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IMPACT OF LETROZOLE TREATMENT ON LIPID PROFILE IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE EARLY BREAST CANCER: A PROSPECTIVE STUDY

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This prospective study aimed to investigate the impact of letrozole treatment on the lipid profile of postmenopausal early breast cancer patients. Sixty postmenopausal women diagnosed with hormone receptor-positive early breast cancer were enrolled in this study. Lipid profile parameters, including TC, LDL-C, HDL-C, and TG, were measured at baseline and at regular intervals during a one-year treatment period with letrozole (2.5 mg/day). Patients' medical history, including previous treatment with tamoxifen, chemotherapy or radiotherapy, was also recorded. All patients have started zoledronic acid through letrozole treatment. Following 4 months of letrozole treatment, a noteworthy increase was observed in TC (p=0.013) and LDL-C (p=0.006) levels compared to baseline values. These elevations reverted to baseline levels after 8 months of treatment. Intriguingly, the observed delayed shifts in TC and LDL-C levels occurred following treatment with zoledronic acid. Furthermore, TC levels decreased significantly after 12 months compared to baseline (p=0.032). HDL-C levels exhibited no significant changes throughout the monitoring periods. TG levels displayed a significant decline after both 8 and 12 months (p=0.015, p=0.018, respectively). Notably, the prior tamoxifen group displayed more pronounced increases in LDL-C and TC levels after 4 months of AI treatment. In contrast, the previous radiotherapy group showed decreased triglyceride levels after 8 and 12 months compared to baseline levels. Letrozole initiation and/or Tamoxifen withdrawal may have adverse effects on lipid profiles, leading to elevated LDL-C and TC levels. Nevertheless, the administration of antiresorption treatment (zoledronic acid) appears to counteract these effects, contributing to an improvement in the lipid profile.

Keywords:*Breast cancer; Letrozole; Postmenopausal women; Lipid profile*

INTRODUCTION

Female breast cancer is a significant health concern worldwide, with an estimated 2.3 million new cases in 2020 alone, accounting for 24.5% of all cancer cases among women. Shockingly, breast cancer has now exceeded lung cancer as the leading cause of death among women, accounting for 15.5% of all cancer mortality[1]. Hormone receptor-positive (HR+) breast cancer is the most prevalent subtype, representing 60-70% of all cases[2-5]. Tumor growth and progression in HR+ breast cancer are dependent on estrogen receptor (ER) signaling, making deprivation of estrogen a crucial therapeutic strategy for managing the disease[6,7]. This is typically achieved through the inhibition of estrogen biosynthesis or the modulation of ER activity, which has shown promising results in halting tumor growth and improving outcomes for patients[8].

In postmenopausal women with (HR+) breast cancer, the third generation of aromatase inhibitors (AIs) as adjuvant endocrine therapy reduces both the recurrence and mortality rates

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of breast cancer. Therefore, AIs are the endocrine therapy of choice[7]. In postmenopausal women, most estrogen is produced in peripheral tissues (adipose tissues, breast, bone, vascular endothelia and brain). AIs inhibit the activity of aromatase enzyme, which transforms androgens to estrogens by a process called aromatization[9]. The third generation of AIs, which includes reversible nonsteroidal AIs (letrozole, anastrozole) and irreversible steroidal AI (exemestane), blocks approximately 98% of body aromatization and leads to excessive estrogen deprivation[10,11].

Despite the primary goal of AI treatment being to suppress estrogen synthesis, it's important to note that estrogen plays other crucial roles in the body. Postmenopausal women, for instance, are susceptible to experiencing negative effects due to lowered estrogen levels such as changes in their lipid profile[12,13], bone metabolism[14,15], and an increased risk of cardiovascular disease[16]. Hence, it is crucial to understand the multifaceted role estrogen plays in the body and how AI treatment may affect other physiological processes.

The excessive deprivation of estrogen by AI treatment has an adverse effect on bone metabolism. As a result, accelerated bone resorption is a common side effect of AI treatment[17,18], which is managed by bisphosphonate treatment (4 mg zoledronic acid every 3 months for 2 years)[19,20]. Previous studies have examined the effects of letrozole treatment on lipid profiles, providing insights into its potential relevance to cardiovascular health. While some investigations have found no statistically significant changes in lipid profiles[21-23], others have revealed a notable increase in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels[24-27]. These changes may bear significance for atherogenic risk index TC/HDL and LDL/HDL[25,27]. Studying alterations in the lipid profile during AI treatment is crucial, as it allows us to evaluate the need for lifestyle modifications or the prescription of lipid-lowering agents, especially considering the prolonged duration of AI therapy spanning several years.

MATERIALS AND METHODS

Patients

Between February 2021 and March 2022, 81 postmenopausal women with estrogen receptor-positive early breast cancer started treatment with letrozole in the Oncology Center of Tishreen University Hospital as adjuvant initial endocrine therapy or after tamoxifen. The lipid profile (LDL-C, HDL-C, TC, and TG) was measured before starting treatment with letrozole and every four months during treatment.

At the initiation of letrozole treatment, patients received letrozole (2.5 mg) orally every day. Baseline characteristics of the patients were comprehensively summarized, encompassing factors such as age, body mass index (BMI), lipid status, prior chemotherapy, radiotherapy, or endocrine therapy. Pathological results, (including tumor grade, histological classification, tumor size, and lymph node involvement) and immunohistochemical assay results (comprising estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, and Ki-67 expression) were obtained for each patient at baseline. Patients with pre-existing medical conditions such as hypothyroidism, diabetes mellitus, liver or renal failure, and a history of cardiovascular disease were excluded from the analysis. Additionally, Patients taking hypolipemic agents or other medications recognized to impact lipid profiles (like beta-blockers, diuretics, or corticosteroids) were excluded if they commenced these treatments before or during the letrozole regimen. The only allowable concurrent treatment alongside letrozole was bisphosphonate (zoledronic acid 4 mg per 3 months). If a patient stopped taking letrozole due to recurrence or intolerance, lipid profile follow-up was terminated. For inclusion in the statistical analysis, patients were required to have undergone a baseline lipid assessment and at least one additional assessment at either 4, 8, or 12 months.

Sample collection and measurement of lipid profile

The lipid profile was measured at the Central Laboratory of Tishreen University.

Venous blood samples for lipid panel analyses were obtained prior to treatment with letrozole and after 4, 8, and 12 months of treatment after an overnight fast, blood samples were collected into heparinized vials in the morning. TC (CHOD-POD, cholesterol oxidase peroxidase), TG (GPO-POD, glycerol-phosphoric acid oxidase peroxidase), HDL-C (direct method), and LDL-C (direct method) were measured using commercially available colorimetric diagnostic kits from "Biosystems" following the provided instructions.

Ethical approval

All procedures undertaken in this study received approval from the Institutional Board of Tishreen University, as evidenced by Ethical Approval No. 510 of 1/12/2020. Written informed consent was obtained from all participants prior to their involvement.

Statistical analysis

Descriptive statistics, including mean, standard deviation, and range, were employed to summarize the lipid parameters at baseline and throughout the letrozole treatment.

To assess the normality of the data distribution, the Shapiro–Wilk test was applied. Subsequently, paired sample t-tests or Wilcoxon signed rank tests were utilized to make comparisons between multiple time points. To ensure rigorous analysis, patients were categorized into groups based on their prior treatment, and lipid profile comparisons were performed within each group to assess any changes in lipid parameters. In this analysis, statistical significance was determined using a p value threshold of ≤ 0.05. The Holm– Bonferroni correction was employed to address the issue of multiple comparisons and reduce the potential for false positives.

RESULTS AND DISCUSSION

Results

Study population

In this study, eighty- one postmenopausal women with early breast cancer were initially enrolled. However, only 60 patients were included in the lipid analysis. Among these patients, complete follow-up data was available for 59 individuals at 4 months, 50 individuals at 8 months, and 51 individuals at 12 months. All patient initiated bisphosphonate treatment (zoledronic acid) after 4 or 6 months of commencing letrozole therapy. Baseline characteristics are the included patients of summarized in **Table 1**.

Lipid parameter comparisons

Lipid parameter comparisons were conducted to assess the impact of letrozole administration on patients' lipid profiles. The findings are summarized in **Table 2**, which presents the total number of patients and their lipid parameters at different time points.

After 4 months of letrozole treatment, a notable increase (p=0.013, 11.5 mg/dl) in total cholesterol (TC) levels was observed compared to the baseline levels. However, TC levels returned to baseline after 8 months (p=0.09) and showed a significant decrease after 12 months (p=0.032, 13 mg/dl) when compared with baseline.

Furthermore, low-density lipoprotein cholesterol (LDL-C) levels exhibited a significant increase after 4 months (p=0.006, 14 mg/dl) but returned to baseline levels after 8 and 12 months (p=0.77, p=0.9). Conversely, high-density lipoprotein cholesterol (HDL-C) levels did not demonstrate any significant changes after 4, 8, and 12 months compared to the baseline levels.

Regarding triglyceride (TG) levels, no significant changes were observed after 4 months (p=0.625). However, there was a significant decrease after 8 months (p=0.015, 23 mg/dl) and 12 months (p=0.018, 26 mg/dl) when compared to the baseline.

Furthermore, the visual representation of the lipid profile changes can be observed in **Fig. 1**, which displays box plots illustrating the levels of lipid profile parameters at each time point.

Table 1: Baseline characteristics.

Age mean (range)	54.5 (39-77)
(years)	
BMI mean (SD)	27.4 (4.3)
(kg/m^2)	
grade	
I	10
II	35
III	15
Histological classification	
IDC	49
IDC+DCIS	3
ILC	6
ILC+IDC	1
mucinous	1
Tumour size (T)	
T1	17
T2	37
T3+T4	4
non available	2
Lymph nodes (N)	
N0	14
N1	25
N2	6
N3	11
non available	4
ER	
positive	58
negative	2
PR	
positive	47
negative	13
HER2 overexpress	
yes	6
no	54
Ki 67	
14%>	22
14-19%	1
20%≤	16
non available	21
Antitumour prior therapy	
Chemotherapy	57
Radiotherapy	39
Tamoxifen	14
Immunotherapy (Herceptin)	6
No prior therapy	1

Abbreviations: BMI: body mass index, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, DCIS: ductal carcinoma in situ, ER: estrogen receptor, PR: progesterone receptor and HER2: human epidermal growth factor receptor 2.

Table 2: Comparison of lipid parameter levels at each time point.

Lipid profile	Time	n	mean ± SD (Range)	Change	*P* value
TC (mg/dl)	initial level	60	202.38 ± 31.96 (143)		
	4 months	59	214.34 ± 34.88 (215)	11.5	0.013
	8 months	50	194.26 ± 32.1 (140)	-9.4	0.09
	12 months	51	190.18 ± 32.44 (145)	-13	0.03
LDL-C (mg/dl)	initial level	60	120.49 ± 26.41 (109)		
	4 months	59	135.45 ± 30.5 (169.4)	14.4	0.006
	8 months	50	122.78 ± 27.66 (111.4)	1.2	0.8
	12 months	51	117.8 ± 26.76 (119)	-3.3	0.9
HDL-C (mg/dl)	initial level	60	56.14 ± 16.3 (80)		
	4 months	59	56.72 ± 14.2 (57.8)	1.7	0.67
	8 months	50	55.35 ± 10.6 (52.3)	0.8	0.34
	12 months	51	55.23 ± 11.92 (58.7)	-0.5	0.69
TG (mg/dl)	initial level	60	164.07 ± 75.95 (376)		
	4 months	59	160.41 ± 63.21 (308)	-4.14	0.62
	8 months	50	149.95 ± 62.83 (320.5)	-23	0.015
	12 months	51	141.8 ± 61.19 (268)	-26.9	0.018

Change is mean of changes from baseline, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride.

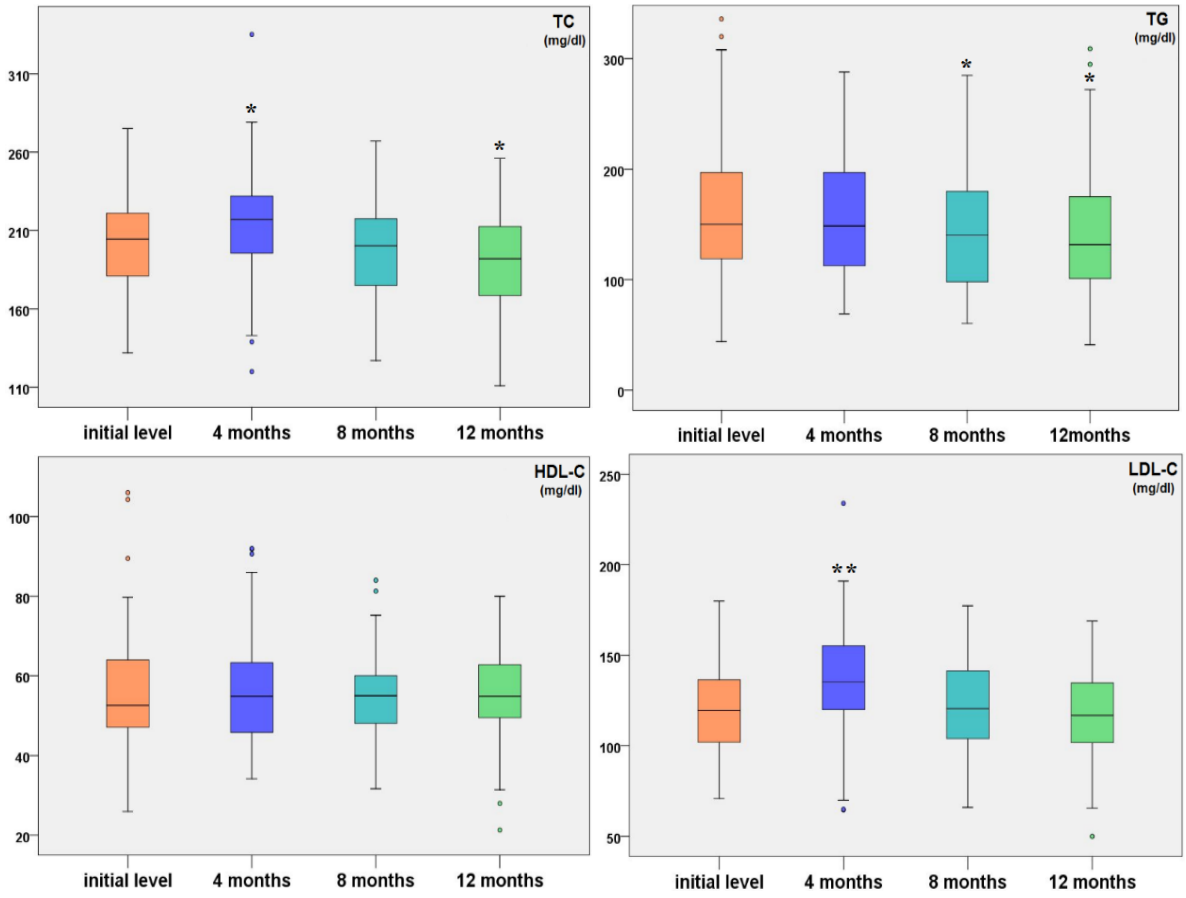

Fig. 1: Comparing Lipid Status Levels at Different Time Points with Baseline**, ***: p<0.05, ****: p<0.01.

Relationship between lipid parameters and immediate preceding letrozole therapy

The distribution of patients in our study according to the immediate preceding letrozole therapies was as follows:

15 patients received chemotherapy (CHEM), 25 patients received radiotherapy (RT), 14 patients received tamoxifen (TAM), 5 patients received herceptin (IT), and 1 patient don't received any previous therapy. Only the patients in the first three groups (CHEM, RT, and TAM) enrolled in statistical analysis to assess the impact of these prior therapies on lipid profile (**Fig. 2**).

For patients with prior use of tamoxifen, LDL-C and TC levels exhibited a significant increase after 4 months (p=0.005, 33 mg/dl; p=0.025, 28 mg/dl respectively), returning to baseline levels after 8 and 12 months. However, these changes were not observed in patients with prior chemotherapy and radiotherapy. In contrast, HDL-C levels did not display any significant changes after 4, 8, and 12 months compared to the baseline levels across all prior therapy groups ($p > 0.05$). Regarding TG levels, no significant changes were observed throughout the study's time points in patients with prior treatment using tamoxifen and chemotherapy ($p > 0.05$). However, patients with prior radiotherapy demonstrated a significant decrease in TG levels after 8 and 12 months (p=0.009, 42 mg/dl; p=0.007, 39 mg/dl, respectively).

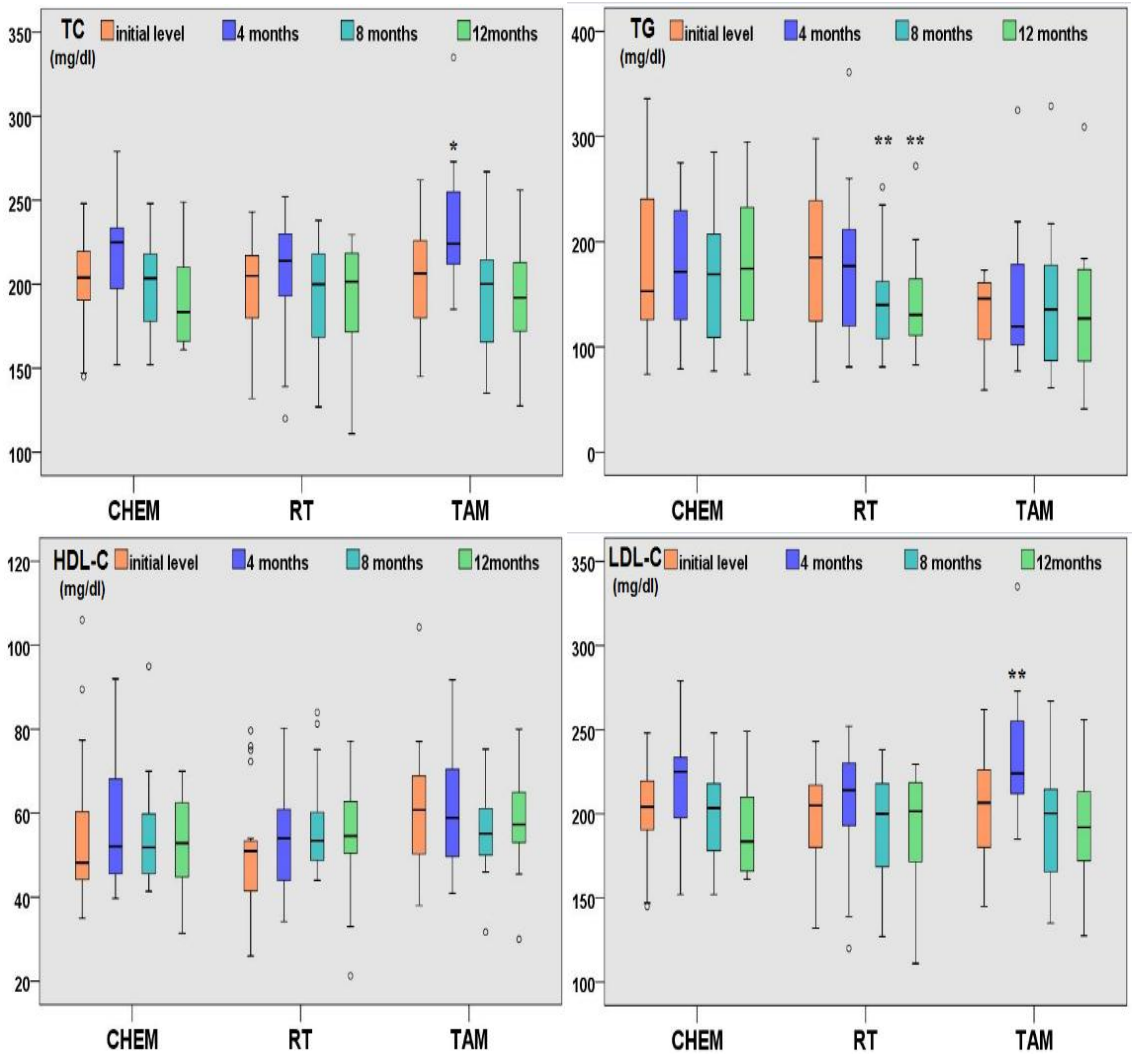

Fig. 2: Comparison of Lipid Parameter Levels over Time Points in Different Prior Therapy Groups. RT: radiotherapy, CHEM: chemotherapy, TAM: tamoxifen, *: p<0.05, **: p<0.01.

Discussion

This study included postmenopausal women early breast cancer who were undergoing endocrine treatment with letrozole, and the lipid profiles were monitored during letrozole treatment, compared to their baseline levels.

The transition to postmenopausal status is accompanied by a decline in estrogen levels, which contributes to the development of an atherogenic lipid profile when compared to premenopausal women[28,29]. Despite this, several studies have indicated that there is no significant correlation between plasma levels of endogenous estrogen in postmenopausal women and their lipid profiles[30,31]. This lack of correlation may be attributed to the fact that peripherally produced estrone plays its metabolic roles at its production sites.

Certain studies have suggested a connection between endogenous androgen levels and lipid profiles among postmenopausal women. Increased levels of Testosterone and free androgen index have been associated with elevated TC and LDL-C levels[32-34].

Endocrine therapy using letrozole for postmenopausal women with breast cancer inhibits the aromatase enzyme, causing a decline in estrogen levels[10,11] and a rise in androgen levels[35-37]. These effects may be partially account for the adverse effects on lipid profiles observed after 4 months of treatment including elevation of TC and LDL-C levels. However, after 8 months, both LDL-C and TC levels returned to their baseline values. Intriguingly, after 12 months, TC levels decreased below the initial baseline levels, despite no significant change in LDL-C levels.

These findings are consistent with the studies conducted by Bell *et al.*[25] and Santa-Maria *et al.*[26], which reported an increase in TC and LDL-C levels after 3 months in patients treated with letrozole, and the changes continued for 2 years in the studies by Wazan *et al.*[24] However Shien *et al.*[21] found no significant changes in TC and LDL-C levels during letrozole treatment, while they observed no significant tendency of TC and LDL-C levels to elevate through time points compared with baseline levels.

Regarding prior therapy, our results demonstrated that patients who had discontinued tamoxifen before initiating letrozole experienced more significant increases in LDL-C and TC levels after 4 months compared to other prior therapy groups. This finding is supported by the study conducted by Bell *et al.*[25], which found that prior tamoxifen use was associated with greater increases in LDL-C after 3 months of AI treatment. It is worth noting that, in the study by Wazan *et al.*[24] [24], all patients had a prior tamoxifen therapy, emphasizing the impact of prior tamoxifen use on LDL-C and TC levels. In contrast, the study by Shien *et al.*[21] observed no significant tendency for LDL-C and TC levels to increase compared to baseline, as they excluded patients with prior tamoxifen therapy.

The observed delayed shifts in TC and LDL-C levels occurred following treatment with zoledronic acid, an anti-resorptive bisphosphonate. Zoledronic acid, an amino-bisphosphonate, exerts its effects by inhibiting the mevalonate pathway, thereby suppressing protein prenylation. Consequently, bone-resorbing function diminishes, leading to bone anti-resorptive effects[38,39]. It's important to note in our study that treatment with zoledronic acid began after 4 to 6 months of initiating letrozole treatment. The mevalonate pathway inhibition triggers a reduction in cholesterol biosynthesis[40,41], which may account for the decrease in TC and LDL-C levels after 8 and 12 months of letrozole treatment.

In our study, we did not observe any significant changes in HDL-C levels across different time points or among patients with different prior therapy backgrounds. These findings align with the studies conducted by Shien *et al.*[21] and Cheung *et al.*[42], which also reported no important changes in HDL-C levels during letrozole treatment. However, it is worth noting that some studies, such as those conducted by Wei Tian *et al.*[43] and Wang *et al.*[23], observed a tendency for HDL-C levels to increase during letrozole treatment. These contrasting findings suggest that the impact of letrozole on HDL-C levels may vary among individuals or populations.

Several mechanisms have been proposed to explain the role of TG in the development of atherosclerosis[44]. However, during letrozole treatment, the current study observed a significant decrease in triglyceride levels after 8 and 12 months compared to baseline levels. This finding aligns with a study conducted by

Wei Tian *et al.*[43], who also reported a decrease in TG levels after 12 months compared to baseline levels. However, other studies such as those by Santa-Maria *et al.*[26] and Bell *et al.*[25] did not find significant changes in TG levels during letrozole treatment.

The prior radiotherapy group exhibited a delayed decline in TG levels. A study investigating the impact of irradiation on lipid metabolism in experimental animals revealed the downregulation of PPARα expression, a crucial transcription factor involved in lipid metabolism. Interestingly, PPARα expression was reactivated after several months, leading to the delayed decrease in TG levels[45]. Additionally, Giskeødegård *et al.*[46] conducted a study examining the evolution of patterns of serum lipoprotein subfractions over a year subsequent to breast cancer radiotherapy, with specific emphasis on patients who had previously experienced chemotherapy. Their findings indicated a reduction in both total TG levels and TG associated with very low-density lipoprotein (VLDL) at the final time point among patients who underwent radiotherapy subsequent to chemotherapy.

While some previous studies[25,26] mainly monitored early lipid profile changes 3 months after starting letrozole treatment, our study, like those of Shien *et al.*[21] and Wazan *et al.*[24], extended the monitoring to a year or more, providing a more comprehensive view. What sets our study apart is the inclusion of patients treated with zoledronic acid, a common therapy for postmenopausal breast cancer patients using aromatase inhibitors. This aspect was not consistently addressed in prior studies. Moreover, while some research, such as the Bell *et al.*[25] study, has explored the impact of prior tamoxifen treatment on lipid profiles, our study also revealed a potential effect of prior radiation therapy on triglyceride levels during letrozole treatment, an aspect not previously addressed in this context.

However, the effect of aromatase inhibitor treatment on lipid metabolism cannot be denied. Our study has shown that, at least to some extent, there is a tendency for an increase in TC and LDL-C levels after 4 months of aromatase inhibitor treatment in the study cohort and in each previous treatment arm. It is worth noting that individual genetic differences may influence letrozole's effect on lipid metabolism[26,47], as well as its pharmacokinetics and plasma concentrations[48], affecting efficacy and side effects.

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تأثير المعالجة بالليتروزول على الصيغة الشحمية لدى النساء بعد انقطاع الطمث والمصابات بسرطان الثدي المبكر إيجابي المستقبلات الهرمونية: دراسة مستقبلية

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هدفت هذه الدراسة المستقبلية إلى دراسة تأثير المعالجة بالليتروزول على الصيغة الشحمية لدى مريضات سرطان الثدي المبكر في مرحلة بعد انقطاع الطمث. شملت الدراسة ستين سيدة بعد انقطاع الطمث تم تشخيصهن بسرطان الثدي المبكر إيجابي المستقبلات الهرمونية. تم قياس متغيرات الصيغة الشحمية والتي شملت الكوليسترول الكلي (TC) وكوليسترول البروتين الشحمي منخفض الكثافة (LDL-C) وكوليسترول البروتين الشحمي مرتفع الكثافة (HDL-C) والشحوم الثلاثية (TG) قبل بدء المعالجة بالليتروزول (٢.٥ ملغ/يوم) ومتابعتها خلال فترة المعالجة بالليتروزول كل ٤ أشهر لمدة عام واحد. تم تسجيل المعالجة السابقة لليتروزول والتي شملت معالجة هرمونية بالتاموكسيفين أو معالجة الكيميائية أو معالجة الإشعاعية. خلال المعالجة بالليتروزول بدأت جميع المريضات المعالجة بحمض الزولدرونيك. بعد ٤ أشهر من المعالجة الليتروزول تمّ تسجيل ارتفاع هام في مستويات TC (p=0.013) وLDL-C (p=0.006) مقارنة مع المستويات البدئية وعادت إلى مستوياتها البدئية بعد ٨ أشهر. الجدير بالذكر أن التغيرات المتأخرة المُلاحظة في مستويات TC وLDL-C ظهرت بعد بدء المعالجة بحمض الزولدرونيك. بالإضافة لذلك انخفضت مستويات TC بشكل كبير بعد ١٢ شهراً مقارنة مع المستويات البدئية (p=0.032). لم تظهر مستويات HDL-C تغيرات هامة خلال فترات المتابعة. أما مستويات TG فقد أظهرت انخفاضاً هاماً بعد ٨ و١٢ شهراً (p=0.015، p=0.018، على الترتيب). كان الارتفاع في مستويات TC وLDL-C بعد أربعة أشهر أكثر وضوحاً في مجموعة المعالجة السابقة بالتاموكسيفين مقارنة مع مجموعتي المعالجة السابقة الإشعاعية والكيميائية. كما أظهرت مجموعة المعالجة الإشعاعية السابقة انخفاضاً في مستويات TG بعد ٨ و١٢ شهراً مقارنة مع مستوياتها البدئية ولم تُلاحظ تغيرات هامة في مجموعة المعالجة الكيميائية. يمكن أن يكون لبدء استخدام الليتروزول و/أو إيقاف استخدام التاموكسيفين تأثيرات سلبية على الصيغة الشحمية، مما يؤدي إلى زيادة مستويات TC وLDL-C. مع ذلك يبدو أن المعالجة المُثبطة لارتشاف العظم (حمض الزولدرونيك) تساهم في تراجع هذه التأثيرات، مما يؤدي إلى تحسين الصيغة الشحمية.