Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Mar 03; 10(B):517-520.
https://doi.org/10.3889/oamjms.2022.8677
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Radiology and Radiotherapy*

OPEN ACCESS

Gall Bladder Stones Formation in Patients with Breast Cancer on Tamoxifen Therapy in Iraqi Female

Israa Jarjees Rasheed Saeed[1]*, Ali Mohsin Hasan[2]

[1]Department of Radiology, Nineveh Health Directorate, Nineveh, Iraq; [2]Department of Radiology, Ghazi AL Hariri Specialized Surgeries Hospital, Baghdad, Iraq

Edited by: Branislav Filipović
Citation: Saeed IJR, Hasan AM. Gall Bladder Stones Formation in Patients with Breast Cancer on Tamoxifen Therapy in Iraqi Female. Open Access Maced J Med Sci. 2022 Mar 03; 10(B):517-520. https://doi.org/10.3889/oamjms.2022.8677
Keywords: Gall bladder stones; Breast cancer; Tamoxifen therapy
***Correspondence:** Israa Jarjees Rasheed Saeed, Nineveh Health Directorate, Nineveh, Iraq. E-mail: israajarjees2@gmail.com
Received: 18-Jan-2022
Revised: 30-Jan-2022
Accepted: 23-Feb-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Tamoxifen has an estrogenic effect on the liver, lead to increase the danger of gallstone development.

AIM: This study aimed to determine the prevalence of gall bladder stones formation during tamoxifen therapy.

METHODS: A prospective casecontrol study enrolled 14 premenopausal and 36 postmenopausal females. The gall bladder condition was assessed by abdominal ultrasound using "Alpinion Portable Color Doppler E-CUBE," in addition, clinical parameters collected as age and weight of patients.

RESULTS: Approximately, 14 (28%) of women were premenopausal their age ranged from (25 to 44) years, and 36 (72%) postmenopausal females their age was between (45 and 78) years. The duration of tamoxifen therapy was (range >–72) months, with 33 control cases. All cases examined by pelvic ultrasound, only 11 (22%) showed gall bladder stones. The gall bladder stones were diagnosed, in 4 of premenopausal, whereas seven patients were postmenopausal. There is a significant relation with gall bladder stones with increase body weight during therapy.

CONCLUSION: There is a significant correlation between gall bladder stones formation and tamoxifen therapy. Postmenopausal women have a higher risk of developing gall bladder stones formation.

Introduction

Tamoxifen is a selective estrogen receptor modulator therapy, which has a complex mechanism of action including anti-estrogenic action in the breast and tissues like those in the breast. In addition, estrogenic effects in other tissues such as endometrial and bone tissues, depending upon the types and the goal genes dignified, It is widely used for the treatment of breast tissue cancer and for chemoprevention in high-risk pre- and postmenopausal women [1]. The most common malignancy in females is breast cancer [2], Tamoxifen has a significant adverse effect such as estrogenic effect on the liver, increase the risk of gallstone development [3], [4]. Tamoxifen is stimulation the pathway of "estrogen-ERα-SREBP-2" occurs inside the liver that enhances cholesterol excretion in the bile, so lithogenicity increased because of cholesterol saturation inside bile [5]. In addition to tamoxifen that causes gallstone other risk factors are; aging, female, contraceptive pills, fatty, gestation, fast decrease in weight, and so on [6]. A widespread common of gallstones more than 80% are "silent" and most persons tolerate biliary pain or problems due to gallstones for years [6]. High prevalence of gallstone occurrence in females take tamoxifen and have breast cancer [7], [8]. The ERα-selective agonist propylpyrazole, enhances hepatic cholesterol production leads to supersaturated bile of cholesterol and gallstones formation [4]. Excessive secretion of biliary cholesterol considered the main cause of cholesterol gallstones [9]. Absorption of intestinal cholesterol increase by high dose estrogen intake because well organize of intestinal sterol arrival carrier Niemann-Pick C1 like 1 protein through the intestinal ERα pathway [10]. Tamoxifen is generally a safe and well-tolerated drug but has other certain adverse effects such as endometrial cancer, thromboembolism, and menopausal symptoms of clinical concern [11], tamoxifen-induced acute pancreatitis with severe hypertriglyceridemia and one event of death [12], [13], [14]. The aim of the study is to determine the prevalence of gall bladder stones formation in tamoxifen treatments by ultra-sonographic examinations.

Methods

This study was employed 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 casecontrol study in hospital-based study carried out during the period of February 2020 through November 2020, There were 14 premenopausal and 36 postmenopausal patients. All patients undergone operating management, chemotherapy, and radiotherapy for the malignancy and were on a systematic observation. Sociodemographic variables including the "age, weight, age at menopause." Any treatment history of breast cancer and medical history of gallstone either found or not were provoked. So if there is no gallstone so this excludes from the study. All patients undergo abdominal ultrasound "Alpinion Portable Color Doppler E-CUBE." A daily dose range from 10 to 40 mg tamoxifen was prescribed for each of the study patients. The data obtained were analyzed with appropriate statistical tests.

Inclusion criteria

1. Females with breast cancer before and after menopause they take tamoxifen and undergo mastectomy
2. Females completed their tamoxifen course.

Exclusion criteria

1. Females on Hormone Replacement Therapy
2. Females taken Oral Contraceptives in the past
3. Females undergone any operations lead to develop gallstones (e.g., Vagotomy)
4. Females have gallstones before take tamoxifen.

Statistical analysis done by SPSS 22, frequency and percentage used for categorical data, mean, median and SD for continuous data. Chi-square used for assessed association between variables. $p \leq 0.05$ is consider significant.

Results

In the present study we had a Fifty- patients receiving tamoxifen treatment were involved in this study, 14 (28%) of whom were premenopausal range their age was between (25 and 44) years, and 36 (72%) postmenopausal range their age was between (45 and 78) years, at the time when they were monitored for ovarian assessment with relation with other changes of uterus post tamoxifen therapy, the control group were 33 cases in which 24 case were premenopausal and 9 of them were post-menopause. All patients enrolled in this study had a history of no Gall bladder stones pre tamoxifen therapy, with routine abdominal ultra-sonographic follow up were done for all patients of this study.

The duration of tamoxifen therapy was (range <6–72) months, in this study we found there's relation between the duration of tamoxifen therapy taken and incidence gall bladder stones, which 11 (22%) of cases would found formation of gall bladder stones, while 33 control cases shown normal gall bladder with no gall bladder stones seen by abdominal ultrasound survey. The p-value shown significant relation between the incidence of gall bladder stones formation and duration of tamoxifen therapy were = 0.029, as shown in (Table 1) below.

Table 1: Relation between the duration of tamoxifen and formation of GB stones

Duration of tamoxifen in months	GB condition		Total (%)	p-value
	Normal	GB stones		
6>	4	2	6 (12)	0.029
6–12	14	2	16 (32)	
13–24	5	2	7 (14)	
25–36	4	2	6 (12)	
37–48	6	1	7 (14)	
49–60	4	0	4 (8)	
61–72	2	2	4 (8)	
Total	39	11	50	

$p \leq 0.05$ (significant), GB: Gall bladder.

The present study shows there's a correlation between the age group of patients and formation of gall bladder stones that measured by ultrasonography study, in which gall bladder stones were diagnosed in 11 (22%) patients, four of these were premenopausal from the premenopausal subgroup patients 14 (28%), while seven patients were postmenopausal were from post-menopausal subgroup patients 36 (72%). The present study shows relation between the age group and incidence of formation of gall bladder stones in which increased incidence postmenopausal patients rather than premenopausal patients with $p = 0.048$, as (Table 2) shown below.

Table 2: Relation between the age group of patients and formation of GB stones

Duration of tamoxifen in months	GB condition (%)		Total (%)	p-value
	Normal	GB stones		
Premenopausal	10 (25)	4 (3)	14 (28)	0.048
Postmenopausal	29 (53)	7 (19)	36 (72)	
	39 (78)	11 (22)	50 (100)	

$p \leq 0.05$ (significant), GB: Gall bladder.

The 50 cases that enrolled in this study, shows the patients had body weight range from (45 to 105 kg), in this study shows relation with gall bladder stones and increase body weight during tamoxifen therapy with $p = 0.018$, as (Table 3) shown below.

Discussion

Tamoxifen is one of the most effective anti-neoplastic treatment, which is prescribed for many female internationals for the adjuvant or palliative management of breast malignancy [15]. In the present study, we found that postoperative adjuvant tamoxifen treatment for breast cancer led to significant gallstone

Table 3: Relation between the incidence of GB stones and body weight of patients with tamoxifen treatment

Wight group in K.G	GB condition (%)		Total (%)	p-value
	Normal	GB stones		
45–55	5 (10)	0 (0)	5 (10)	0.018
56–65	3 (6)	5 (10)	8 (16)	
66–75	13 (26)	2 (4)	15 (30)	
76–85	9 (18)	2 (4)	11 (22)	
86–95	2 (4)	2 (4)	4 (8)	
96–105	7 (14)	0 (0)	7 (14)	
Total	39 (78)	11 (22)	50 (100)	

$p \leq 0.05$ (significant), GB: Gall bladder.

formation, which noticed that 11 (22%) of 50 tamoxifen-treated female patients complaining from gall bladder stones formation, The time of tamoxifen treatment of these women was range (<6–72) months, With regard to Tamoxifen treatment among our investigated women the daily dose ranged from 10 to 40 mg. The duration of Tamoxifen use was categorized as <6, 6–12, 13–24, 25–36, 37–48, 49–60, and 61–72 months, respectively. The present study shows there's relation between the duration of tamoxifen therapy taken and incidence gall bladder stones, which 11 (22%) of cases would found the formation of gall bladder stones, while 33 control cases shown normal gall bladder with no gall bladder stones seen by abdominal ultrasound survey. Significant relation between the incidence of gall bladder stones formation and duration of tamoxifen therapy was = 0.029, this agree with Turkish study (Akin *et al*. 2003) [9], which were a retrospective cohort study had proved that postoperative adjuvant tamoxifen therapy for breast carcinoma led to significant gallstone formation in patients after 5 years, The apparent increase in gallstone formation at the end of the 3rd year of tamoxifen use underlines the fact that a minimum of 3 years is needed to see the estrogenic effects of tamoxifen. This shows the incidences of gallstones being detected in 171 tamoxifen-treated patients, also the present study agree with (Mohamed *et al*. 2009) [16], all patients follow up by abdominal ultrasound in duration of 5 years, so that 33% of patients have tamoxifen develop gallstone for more than 3 years. The significant increase in gallstone formation in patients who received tamoxifen might be related to the estrogenic effects of tamoxifen. Tamoxifen stimulates the adrenal gland to produce dehydroepiandrosterone and then estrone and estradiol in peripheral tissues. Elevated estrogen levels may affect gallbladder motility, increase the cholesterol saturation of bile, decrease the bile acids, and cause decreased bile flow. Hepatic effects of tamoxifen administration itself were reported to be cholestatic in nature [17]. This study shows there's correlation between the age group of patients and formation of gall bladder stones that measured by ultrasonography study, which gall bladder stones were diagnosed in 11 (22%) patients, four of these were premenopausal (28.6%) from the premenopausal subgroup patients 14 (28%), while seven patients were postmenopausal were (19.4%) from post-menopausal subgroup patients 36 (72%). The present study shows relation between age group and the incidence of formation of gall bladder stones in which increased incidence postmenopausal patients rather than premenopausal patients with p = 0.048, this agree with Turkish study (Akin *et al*. 2003) [9]. A retrospective cohort paper done in Turkey stated that high risk of gallstone development in postmenopausal breast cancer females who are taking tamoxifen, the mean age patients that involved in the study were 64.8 ± 9.6 years (range: 55–84 years). The present study shown, the patients involved in the study had body weight range from (45 to 105 kg), in this study shows relation with gall bladder stones and increase body weight during tamoxifen therapy with p = 0.018, this result disagree with the Turkish study (Akin *et al*. 2003) [9], in which There was no statistically significant difference regarding the body weight of patients and incidence of gall bladder stones with p = 0.073.

Conclusion

There is a significant correlation between gall bladder stones formation and tamoxifen therapy. Postmenopausal women have a higher risk of developing gall bladder stones formation than premenopausal patients.

Limitation of Study

In our study which done to assess the relation between tamoxifen therapy receive &gall bladder stones formation for 1 year follow up after course of therapy which short time and need follow up for longer time more than 1 year to enforce the relation in between. In our study there was no gene study done to assess the discrepancy due to genetic difference at receptor level.

Ethical Committee

The ethical approval done as the requirements of Oncology and Nuclear medicine specialist Hospital, Mosul health directorate, Mosul/Iraq.

Contributions

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

References

1. Gultekin IB, Imamoglu GI, Gultekin S, Yilmaz EA, Yilmaz Z, Alkan A, *et al*. Elastosonographic evaluation of endometrium in women using tamoxifen for breast cancer. Niger J Clin Pract. 2019;22(1):92-100. https://doi.org/10.4103/njcp.njcp_387_16
   PMid:30666026
2. Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, *et al*. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma *in situ* (IBIS-II DCIS): A double-blind, randomised controlled trial. Lancet. 2016;387(10021):866-73. https://doi.org/10.1016/S0140-6736(15)01129-0
   PMid:26686313
3. Howell A. The endocrine prevention of breast cancer. Best Pract Res Clin Endocrinol Metab. 2008;22(4):615-23. https://doi.org/10.1016/j.beem.2008.09.002
   PMid:18971122
4. Kline L, Karpinski E. Gallbladder motility and the sex of the guinea pig. Physiol Rep. 2016;4(12):e12843. https://doi.org/10.14814/phy2.12843
   PMid:27354545
5. Chimed T, Sandagdorj T, Znaor A, Laversanne M, Tseveen B, Genden P, *et al*. Cancer incidence and cancer control in Mongolia: Results from the national cancer registry 2008-12. Int J Cancer. 2017;140(2):302-9. https://doi.org/10.1002/ijc.30463
   PMid:27716912
6. Lee SS, Byoun YS, Jeong SH, Kim YM, Gil H, Min BY, *et al*. Type and cause of liver disease in Korea: Single-center experience, 2005-2010. Clin Mol Hepatol. 2012;18(3):309-15. https://doi.org/10.3350/cmh.2012.18.3.309
   PMid:23091812
7. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: Cholelithiasis and cancer. Gut Liver. 2012;6(2):172-87. https://doi.org/10.5009/gnl.2012.6.2.172
   PMid:22570746
8. Kim YA, Lee S, Jung JW, Kwon YJ, Lee GB, Shin DG, *et al*. Severe acute pancreatitis due to tamoxifen induced hypertriglyceridemia with diabetes mellitus. Chin J Cancer Res. 2014;26(3):341-4. https://doi.org/10.3978/j.issn.1000-9604.2014.05.01
   PMid:25035662
9. Akin ML, Uluutku H, Erenoglu C, Karadag A, Gulluoglu BM, Sakar B, *et al*. Tamoxifen and gallstone formation in postmenopausal breast cancer patients: Retrospective cohort study. World J Surg. 2003;27(4):395-9. https://doi.org/10.1007/s00268-002-6468-4
   PMid:12658480
10. Stokes CS, Krawczyk M, Lammert F. Gallstones: Environment, lifestyle and genes. Dig Dis. 2011;29(2):191-201. https://doi.org/10.1159/000323885
    PMid:21734384
11. Kawase A, Araki Y, Ueda Y, Nakazaki S, Iwaki M. Impact of a high-cholesterol diet on expression levels of Niemann-Pick C1-like 1 and intestinal transporters in rats and mice. Eur J Drug Metab Pharmacokinet. 2016;41(4):457-63. https://doi.org/10.1007/s13318-015-0269-2
    PMid:25716431
12. Etori S, Nakano R, Kamada H, Hosokawa K, Takeda S, Fukuhara M, *et al*. Tamoxifen-induced lung injury. Intern Med. 2017;56(21):2903-6. https://doi.org/10.2169/internalmedicine.8649-16
    PMid:28943550
13. Singh HK, Prasad MS, Kandasamy AK, Dharanipragada K. Tamoxifen-induced hypertriglyceridemia causing acute pancreatitis. J Pharmacol Pharmacother. 2016;7(1):38-40. https://doi.org/10.4103/0976-500X.179365
    PMid:27127396
14. Sumino H, Murakami M. Investigation of atherosclerosis in postmenopausal women: Alteration of atherosclerosis-associated factors and vascular atherosclerosis by oral and transdermal estrogen replacement. Rinsho Byori. 2013;61(3):256-62.
    PMid:23785796
15. Bellet M, Gray KP, Francis PA, Láng I, Ciruelos E, Lluch A, *et al*. Twelve-month estrogen levels in premenopausal women with hormone receptor-positive breast cancer receiving adjuvant triptorelin plus exemestane or tamoxifen in the suppression of ovarian function trial (SOFT): The SOFT-EST substudy. J Clin Oncol. 2016;34(14):1584-93. https://doi.org/10.1200/JCO.2015.61.2259
    PMid:26729437
16. Mohamed A, Kadambari D, Bhuvaneswari V. Tamoxifen use and gallstone formation in postmenopausal breast cancer patients in South Indian population. Indian J Cancer. 2009;46(2):151-4. https://doi.org/10.4103/0019-509x.49154
    PMid:19346650
17. Ahbeddou N, Belbaraka R, Fetohi M, Errihani H. Tamoxifen-induced hepatotoxicity. Indian J Cancer. 2011;48(3):385. https://doi.org/10.4103/0019-509X.84935
    PMid:21921356