ORIGINAL ARTICLE

ASSOCIATION OF WEIGHT CHANGE IN BREAST CANCER PATIENTS UNDERGOING TAMOXIFEN TREATMENT AT A TERTIARY CARE CENTRE, SINDH, PAKISTAN

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Background: Tamoxifen is a selective oestrogen receptor modulator; in the breast, it decreases the growth and proliferation of breast epithelial cells. We assessed the weight change after Tamoxifen use in breast cancer patients. **Methods:** This was a single-centred, prospective, observational cohort study. All patients diagnosed with breast cancer with ER and/or PR positivity were enrolled in the study. Out of these, 90 patients who have been prescribed Tamoxifen treatment either in adjuvant or palliative setting gave their consent to participate. Demographic data, treatment plan, menstrual status, weight, BMI, serum fasting lipid profile, change in diet, and change in physical activity were recorded at the time of diagnosis and then quarterly until 1 year of treatment. Results: A mean age of 42.12±8.5 years was reported, and the mean weight was 62.22±10.6 kg. The majority of the patients, i.e., 68 (75.55%) had advanced tumour stages (III and IV). The study reported that the mean weight of the patients changed significantly at different time intervals during the treatment course (p<0.0005). Moreover, there was an upward trend in weight from the time of starting Tamoxifen to 3-months (62.22±1.51 kg vs 62.88±1.45 kg, respectively). There was a statistically significant increase in weight at 6-month, 9-month, and 12-month of Tamoxifen treatment (63.72±1.46 kg, 64.35±1.42 kg, 65.12±1.44 kg, respectively). Also, most of the patients gained weight as time passed by. **Conclusion:** This study indicated that Tamoxifen has a significant correlation with the increase in weight in hormone receptor-positive breast cancer patients in our population.

Keywords: Tamoxifen; Weight change; ER+ and/or PR+

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INTRODUCTION

Breast cancer is one of the most diagnosed cancers in women globally, and accounts for about 30% of all new cases.[1] The incidence rates increased from 2006 to 2015 by approximately 1.8% per year among Asian/Pacific Islander women.[2] In Pakistan, breast cancer has become a huge burden as about 1 in 9 women are estimated to develop breast cancer once in their lifetime.[3]

Among the different molecular subtypes of breast cancer, hormone receptor positive (which means oestrogen receptor–positive and/or progesterone receptor–positive, breast cancer comprises about 75% of all breast cancers.[4] Tamoxifen is a selective oestrogen receptor modulator; in breast tissue it blocks the transcriptional activity of oestrogen receptors by directly binding to them that leads to decrease in growth and proliferation of breast cancer epithelial cells.[5]

Tamoxifen is the most widely used hormonal therapy in breast cancer worldwide.[6] It decreases progression of breast cancer in women. However, it has recently been observed that patients who are on tamoxifen treatment often remain unaware of its possible side effects. Therefore, it is essential to counsel the patients about these side effects so that they can prepare themselves emotionally, hence, improve treatment compliance.[7]

Several studies showed that adherence to Tamoxifen is often suboptimal, ranging from 53–86%.[8–10] The long-term use of Tamoxifen may result in certain side effects that may lead to its non-adherence. In both pre- and post-menopausal women, the use of endocrine treatment is associated with changes in weight during the first two years of treatment.[11] However, changes in weight associated with the Tamoxifen use is a debatable issue.

There have been many studies reporting on the effects of Tamoxifen on weight change, but there is no data available to address this issue in our population, hence we have prospectively assessed the effects of Tamoxifen on weight change in breast cancer patients coming to tertiary care centre Jinnah Postgraduate Medical Centre, Karachi.

MATERIAL AND METHODS

This was a cohort study conducted at the Oncology Ward of Jinnah Postgraduate Medical Center, the largest public sector tertiary care hospital in Karachi. All patients referred to oncology ward of Jinnah Postgraduate Medical Center, Karachi, Pakistan between June 21, 2017 to July 1, 2019 for the diagnosis and management of breast cancer participated in the study. Patients were selected using non-probability convenience sampling technique. Ethical approval from Institutional Review Board (IRB) was taken from JPMC Research Department. The inclusion criteria for the present study was histologically proven breast cancer patients who presented at Oncology Department, JPMC during the study period between 2017 and 2019. Informed verbal and written consent were procured from the patients prior to the data collection process.

Data was collected using a pre-defined pro forma and retrieved patient's sociodemographic profile, tumour site, and histological grade at the time of diagnosis. Weight and height of patients were also recorded at each follow-up visit, which was measured by a trained nursing staff who had an experience of more than 5 years and was blinded to the objectives of the study. Electronic weight machines and inch tape were used to measure weight and height, respectively. Baseline laboratory tests, lipid profile tests, and tamoxifen dose and compliance of the patients were also registered. Any change in diet or physical activity were self-reported by the patients. The patients were asked to maintain a diary of their routine activities and their daily diet. Any adverse events or effects were recorded.

Initially 250 patients diagnosed breast cancer patients with hormone positive status were enrolled in the study. Out of these 90 patients participated in this study who were started on Tamoxifen either in adjuvant or in palliative setting. The patients were followed up for a year and their weight, serum fasting lipid profile, change in diet and change in physical activity were observed during their visit at baseline then 3, 6, 9 and 12 months. The weight changes were correlated with the time period during Tamoxifen study.

Data were analysed through SPSS version 20 using Repeated Measure ANOVA with a Greenhouse-Geisser correction to observe statistical significance between the weight changes and period of Tamoxifen treatment. A p-value of <0.05 was set as statistical cut-off for significance.

RESULTS

We included ninety patients in this study. The mean age and standard deviation (SD) of the patients was found to be 42.12 (8.5) years and mean weight (SD) was 62.22 (10.6) kg. Majority of the patients, i.e., 68 (75.55%) belonged to advanced tumour stages (III and IV) and more than half of them were pre-menopausal 56 (62.22%). Table 1 summarize the detailed demographics of participants of the study. Table-2 indicates the mean weight of the patients at the time of diagnosis (62.22 kg), 3 months (62.88 kg), 6 months (63.72 kg), 9 months (64.35 kg), and 12 months (65.12 kg) of Tamoxifen treatment.

Table-3 demonstrates the results of repeated measures ANOVA with a Greenhouse-Geisser correction. The statistical test determined that mean weight differed significantly between timepoints {F (1.529, 136.059) = 36.265, $p<0.0005$}. Post hoc tests using the Bonferroni correction revealed that there is an increase trend in weight from the time of starting Tamoxifen to 3-months of its treatment (62.22±1.51 kg vs 62.88±1.45 kg, respectively), which was statistically significant (p = .044). The test also revealed that there is statistically significant increase in weight at the 6-month, 9-month, and 12-month of Tamoxifen treatment (63.72±1.46 kg; p=0.000, 64.35±1.42 kg; p=0.000, 65.12±1.44 kg; p=0.000, respectively. Figure-1 demonstrates the number of patients with the change in weight at different time intervals of Tamoxifen treatment. The weight changes were divided into four categories namely weight loss (less than -1 kg), stable (between -1 and 1 kg), moderate weight gain (more than 1but less than 4 kg) and severe weight gain (more than 4 kg). During the Tamoxifen treatment when the weight of the patients is measured at 3 months, Weight (3mo.); only 5 patients had weight loss, 63 had stable weight, 20 had a moderate weight gain and 2 of them suffered severe weight gain. Measurements at 6^{th} months Weight (6mo.): reveal that out of 90 patients, 5 were still in weight loss category, 31 were stable, 48 had a moderate weight gain and 6 gained weight more than four kilograms. Study at the ninth months and twelfth month showed that number of patients in the categories of weight loss and severe weight gain remained more or less the same. The trend in latter half year change drastically. Number of patients with the stable weight at 6^{th} and 12^{th} month were only 16 and 10, respectively. The number of patients with weight gain of one to four kilograms grew to 60 and 64, respectively.

Table-4. shows mean weight (SD) at diagnosis, 3 months, 6 months, 9 months, and 12 months of treatment was assessed according to the Stage of cancer, it revealed that the mean weight of patients with stage 4 remains stable until 6 months of Tamoxifen treatment. It also shows that there is significant increase trend in weight from 6 months to 9 months and then from 9 months to 12 months (p-value <0.05). In postmenopausal women, the mean weight + at diagnosis, 3 months, 6 months, 9 months, and 12 months of treatment was 64.3 + 15.2 kg, 63.9 + 13.2 kg,

64.7 + 14.5 kg, 65.5 + 13.6 kg, and 65.9 + 13.0 kg, respectively. Post-menopausal women were heavier than pre-menopausal women. Furthermore, in this study the increase in weight has no correlation with change in physical activity and change in diet (p. value> 0.05). Additionally, with Tamoxifen there was significant reduction in fasting serum cholesterol by 32.29mg/dl at 12 months (p< 0.05). Moreover, there was significant reduction in Triglyceride & Low-density lipoprotein level by 42.19 mg/dl and 24.11 mg/dl at 12 months (p<0.05) respectively. However, no significant difference was observed in High density lipoprotein level at 12 months after using Tamoxifen.

Table-1: Demographic& clinical history of patients (n=90)

Age (years)	42.12 ± 7.98
Body Weight, kg	62.22 ± 14.29
Height, cm	153.02 ± 6.76
Age groups	
<40	25 (27.78%)
40-45	40 (44.44%)
>45	25 (27.78%)
Stage	
I	2 (2.22%)
II	20 (22.22%)
III	46 (51.11%)
IV	22 (24.44%)
BMI	
<18.5	6 (6.67%)
18.5-24.9	30 (33.33%)
>25	54 (60%)
Menopausal Status at time of Diagnosis	
Pre-menopausal	56 (62.22%)
post-menopausal	34 (37.78%)
Number of Pregnancies	
0	11 (12.22%)
1	7 (7.78%)
2	11 (12.22%)
>3	61 (67.78%)

Table-2: Mean Weight + SD of participants at diagnosis and follow-ups.

Time Interval	Mean ± St. D
Weight (dx)	62.22 ± 14.29
Weight (3 mo)	62.88 ± 13.74
Weight (6 mo)	63.72 ± 13.84
Weight (9 mo)	64.35 ± 13.49
Weight (12 mo)	65.12 ± 13.7

Table-3: Mean Difference of weight between different time intervals of start of treatment.

time	duration	mean difference	std. error	significance
Weight (dx)	Weight (3 mo)	0.661	0.226	0.044
Weight (dx)	Weight (6 mo)	1.5	0.3	<0.0001
Weight (dx)	Weight (9 mo)	2.133	0.356	<0.0001
Weight (dx)	Weight (12 mo)	2.906	0.449	<0.0001
Weight (6 mo)	Weight (12 mo)	1.406	0.212	<0.0001

Table-4: Mean distribution of weight at diagnosis, 3 months, 6 months, 9 months & 12 months with respect to Tumor stage & menstrual status of participants

	weight (dx)	weight (3 mo)	weight (6 mo)	Weight (9 mo)	Weight (12 mo)
Stage 1	43±9.8	44±7.1	46±1.4	49.5±0.7	51.5±4.9
Stage 2	58.5±14.8	60±14.7	61±14.8	61.9±14.8	63.5±15.1
Stage 3	60.2±8.5	60.2±8.6	61.5±8.1	62.2±8.9	62.3±8.7
Stage 4	67.5±21.6	66.2±18.2	66.7±18.3	67.4±18.6	68±18.7
pre-menopausal	59.3±13	59.7±13.8	60.8±13.2	61.7±12.9	62.4±12.7
post-menopausal	64.3±15.2	63.9±13.2	64.7±14.5	65.5±13.6	65.9±13

Table-5: Percentage of patients with reference to change in physical activity and change in diet

change in physical activity	
yes	11 (12.2%)
no	79 (87.8%)
change in diet	
yes	12 (13.3%)
no	78 (86.7%)

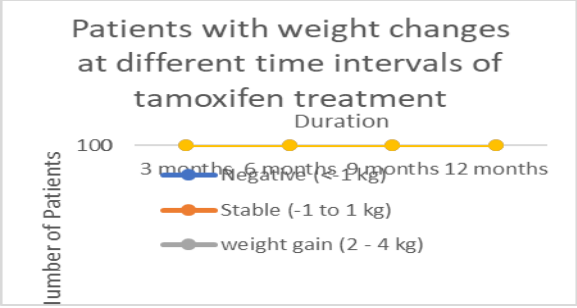

Figure-1: Frequency of patients with weight changes at different time intervals of Tamoxifen Treatment

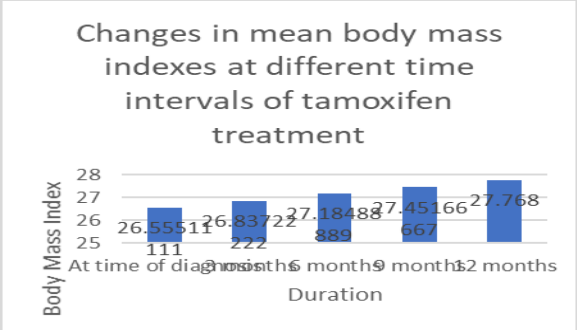

Figure-2: Changes in body mass index at different time intervals of Tamoxifen Treatment

DISCUSSION

The positive effects of Tamoxifen use in breast cancer patients and its role in reducing the recurrence rate has made this drug very popular in the treatment of breast cancer. To find out the duration of Tamoxifen therapy that could prove the most effective in breast cancer patients, a collaborative meta-analysis of individual patient data was carried out in 2011 showing that the use of adjuvant

Tamoxifen therapy over a period of 5 years greatly reduced the 15-year risk of breast cancer recurrence and death.[11] However, a prolonged therapy means more side effects.[12] Numerous studies have reported the undesirable side effects of Tamoxifen therapy like vision problems, vaginal discharge hot flashes, insomnia, joint aches and weight gain.[13,14]

The studies that have reported the weight gain in the patients on Tamoxifen treatment emphasizes the immense need for studies on the pattern of change in weight over the period of Tamoxifen treatment. However, majority of the research on effects of Tamoxifen overweight and BMI has been conducted in the west, particularly USA, it was important to check the effects of Tamoxifen use in Pakistani population. We conducted a simple cross-sectional study with convenience sampling in the largest tertiary care hospital of Karachi. Therefore, the purpose of this study was to explore the relationship between the rate of weight change during Tamoxifen treatment.

The current study highlighted the significance of tamoxifen in breast cancer treatment and its association with weight gain among patients. A statistically significant relationship between weight gain and women receiving Tamoxifen therapy was observed.

Numerous studies have reported the effect of Tamoxifen on weight and BMI. To the best of our knowledge there are no local studies on the relationship of weight gain and Tamoxifen treatment. However, our findings are consistent with an internationally published study carried out by Nyrop KA and colleagues to assess the association of weight change with endocrine therapy use.[14] Descriptive statistics were used to compare pre- and post-menopausal breast cancer patients. The study reported a significant increase in relative risk of weight gain in premenopausal women. Tamoxifen treatment had weight gain significant at all time intervals up to 3 years. When compared, the weight gain in control group was non-significant at nine months and three years and was only marginally significant at three, twenty-four, and thirty months.

As compared to postmenopausal women the weight gain was greater in premenopausal women on Tamoxifen. Again, there was a statistically significant relationship of the absolute weight gain in the tamoxifen group, in both premenopausal and postmenopausal women (premenopausal $p<0.01$, postmenopausal $p<0.05$), but not in the control group.[15] These finding support our study by demonstrating a statistically significant relationship between weight gain and different time intervals of the Tamoxifen treatment.

A study checking the effect of Tamoxifen on body fat distribution was carried out in Korea and found no significant correlation between the two.[16] The subcutaneous and visceral fat thickness was checked via CT in 325 patients who received Tamoxifen vs non-Tamoxifen users and control group. There was no evidence of obesity found in post-operative breast cancer patient on endocrine therapy.

As we have seen that most of these studies were conducted in the west and due to demographic difference results could vary in this region.[17,18] There is a scope of further studies with a controlled group. So, all in all the findings of this study is that there is a statistically significant relationship between the weight change and Tamoxifen treatment.

CONCLUSION

This study shows Tamoxifen has a significant correlation with increase in weight in hormone receptor positive breast cancer patients in our population. Counselling of these patients with respect to this potential side effect and to maintain a healthy weight by balanced diet and exercise is needed.

AUTHORS' CONTRIBUTION

AS: concept development, data collection, write up, proof reading. GH: Proof reading. All other authors contributed equally.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
2. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 2016;17(S3):43–6.
3. Athar A. Knowledge, attitude and practices of Pakistani women for early breast cancer detection. Breast 2018;41:S21.
4. Xia Y, Fan C, Hoadley KA, Parker JS, Perou CM. Genetic determinants of the molecular portraits of epithelial cancers. Nat Commun 2019;10(1):5666.
5. van Seijen M, Lips EH, Thompson AM, Nik-Zainal S, Futreal A, Hwang ES, *et al*. Ductal carcinoma in situ: to treat or not to treat, that is the question. Br J Cancer 2019;121(14):285–92.
6. Thorneloe RJ, Hall LH, Walter FM, Side L, Lloyd KE, Smith SG. Knowledge of potential harms and benefits of tamoxifen among women considering breast cancer preventive therapy. Cancer Prev Res (Phila) 2020;13(4):411–22.
7. Yan Y, Zhang L, Tan L, Ma X, Zhang Y, Shao S, *et al*. Endocrine Therapy for Ductal Carcinoma In Situ (DCIS) of the Breast with Breast Conserving Surgery (BCS) and Radiotherapy (RT): a Meta-Analysis. Pathol Oncol Res 2020;26(1):521–31.
8. Raghavendra A, Sinha AK, Valle-Goffin J, Shen Y, Tripathy D, Barcenas CH. Determinants of weight gain during adjuvant endocrine therapy and association of such weight gain with recurrence in long-term breast cancer survivors. Clin Breast Cancer 2018;18(1):e7–13.

9. Zhang X, de Oliveira Andrade F, Zhang H, Cruz I, Clarke R, Gaur P, *et al*. Maternal obesity increases offspring's mammary cancer recurrence and impairs tumour immune response. Endocr Relat Cancer 2020;27(9):469–82.
10. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Caviglia S, Avino F, Cortesi L, *et al*. Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. J Clin Oncol 2019;37(19):1629–37.
11. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, *et al*. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378(9793):771–84.
12. Zivian MT. 2–60 Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective. Breast Dis 2007;2(18):201–2.
13. Nyrop KA, Lee JT, Deal AM, Ki Choi S, Muss HB. Weight-Related Communications Between Oncology Clinicians and Women with Obesity at Early Breast Cancer Diagnosis: Findings From a Review of Electronic Health Records. Nutr Cancer 2020;72(4):576–83.
14. Nyrop KA, Deal AM, Lee JT, Muss HB, Choi SK, Wheless A, *et al*. Carey LA, Shachar SS. Weight gain in hormone receptor-positive (HR+) early-stage breast cancer: is it menopausal status or something else? Breast Cancer Res Treat 2018;167(1):235–48.
15. Hoskin PJ, Ashley S, Yarnold JR. Weight gain after primary surgery for breast cancer-effect of tamoxifen. Breast Cancer Res Treat 1992;22(2):129–32.
16. Kim KW, Kim HA, Park JC, In HU, Oh BH. Prevalence of Obesity in Patients with Postoperative Breast Cancer: Effect of Tamoxifen and Abdominal Fat Distribution on Computed Tomography. Korean J Fam Med 2016;6(3):148–54.
17. Pan HJ, Chang HT, Lee CH. Association between tamoxifen treatment and the development of different stages of nonalcoholic fatty liver disease among breast cancer patients. J Formos Med Assoc 2016;115(6):411–7.
18. Nyrop KA, Williams GR, Muss HB, Shachar SS. Weight gain during adjuvant endocrine treatment for early-stage breast cancer: what is the evidence? Breast Cancer Res Treat 2016;158(2):203–17.

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