 of them were Grade I fatty liver & 1 case was Grade II fatty liver, no cases seen had Grade III. 32 patients were postmenopausal were from post menopausal subgroup patients 36 (72%), in which 16 of them had fatty liver Grade I, & 16 of them had fatty liver Grade II, no cases seen had Grade III. The present study shows relation between age group and formation of fatty liver in which increased incidence in postmenopausal patients more than premenopausal patients with P-value =.043, while in control cases we found 6(18.2%) cases had fatty liver in different grade from 33 total cases 3 of them were grade II in premenopausal age group , while 3 cases were postmenopausal patients age group in which 1 case was Grade I fatty liver & 2 cases were Grade II, this result disagree with Taiwan study (Pan H-J. et al 2015) [17], in which the baseline characteristics of both groups did not significantly differ in terms of age with P.V= 0.260, also disagree with china study(Wang Y M. et al 2017) [23] Among the 646 participants who were diagnosed with NAFLD on ultrasonography, 221 of them were classified into the NAFLD group There were no significant differences in age, with P-V=0.386. The patients had body weight range from (45 – 105 kg), in this study shows a highly significant relation with incidence of fatty liver and increase body weight during tamoxifen therapy in which higher percentage of incidence of grade I fatty liver about 8 cases from 26 cases with grade I, in which the patients within body weight group (66-75) Kilogram,& higher percentage of incidence of grade II fatty liver about 9 cases from 17 cases with grade II in which the patients within body weight group (76-85) Kilogram, with P.V =0.001, while in control cases only one case seen with fatty liver grade I with weight body group (76-85) K.G, & highest prevalence of grade II fatty liver were 2 cases on weight group (86-95) K.G from 5 cases with grade II fatty liver, which control cases shows low relation with weight age group in comparison with incidence of fatty liver were founded of patient of breast cancer which had receiving tamoxifen therapy in this study. This disagree with (Pan H-J. et al 2015) [17], which shows body weight was less likely to be the cause of fatty liver , which mean weight of cases 59.1 ± 9.7 while control cases mean weight 58.9 ±9.2 with P-V= 0.775.

Conclusion

The present study result suggests that tamoxifen is associated with increased risk of fatty liver development, that tamoxifen has a strong influence on hepatic fat content and is strongly associated with the frequent development of hepatic steatosis in patients with breast cancer, in this study was (86%),The severity of fatty liver is associated with duration of tamoxifen. regular abdominal ultrasound checkup, not just for detecting liver nodules, but also for identifying fatty liver change, is crucial ,A 6 months ultrasound studies are useful for detecting and monitoring the clinical course of tamoxifen-induced hepatic steatosis.In this study we had found that Risks of fatty liver development were high body weight, and postmenopausal age group, this finding might be used for clinicians to carful follow up this group of patients and put a regimen of healthy diet and regular

exercise , also encourage patients who have experienced side effects to take non-pharmacological or pharmacological interventions or even change the treatment

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