ORIGINAL ARTICLE

EFFECT OF TAMOXIFEN ON PLASMA LIPID PROFILE IN PATIENTS OF BREAST CANCER

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Background: To evaluate the effect of Tamoxifen on plasma lipid profile in breast cancer patients presenting at tertiary care hospitals. **Methods:** It was a longitudinal study conducted at the Department of Oncology of Jinnah Postgraduate Medical Center from December 2018 to November 2019. Eighty-eight females aged 26–66 years diagnosed with breast cancer were included in the study using a non-probability consecutive sampling technique. Detailed gynaecological and clinical investigations and detailed history were taken. The blood samples of all the patients were collected and the plasma lipid profile was measured before initiation of Tamoxifen treatment and three- and six-months post-treatment at the clinical laboratory. The plasma lipid profile includes the measurement of Total cholesterol (mg/dl), Triglyceride(mg/dl), High-density Lipoprotein (mg/dl) & Low-density Lipoprotein (mg/dl). SPSS version 23 was used to analyse data. **Results:** After treatment, there was a significant reduction in serum cholesterol & Low-density Lipoprotein level by 20.54 mg/dl & 16.46 mg/dl at 3 months ($p<0.05$), moreover there was a significant increase in Triglyceride by 22.14 at 3 months ($p<0.05$). No significant difference was observed in High density lipoprotein level at 3 months after using Tamoxifen. At 6 months there was a significant reduction in serum cholesterol and low-density lipoprotein by 32.29mg/dl and 24.11 mg/dl at 6 months ($p<0.05$), moreover there was a significant increase in Triglyceride level by 42.19 mg/dl at 6 months ($p<0.05$). No significant difference was observed in High-density lipoprotein level at 6 months after using Tamoxifen. **Conclusion:** Total cholesterol and Low-density Lipoprotein levels showed significant reduction over the period of six months from the baseline with the use of Tamoxifen. Hence Tamoxifen should be considered to have an added advantage on lipid metabolism and therefore, can reduce the risk of cardiovascular events.

Keywords: Tamoxifen; Plasma lipid profile; Total cholesterol; Cardiovascular events; Breast cancer

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INTRODUCTION

Breast cancer (BC) is the second frequent malignancy and 2nd leading cause of mortality among females globally. In 2016, about 246,660 new cases of BC and 40,450 deaths due to breast cancer among females has been estimated.[1] Due to early detection and advancements in treatment, the death rate of female patients with breast cancer has been reduced to 36% from the highest rates.[2]

The early detection of Breast Cancer followed by treatment for the cure of Breast Cancer includes chemotherapy, surgery, radiotherapy and hormonal therapy.[3] These treatments depend on the stage of tumour and oestrogen receptor (ER) status PR (status) and HER 2 neu status of the patients.[3,4] Tamoxifen (Tmx) is an anti-oestrogen, the mainstay hormonal therapy in Breast Cancer at all stages and represents the advancement in clinical practice.[4,5] The Tamoxifex has positive estrogenic effect on cardiovascular factors by reducing serum total cholesterol (TC) & low-density lipoprotein cholesterol (LDL-c) which significantly decreases the odds of myocardial infraction[2,3,6–13], however no significant change have been found in triglyceride (TG), very low-density lipoprotein cholesterol (VLDL-c) and high density lipoprotein cholesterol (HDL–c) among pre and post-menopausal females[8,10,13,14].

During recent years the incidence of Breast cancer is rising in Pakistan and most of the researches on the effect of Tmx have been conducted outside of the Pakistan. International data isn't applicable in our population because of different genetic makeup than the west where most studies have been conducted. in addition, lack of healthcare facilities, delay in presentation, unavailability of screening and treatment of breast cancer adds further. Therefore, in this study we have evaluated the effect of Tmx on plasma lipid profile in breast cancer patients presenting at tertiary care hospital. This study would be helpful for Breast cancer patients in our population in integration of Tmx and monitoring its impact on cardiovascular risk factors.

MATERIAL AND METHODS

It was a longitudinal study conducted at the department of medical oncology of Jinnah Postgraduate Medical Center from December 2018 to November 2019. The sample size was estimated using Open Epi online sample size calculator by taking statistics for LDL value pre-treatment

as 153.77±32.47 mg/dl and post treatment as 132.51±28.33 among post menopause women[3], power of test as 80% and 95% confidence level, the calculated sample size came out as 88. All the females of age 26–66 years diagnosed with breast cancer were included in the study using non-probability consecutive sampling technique. Females having hormone receptor negative breast cancer, pre-existing endometrial carcinoma, thyroid dysfunction, diabetes mellitus, hypertension or renal or liver impairment were excluded from the study. Patients on cholesterol reduction medication or having pregnancy were also excluded. The ethical review committee approval was sought before the conduct of study. Informed written and verbal consent was taken from all the patients. Detailed gynaecological and clinical investigations and detailed history were noted of all the females. The blood samples of all the females were collected and plasma lipid profile was measured before initiation of Tamoxifen treatment, at three months and finally six months post treatment at clinical laboratory. The plasma lipid profile includes the measurement of serum cholesterol, Triglyceride, low density lipoprotein & high-density Lipoprotein. SPSS version 23 was used to analyse data. Mean & SD was reported for all continuous variables whereas frequencies & percentages were computed for all qualitative variables. Paired t-test was used to compare pre and post measurements of plasma lipid profile. $p<=0.05$ was taken as statistically significant.

RESULTS

In the present study total of 88 females with breast cancer were enrolled. The mean age & BMI of the patients were reported as 43.7±9.42 years & 29.7±16.17 kg/m^2. Half of the females were Urdu speaking (51.1%) & multipara (81.1%). About 70.5% of the females had post-menopausal status, 59.1% had stage 2 and 65.9% had intermediate grade of tumour. Fifty-eight females showed no family history of Breast cancer and 79.5% had positive nodal status. In 56 females left side of the breast was involved and the most common pathological type of breast tumour was invasive ductal (94.3%). The hormonal status such as ER, PR, and Her 2 Neu were found positive in 96.6%, 93.2% and 18.2% patients respectively. Most of the patients (92%) received adjuvant setting and 94.3% had chemotherapy exposure. (Table-1) After treatment there was significant reduction in serum cholesterol & LDL level by 20.54 mg/dl & 16.46 mg/dl at 3 months ($p< 0.05$), moreover there was significant increase in Triglyceride by 22.14 at 3 months ($p<0.05$). No significant difference was observed in high density lipoprotein level at 3months after using Tamoxifen. At 6 months there was significant reduction in serum cholesterol & Low-density lipoprotein by 32.29 mg/dl and 24.11 mg/dl at 6 months ($p<0.05$), moreover there was significant increase in Triglyceride level by 42.19 mg/dl at 6 months ($p<0.05$). No significant difference was observed in high density lipoprotein level at 6 months after using Tamoxifen. In premenopausal females after administration of Tamoxifen therapy for 6 months, there was significant decrease in serum cholesterol levels by 27.95 mg/dl and Low-density protein level by 22.37 mg/dl at 6 months, whereas triglyceride level increased by 41.1 mg/dl ($p<0.05$). Similarly in postmenopausal, there was also significant decrease in serum cholesterol levels by 42.61 mg/dl and Low-density lipoprotein level by 28.27 mg/dl at 6 months, whereas triglyceride level increased by 44.76 mg/dl ($p<0.05$). (Table-3)

The most frequent side effects due toxicity of Tamoxifen were reported as hot flashes in 43.5%, vaginal discharge in 29% and weight gain in 9.7% in premenopausal women, while In post-menopausal, most of the females experienced vaginal discharge (38.5%) followed by hot flashes (26.9%) and weight gain (7.7%).

Table-1: Baseline characteristics of study participants (n=88)

Quantitative variables	**Mean**	**SD**	**Qualitative variables**	**n**	**%**
Age (years)	43.7	9.42	**Family History of breast cancer**		
BMI (kg/m^2)	29.7	16.17	Yes	30	34.1
Qualitative variables	**n**	**%**	No	58	65.9
Ethnicity			**Nodal status**		
Urdu	45	51.1	Yes	70	79.5
Sindhi	16	18.2	No	18	20.5
Punjabi	11	12.5	**Site of breast**		
Pushto	11	12.5	Right	32	36.4
Balochi	3	3.4	Left	56	63.6
Other	2	2.3	**Pathological type of tumour**		
Parity			invasive Ductal	83	94.3
Null	21	23.9	ductal carcinoma in situ	1	1.1
1	4	4.5	invasive Lobular	4	4.5
2	11	12.5	**Hormonal status**		
More than 2	52	59.1	ER +ve	85	96.6
Menstrual Status			PR +ve	82	93.2
Pre menopause	62	70.5	HER 2 NEU +ve	16	18.2
Post menopause	26	29.5	**Treatment setting**		
Stage of Tumour			Adjuvant setting	81	92
2	52	59.1	Palliative setting	7	8
3	30	34.1	**Any other treatment**		
4	6	6.8	Surgery	80	90.9
Grade of tumour			Chemotherapy	83	94.3
Low	4	4.5	Radiotherapy	77	87.5
Intermediate	58	65.9	Hormonal therapy	38	43.2
High	26	29.5			

Table-2: Effect of tamoxifen on plasma lipids profile

LIPID PROFILE	Pre-treatment (Baseline)		At three months			Post-treatment (After 6 months)		*p*-value
	Mean	SD	Mean	SD	*p*-value	Mean	SD	
Serum cholesterol	185.97	20.17	165.43	21.07	0.001	153.68	17.9	0.001
Triglyceride	155.86	45.66	178	40.39	0.001	198.05	40.98	0.001
HDL	37.63	7.27	38.61	5.28	0.203	37.45	3.58	0.829
LDL	117.7	13.68	101.24	15.14	0.001	93.59	10.7	0.001

Table-3: Mean change in plasma lipids among pre-menopausal and postmenopausal patients of breast cancer after treatment with tamoxifen

Menstrual Status	Lipid profile	Pre-treatment (Baseline)		Post-treatment (After 6 months)		*p*-value
		Mean	SD	Mean	SD	
Pre menopause (n=62)	**Serum cholesterol**	184.42	21.07	156.47	18.58	0.001
	Triglyceride	152.19	48.49	193.29	45.38	0.001
	HDL	37.60	7.23	37.76	3.62	0.864
	LDL	116.60	12.36	94.23	9.51	0.001
Post menopause (n=26)	**Serum cholesterol**	189.65	17.70	147.04	14.41	0.001
	Triglyceride	164.62	37.49	209.38	25.10	0.001
	HDL	37.69	7.50	36.73	3.45	0.571
	LDL	120.35	16.37	92.08	13.21	0.001

DISCUSSION

Breast cancer is the most frequent malignancy, a global health issue and a leading cause of mortality among women.[15] Tamoxifen has been used as the main stay for the treatment of females with hormone-positive breast cancer since the year 1970s.[16] Tamoxifen interacts with oestrogen-dependent propagation of cancer cells in the breast and shows a positive effect on plasma lipid profiles. Researchers showed that with utilization of Tamoxifen, independent of lymph node or menopausal status, chance of recurrence of ER positive breast cancer is diminished to half and causes 28% reduction in death rates.[17] In the present study the effect of Tamoxifen on plasma lipid profile in breast cancer patients was evaluated.

In the present study, the serum cholesterol level significantly decreases from baseline 185.97±20.17 mg/dl to 153.68±17.90 mg/dl at 6 months after treatment with Tamoxifen (p<0.05).

In the study by Lin C *et al*. found that serum total cholesterol level significantly decreases by 17.19 mg/dl from 196.71±36.58 to 179.58±35.50 after treatment with Tamoxifen for four weeks (p<0.05)[18] *et al*., Lewis S & Markopoulos C *et al*. also found the significant reduction in total cholesterol level after intervention of Tamoxifen in their researches.[19–21] However, dissimilar results were observed in study by Hozumi *et al*. concluded that there is no change in total cholesterol level after the therapy with Tamoxifen.[22]

In the present study, the Triglyceride level significantly increased by 42.19 mg/dl from baseline 155.86±45.66 mg/dl to 198.05±40.98 after six months of treatment with Tamoxifen (p<0.05). In another similar study by Ali ZAM *et al*. found serum TG level decrease by 20.9 mg/dl from baseline 120.8–95.5 mg/dl after 3 months of adjuvant Tamoxifen treatment (p<0.001).[6] Whereas Markopoulos C *et al*. in their study found that serum TG levels significantly raised from baseline after one year of Tmx therapy.[21] In another study by Liu CL *et al*. also showed significant increase in TG level at 15 months after therapy with Tmx, however, the extent of increase was insignificant clinically in 102 patients.[18] Gupta S *et al*. & Lin C *et al*. found that TG level didn't reduce and showed no significant change in TG level pre & post Tmx therapy.[3,18]

The high HDL levels also identified as the "good cholesterol", protect against cardiac disease whereas it is also related with increased incidence of breast cancer.[23] In the present study no significant change was observed in mean HDL level at 3 and 6 months after using Tamoxifen (p>0.05). Lin C *et al*. found reduction of 2.68 mg/dl in HDL level from baseline after Tmx treatment (18). In Phase 1 trial by Goetz MP *et al*. found the median change of -3.5mg/dl over the time (IQR: −53 to 20 mg/dL).[24] Whereas Ali ZAM *et al*. found that HDL level significantly increases by 10mg/dl after 3 months of adjuvant Tamoxifen treatment from baseline 45mg/dl to 49.5 mg/dl (p=0.001).[6] In a study by Gopinath M et al. evaluate the efficacy of Tamoxifen versus controls which showed no statistically significant relation in HDL levels among breast cancer patients.[25]

The decrease in level of Low-density lipoprotein reduces the chances of cardiovascular events among females by almost 46%.[14] In the present study, there was significant reduction in Low density lipoprotein level by 24.11 mg/dl at 6 months (p<0.05). Similar results have been observed in the studies by Gupta S et al., Lin C *et al*., Markopoulos C *et al*.,

Gaibar M et al. and Gopinath M *et al*. that Low density lipoprotein level significantly decrease after the use Tamoxifen (p<0.05).[3,18,21,25,26] However, no significant difference was observed in Low density lipoprotein level before and after treatment with Tamoxifen in the study by Ali ZAM *et al* (p>0.05).[6] In the present study the effect of Tamoxifen on plasma lipid profile was stratified with respect to menstrual status and found that there was significant decrease in serum cholesterol levels and Low density lipoprotein level, whereas Triglyceride level significantly increased at 6 months (p<0.05) among both pre and postmenopausal women however High density lipoprotein level remains insignificant among them. Gupta S *et al*. in their study found significant decrease in total cholesterol and Low density lipoprotein level (p<0.05) at three & six months, whereas triglyceride and high density lipoprotein remain unchanged in pre and postmenopausal breast cancer patients after treatment with Tamoxifen.[3] A comparative trial of Tamoxifen versus aromatase inhibitors was conducted among postmenopausal females by Hong N *et al.* showed that total cholesterol level significantly reduced over the period of one year in women who were taking Tamoxifen as compared to women who were taking aromatase inhibitors, moreover High density lipoprotein level in both groups raised slowly over the duration of 1 year and no significant change was found between both groups for High density lipoprotein & Triglyceride levels.[27] In a large clinical trial by Cancer Research UK found better outcomes among females who received Tamoxifen for five years as compared to those who received two years of Tamoxifen therapy and the advantages of five year use of Tamoxifen were observed in both premenopausal and postmenopausal females.[28]

The adverse effects of Tamoxifen influence the quality of life and adherence to therapy in breast cancer patients.[29] Females of age more than 55 years are at higher risk of having deep vein thrombosis, stroke, uterine cancer & pulmonary embolism post Tamoxifen treatment, however more common side effects of Tamoxifen are vaginal discharge and hot flashes.[30] In the present study, the common side effects due toxicity of Tamoxifen were reported as hot flashes, vaginal discharge & weight gain in both premenopausal and postmenopausal females. Lorizio W *et al*. conducted a study to identify the side effects of Tamoxifen and found that 64% females experienced hot flashes, followed by sleep problems (36%), dryness in vagina (35%) and 6% had experienced depression, weight gain, mood swings or irritability.[31] Gupta S *et al*., showed hot flashes in 14.28% & 17.75%, night sweating in 7% & 11%, vaginal discharge in 7.14% & 7.1% and pruritis vulvae in 14.28% 5.91% of the pre and post-menopausal females.[3]

CONCLUSION

Total cholesterol and Low-density Lipoprotein levels showed significant reduction over the period of six months from the baseline with the use of tamoxifen. Hence Tamoxifen should be considered to have an added advantage on lipid metabolism and therefore, can reduce the risk of cardiovascular events.

AUTHORS'S CONTRIBUTION

Bhunisha: Conception and design of study, Developed the methodology. GH: Review it critically for important intellectual content and made the final changes. ZS: Literature review and data collection. PM: Analysis and interpretation of data. PK: Literature review, wrote the manuscript. RR: Data collection and interpretation.

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