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Aromatase inhibitors versus tamoxifen: serum biochemical profile and imaging studies in Latin American women with ER$^+$ breast cancer

Inibidores de aromatase versus tamoxifeno: perfil bioquímico sérico e exames de imagem em mulheres latino-americanas com câncer de mama RE$^+$

Inhibidores de la aromatasa versus tamoxifeno: perfil bioquímico sérico y análisis de imágenes en mujeres latinoamericanas con cáncer de mama RE$^+$

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ABSTRACT
The estimated global incidence of new breast cancer cases is 2.26 million, and 75% of these cases are estrogen receptor positive (ER^+). Treatment involves the use of tamoxifen (TX) or aromatase inhibitors (AIs), such as anastrozole and letrozole. The use of these medications is associated with changes in blood cholesterol levels and hepatic steatosis, and TX promotes steatosis more than AIs. Thus, the aim of this study was to determine the effect of TX and AIs on the incidence of hepatic steatosis and on biochemical markers in women with ER^+ breast cancer. A cross-sectional study was performed between 2021 and 2024 comprising 38 women with ER^+ breast cancer who received TX or AIs in a public hospital in Brazil. Primary data were collected through interviews and secondary data were obtained through medical records, including blood count, lipid profile, liver profile, and ultrasound (US) results. Of the 34 women with ER^+ breast cancer, with a mean age of 56.67 ± 12.38 years, those who used AIs had higher LDL (Low-density lipoprotein) ($p < 0.001$), MCV (Mean corpuscular volume) ($p = 0.033$), NEU (Segmented neutrophils) ($p = 0.044$), and ALP (Alkaline phosphatase) ($p = 0.019$) values than those in the TX Group, all throughout the treatment. The women who had hepatic steatosis at baseline based on US had no changes after treatment. Our results suggest that adjuvant therapy for ER^+ breast cancer in women was not associated with an increase in liver enzymes, with the exception of ALP, or the development of hepatic steatosis. However, Ais increased LDL values, a fact that should be considered when choosing the treatment, especially in women with risk factors, such as diabetes mellitus (DM), obesity, and dyslipidemia.

Keywords: steatosis, breast cancer, aromatase inhibitor, tamoxifen.

RESUMO
O câncer de mama tem incidência estimada de 2,26 milhões de casos novos no mundo todo, e 75% destes são receptores de estrogênio positivo (RE^+). O tratamento envolve o uso de tamoxifeno (TX) ou inibidores de aromatase (IAs), como anastrozol e letrozol. O uso destas medicações está associado com alterações no nível de colesterol sanguíneo e esteatose hepática, e o TX

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promove mais esteatose que os IAs. Desta maneira, o objetivo deste estudo foi observar o efeito do TX e dos IAs na incidência de esteatose hepática e nas mudanças dos marcadores bioquímicos em mulheres com câncer de mama RE^+. Foi realizado um estudo transversal entre 2021 e 2024 com 38 mulheres com câncer de mama RE^+ que fizeram uso de TX ou IAs em um hospital público no Brasil. Foram coletados dados primários através de entrevistas, e dados secundários por meio de registros médicos, como hemograma, perfil lipídico, perfil hepático e resultados de ultrassonografia (US). De 34 mulheres com câncer de mama RE^+, com idade média de 56,67 ± 12,38 anos, as pacientes que utilizaram IAs apresentaram valores maiores de LDL (Lipoproteína de baixa densidade) ($p < 0,001$), VCM (Volume corpuscular médio) ($p = 0,033$), NS (Neutrófilos segmentados) ($p = 0,044$) e FA (Fosfatase alcalina) ($p = 0,019$) quando comparados com grupo TX ao longo do tratamento. As mulheres que apresentaram esteatose hepática na linha de base pela US não tiveram alterações após o tratamento. Nossos resultados sugerem que a terapia adjuvante para câncer de mama RE^+ em mulheres não esteve associada ao aumento de enzimas hepáticas – exceto FA – ou ao desenvolvimento de esteatose hepática, mas os IAs aumentaram os valores de LDL, o que deve ser considerado no momento de escolha do tratamento, principalmente em mulheres com fatores de risco como diabetes mellitus (DM), obesidade e dislipidemia.

Palavras-chave: esteatose, câncer de mama, inibidor de aromatase, tamoxifeno.

RESUMEN

El cáncer de mama tiene una incidencia estimada de 2,26 millones de casos nuevos en todo el mundo, y el 75% de ellos son receptores de estrógeno positivos (RE^+). El tratamiento implica el uso de tamoxifeno (TX) o inhibidores de la aromatasa (IA), como anastrozol y letrozol. El uso de estos medicamentos se asocia con cambios en los niveles de colesterol sanguíneo y esteatosis hepática, y el TX promueve más esteatosis que los IA. Por lo tanto, el objetivo de este estudio fue observar el efecto del TX y los IA sobre la incidencia de esteatosis hepática y los cambios en marcadores bioquímicos en mujeres con cáncer de mama RE^+. Se realizó un estudio transversal entre 2021 y 2024 con 38 mujeres con cáncer de mama RE^+ que utilizaron TX o IA en un hospital público de Brasil. Los datos primarios se recolectaron a través de entrevistas, y los datos secundarios a partir de registros médicos, como hemograma, perfil lipídico, perfil hepático y resultados de ultrasonido (US). De 34 mujeres con cáncer de mama RE^+, con edad media de 56,67 ± 12,38 años, las pacientes que utilizaron IA presentaron valores más elevados de LDL (Lipoproteínas de baja densidad) ($p < 0,001$), VCM (Volumen corpuscular medio) ($p = 0,033$), NS (Neutrófilos segmentados) ($p = 0,044$) y FA (Fosfatase alcalina) ($p = 0,019$) en comparación con el grupo TX a lo largo del tratamiento. Las mujeres que presentaban esteatosis hepática al inicio del estudio ecográfico no mostraron cambios después del tratamiento. Nuestros resultados sugieren que la terapia adyuvante para el cáncer de mama RE^+ en mujeres no se asoció con un aumento de las enzimas hepáticas – excepto la FA – ni con el desarrollo de esteatosis hepática,

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sin embargo, los IA aumentaron los valores de LDL, lo que debe ser considerado al momento de elegir el tratamiento, especialmente en mujeres con factores de riesgo como diabetes mellitus (DM), obesidad y dislipidemia.

Palabras clave: esteatosis, cáncer de mama, inhibidores de la aromatasa, tamoxifeno.

1 INTRODUCTION

Currently, the estimated global annual incidence of new breast cancer is 2.26 million. Additionally, 75% of breast cancer patients express ER^+ (Early Breast Cancer Trialists' Collaborative Group; Davies *et al.*, 2011). In Brazil, there are 73,610 new cases annually, whereas in the central–west region and in the state of Mato Grosso do Sul there are 4,950 and 910 new breast cancer cases annually, respectively (INCA, 2022).

Breast cancer is treated with surgery, chemotherapy, radiotherapy, and hormone therapy with tamoxifen (TX) or aromatase inhibitors (AIs), such as anastrozole and letrozole (Waks; Winer, 2019). TX acts as a competitive antagonist and agonist of estrogen receptors in tissues (Yager; Davidson, 2006) as well as inhibits GH (growth hormone) synthesis and alters β-oxidation, LDL, and very low-density lipoprotein (VLDL) levels (Birzniece *et al*., 2010). Moreover, AIs directly decrease estrogen levels in the body (Joshi; Press, 2018), and this reduction can result in dyslipidemia (Akyol *et al.*, 2017). The main adverse effects of AIs are decreased bone mineral density, hot flushes, dyslipidemia, cardiovascular problems, dyspareunia, and vaginal dryness (Lintermans; Neven,

2015). Conversely, TX can cause hot flushes, thromboembolic events, endometrial cancer, thrombocytopenia, and irregular menstruation (Osborne, 1998).

In addition, there appears to be a relationship between the drugs used to treat breast cancer, the metabolic profile of women, and hepatic steatosis (Osman; Osman; Ahmed, 2007). In general, nonalcoholic fatty liver disease (NAFLD) is a condition caused by the dysregulation of cholesterol homeostasis

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and its accumulation in liver cells (Arguello *et al*., 2015), and ranges from isolated steatosis to nonalcoholic steatohepatitis (NASH) (Lomonaco *et al*., 2013). In addition, it is strongly associated with insulin resistance, metabolic syndrome (Bugianesi *et al.*, 2004), hepatocellular cancer, and breast cancer (Kim, 2018). In clinical practice, steatosis is diagnosed using biochemical tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and bilirubin] and imaging exams, such as US (Jepsen; Grønbæk, 2011) and computed tomography (CT), which are widely used (Karcaaltincaba; Akhan, 2007). The incidence of hepatic steatosis in women with breast cancer is 30%–35% (Kwak *et al.*, 2019; Taroeno-Hariadi *et al.*, 2021).

The high incidence of steatosis in women with breast cancer seems to be related to the medications used in hormone therapy. In fact, there is evidence that TX promotes steatosis more than AIs (Hong *et al.*, 2017). There is still controversy regarding the relationship between steatosis and the use of AIs (Bundred, 2005). The relationship between steatosis and changes in biochemical markers, such as GGT, ALP, AST, ALT, and bilirubin, remains debatable (Lin *et al.*, 2014). The relationship between these medications and hepatic steatosis, cholesterol levels, and markers of liver damage is still uncertain and more studies are required.

The aim of the present study was to compare the effect of TX and AIs on the occurrence of hepatic steatosis and on longitudinal changes in biochemical and lipid serological markers during hormone therapy in women with ER^+ breast cancer.

2 METHODS

2.1 STUDY DESIGN

This was an observational, descriptive, cross-sectional study. The target population of this study consisted of women with ER^+ breast cancer who received

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TX or AIs (letrozole or anastrozole). This research was approved by the CEP/UFMS (Ethics Committee for Research on Human Beings of the Federal University of Mato Grosso do Sul) under opinion No. 5,015,818 through CAAE No. 51778721.00000.0021. This study was conducted between January 2021 and 2024 in a public hospital in the state of Mato Grosso do Sul. The nonprobability sampling method was used and 38 patients were selected, four of whom were lost to follow-up. The 34 patients were subdivided into two groups: Tamoxifen Group (TX Group)— those treated with tamoxifen 20 mg, and Aromatase Inhibitors Group (AI Group)— those treated with anastrozole 1 mg or letrozole 2.5 mg. Eighteen women were in the TX Group and 16 women were in the IA Group. The study excluded the following individuals: women <18 years of age; pregnant women; women with a previous diagnosis of liver cirrhosis, hepatitis B or C, DM combined with target organ damage; women with a history of liver transplantation; and women with alcohol use disorder (American Psychiatric Association, 2022). Data related to the patients' epidemiological profile, such as mean age, mean height, mean weight, body mass index (BMI), abdominal circumference, alcohol use (>7 doses per week and ≤3 doses on one occasion), obesity, and ethnicity are described in the results and shown in Table 1.

2.2 CLINICAL DATA COLLECTION

The study used primary and secondary data for analysis. After the women signed the Free, Prior and Informed Consent (FPIC), the primary data were collected through a questionnaire. Subsequently, physical examinations were performed by trained physicians in a reserved room of the public hospital. The questionnaire collected complaints related to liver disorders, physiological and social history, past medical history, and family history. Anthropometric data (weight, height, BMI, and abdominal circumference) were collected during the physical examination. Abdominal circumference (in cm) was measured with a tape measure at the midpoint between the last rib and the iliac crest. Weight was

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measured in kilograms using a LD1050 scale (Líder, Araçatuba/SP, Brazil) and height was measured in meters using a tape measure. Secondary data were obtained from online medical records in computerized systems. The data consisted of simple blood count, glycated hemoglobin (HbA1C), lipid profile [high-density lipoprotein (HDL), VLDL, LDL, and triglycerides (TG)], liver function tests (AST, ALT, GGT, and ALP) (Thapa; Walia, 2007; Woreta; Alqahtani, 2014), and imaging exams to investigate hepatic steatosis and portal vein diameter (liver US). The results of the tests and exams (blood count, lipid count, markers of liver function and damage, and US) were analyzed at two different time points, before and after the use of breast cancer medication. The first data collection, referred to as the "before moment," was performed as close as possible to the start of treatment with the medications; the second data collection, referred to as the "after moment," was performed 3–5 years after a treatment period. The collection methods were the same in both the groups. Primary and secondary data have different collection time points because of missing information during data collection or the participants' own choice.

2.3 STATISTICAL ANALYSIS

The effects of the moment of analysis (before and after medication use), medication (medication used by each group), and the interaction between these two factors on the quantitative variables assessed in this study were analyzed by two-way repeated measures ANOVA using Bonferroni correction. The association between the medications used and the presence of hepatic steatosis assessed by US was evaluated using Pearson's chi-square test. The additional results of this study are presented in the form of descriptive statistics or tables. The statistical analysis was performed using the Statistical Package for the Social Science (IBM SPSS) software, version 23.0 (Rowe, 2007), with a significance level of 5%.

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3 RESULTS

3.1 CHARACTERISTICS OF WOMEN WITH ER⁺ BREAST CANCER

The mean age of the participants was 56.67 ± 12.38 years; however, it was higher in the AI Group (60.32 ± 14.84 years) than in the TX Group (53.43 ± 8.90 years). The mean height of the participants was 1.58 ± 0.06 m, being higher in the TX Group (Table 1).

Weight, BMI, and abdominal circumference are strongly correlated with hepatic steatosis and the pharmacokinetics of the medications. BMI was high among the participants (29.63 ± 7.33 kg/m²) relative to normal values (WHO, 2010) and was higher in the TX Group; thus, representing grade 1 obesity (32.11 ± 8.11 kg/m²) in this group. The participants mean weight was similar to that of their BMI, being higher in the TX Group (78.55 ± 19.30 kg) than in the AI Group (67.71 ± 13.07 kg). Abdominal circumference was similar in both groups, with a total mean of 95.22 ± 13.26 cm (Table 1), i.e., above the value recommended by the WHO (2011).

The data on the patients' physiological and psychosocial history (alcohol use and obesity) is strongly related to liver disease and the poor socioeconomic conditions of the participants. Alcohol use refers to women who consumed alcohol in moderation (maximum of seven doses per week and no more than three on one occasion) (American Psychiatric Association, 2022). This was observed in 14.70% of the patients, and was four times more prevalent in Group AI (11.76%) than in Group TX (2.94%). Obesity was defined according to BMI (WHO, 2010), with 34.38% prevalence (12.50% in Group AI and 21.88% in Group TX). With regard to ethnicity, there were a higher percentage of brown individuals

(52.94%) and this prevalence was significant in Group TX (32.35%), whereas Group AI had a predominance of white individuals (26.47%) (Table 1).

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Table 1. General information related to the epidemiological profile of patients at baseline for AI and TX Groups.

Characteristic	AI Group	TX Group	Total
Age (years)	60.32 ± 14.84 (16)	53.43 ± 8.90 (18)	56.67 ± 12.38 (34)
Height (m)	1.58 ± 0.06 (16)	1.59 ± 0.05 (16)	1.58 ± 0.06 (32)
Weight (kg)	67.71 ± 13.07 (16)	78.55 ± 19.30 (18)	73.44 ± 17.31 (34)
BMI (kg/m²)	27.15 ± 5.66 (16)	32.11 ± 8.11 (16)	29.63 ± 7.33 (32)
Abdominal circumference (cm)	94.67 ± 15.50 (12)	95.67 ± 11.72 (15)	95.22 ± 13.26 (27)
Alcohol use			
Yes	4 (11.76%)	1 (2.94%)	34 (100%)
No	12 (35.30%)	17 (50%)	
Obesity according to BMI			
Yes	4 (12.50%)	7 (21.88%)	32 (100%)
No	12 (37.50%)	9 (28.12%)	
Ethnicity			
White individuals	9 (26.47%)	5 (14.71%)	34 (100%)
Brown individuals	7 (20.59%)	11 (32.35%)	
Black individuals	0	2 (5.88%)	

The table shows the mean and standard deviation and number of participants.
Source: Prepared by the authors.

3.2 BLOOD CELL COUNT ANALYSIS

The blood count results were divided into red blood cell analysis, white blood cell analysis, and platelet count (Table 2 and Figures 1 and 2).

Regarding the parameters related to red blood cells (RBC, HCT, MCV, MCH, CHCM, RDW, and Hb), only MCV was significantly higher ($p = 0.033$) in Group TX than in Group AI. Despite this, the mean MCV at the start of treatment with TX was below the reference values and normalized after taking the medication ($p = 0.186$). The variables, RBC, HCT, MCH, CHCM, RDW, and Hb, were not statistically significant and were within the reference values during the treatments.

The results of the leukocyte and platelet counts (WBC, NEU, LYM, MONO, EOS, BASO, and PLT) remained within the reference values. There was a difference in NEU between the treatment groups ($p = 0.044$), with an increase in Group AI and a decrease in Group TX. However, the results of WBC, LYM, MONO, EOS, BASO, and PLT were not statistically significant.

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Table 2. Blood count analysis before and after breast cancer treatment with aromatase inhibitors or tamoxifen.

	Moment				Mean/Moment effect *p*		
	Before		After				
Variable	**AI Group**	**TX Group**	**AI Group**	**TX Group**	**Med:**	**Mom:**	**Inter:**
RBC (cells/µL)	4.59 ± 0.46 (14)	4.36 ± 0.41 (16)	4.47 ± 0.33 (14)	4.38 ± 0.39 (16)	0.136	0.605	0.487
HCT (%)	39.32 ± 3.46 (15)	40.12 ± 12.45 (16)	39.55 ± 3.06 (15)	42.08 ± 13.03 (16)	0.490	0.650	0.721
MCV (fL)	85.82 ± 5.83 (15) [a]	75.94 ± 21.59 (16) [b]	89.76 ± 6.11 (15) [a]	82.51 ± 19.74 (16) [b]	0.033 *	0.186	0.739
MCH (pg/cell)	28.98 ± 2.44 (15)	29.61 ± 2.03 (16)	29.16 ± 3.39 (15)	29.59 ± 3.11 (16)	0.455	0.907	0,883
MCHC (g/dL)	33.70 ± 1.41 (15)	32.80 ± 5.55 (16)	33.19 ± 1.07 (15)	31.89 ± 5.26 (16)	0.280	0.486	0.846
RDW (%)	13.72 ± 1.33 (15)	13.55 ± 1.20 (16)	13.99 ± 1.76 (15)	13.24 ± 1.29 (16)	0.204	0.963	0.422
Hb (g/dL)	13.23 ± 1.05 (15)	12.81 ± 1.25 (16)	13.35 ± 1.05 (15)	14.81 ± 7.84 (16)	0.623	0.312	0.369
WBC (cells/µL)	$6.02\times10^3 \pm 1.50\times10^3$ (15)	$6.98\times10^3 \pm 2.23\times10^3$ (16)	$6.72\times10^3 \pm 1.70\times10^3$ (15)	$6.83\times10^3 \pm 3.01\times10^3$ (16)	0.343	0.623	0.453
NEU (%)	55.80 ± 11.60 (15) [a]	52.56 ± 11.69 (16) [b]	60.67 ± 9.08 (15) [a]	51.50 ± 14.25 (16) [b]	0.044 *	0.530	0.329
LYM (%)	32.40 ± 9.29 (15)	32.94 ± 13.58 (16)	28.73 ± 8.82 (15)	36.19 ± 13.11 (16)	0.176	0.943	0.241
MONO (%)	7.33 ± 1.45 (15)	9.62 ± 5.20 (16)	7.87 ± 2.45 (15)	7.31 ± 2.52 (16)	0.298	0.287	0.091
EOS (%)	2.80 ± 2.30 (15)	2.94 ± 2.041 (16)	2.13 ± 2.33 (15)	4.06 ± 4.48 (16)	0.187	0.768	0.252
BASO (%)	0.87 ± 0.64 (15)	0.56 ± 0.81 (16)	0.33 ± 0.49 (15)	0.50 ± 0.73 (16)	0.677	0.064	0.240
PLT (cells/µL)	$2.54\times10^5 \pm 5.73\times10^4$ (15)	$3.31\times10^5 \pm 1.53\times10^5$ (16)	$2.40\times10^5 \pm 5.27\times10^4$ (15)	$2.61\times10^5 \pm 1.11\times10^5$ (16)	0.068	0.114	0.290

The table shows the mean and standard deviation and number of participants.
*: there was a significant difference. Mom: moment (influence of time on the dependent variables, regardless of the medication used). Med: medication (influence of the medication on the dependent variables, regardless of the time elapsed). Inter: interaction (influence of independent variables - time and medication - on dependent variables). RBC: Red blood cells; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red blood cell distribution width; Hb: Hemoglobin; WBC: White blood cells (Leukocytes); NEU: Segmented neutrophils; LYM: Lymphocytes; MONO: Monocytes; EOS: Eosinophils; BASO: Basophils; and PLT: Platelets. Two-way repetitive ANOVA with Bonferroni correction were performed.
Source: Prepared by the authors.

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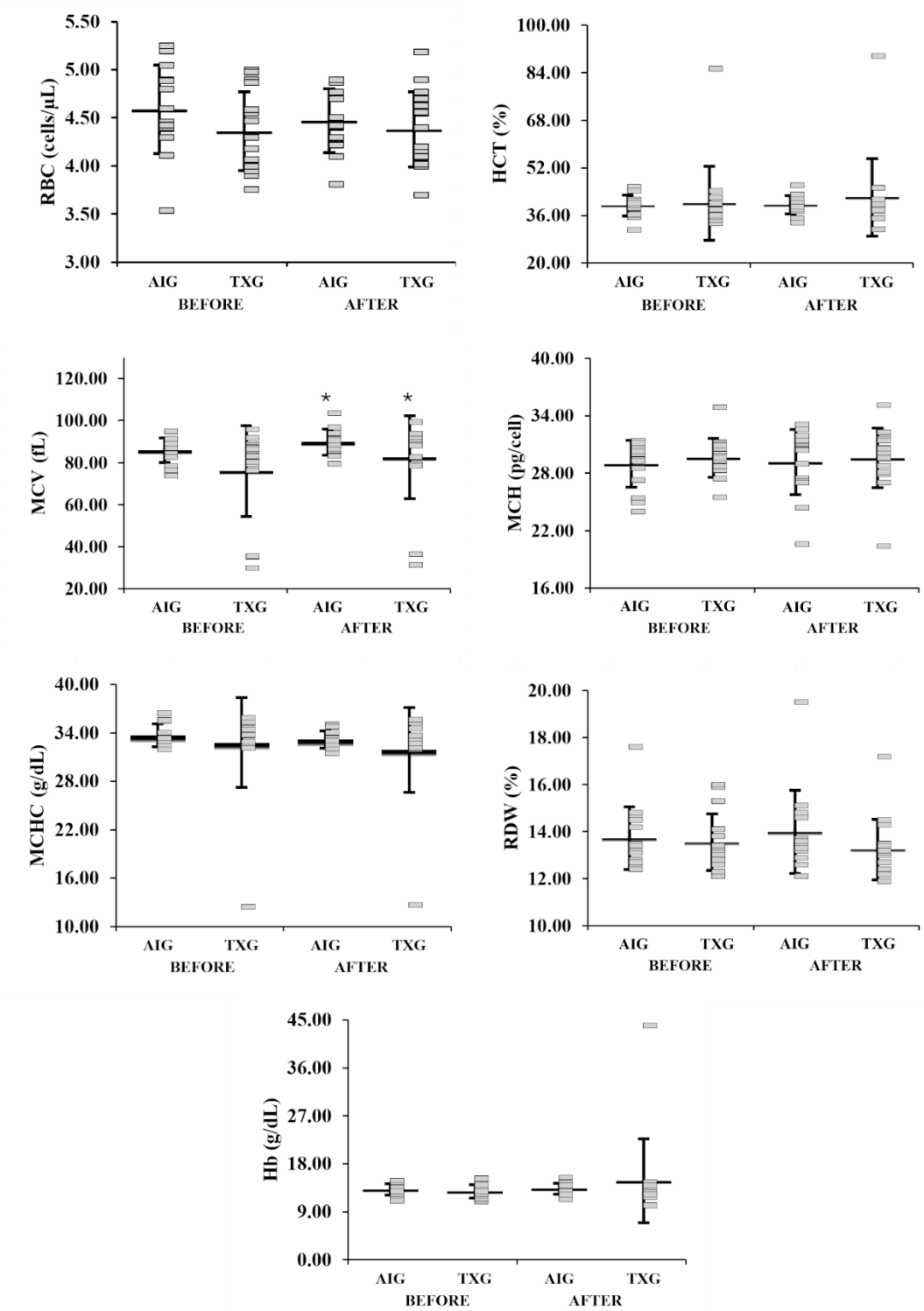
Figure 1. Blood count values before and after breast cancer treatment using aromatase inhibitors and tamoxifen.



The figure shows the mean, standard deviation, and participants.
***:** there was a significant difference, as shown in Table 2. AIG: Aromatase Inhibitors Group.
TXG: Tamoxifen Group.
Source: Prepared by the authors.

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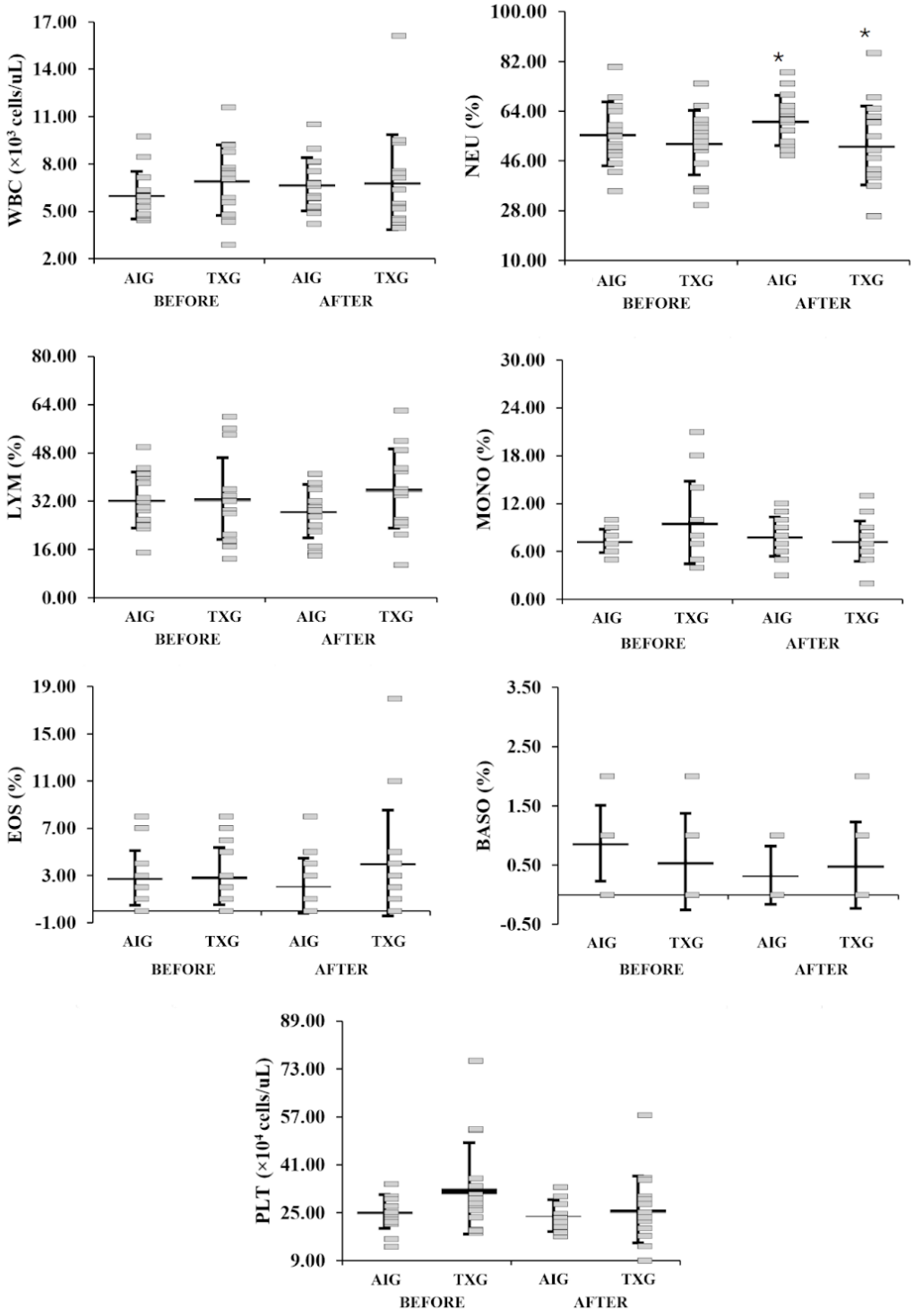
Figure 2. White blood cells and platelet counts before and after breast cancer treatment using aromatase inhibitors and tamoxifen.



The figure shows the mean, standard deviation, and participants.
***:** there was a significant difference, as shown in Table 2. AIG: Aromatase Inhibitors Group.
TXG: Tamoxifen Group.
Source: Prepared by the authors.

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3.3 BIOCHEMICAL BLOOD PARAMETERS

With regard to the biochemical blood tests (HbA1C, TG, HDL, VLDL, LDL, AST/ALT ratio, GGT, and ALP), variables relating to the insulin resistance profile, lipid profile, liver damage, and bile duct damage were collected, respectively, as shown in Table 3 and Figure 3. LDL increased over the course of treatment in Group AI, reaching above the upper limit compared to Group TX ($p < 0.001$), and there was no significant influence of time or of the interaction between time and medication. ALP was significantly different between the two groups, regardless of the moment or the interaction, with an increase in Group TX and a decrease in Group AI ($p = 0.019$). However, the variables HbA1C, TG, HDL, VLDL, AST/ALT ratio, and GGT were not statistically related to time, medication, or the interaction between them. However, HbA1C was above the reference value in both groups, regardless of the moment. GGT increased above the reference value in Group TX ($p = 0.811$) and was above the reference value in Group AI at both moments, but without statistical significance.

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Table 3. Data regarding liver condition before and after treatment with aromatase inhibitors or tamoxifen.

	Moment				Mean/Moment effect		
	Before		After		*p*		
Variable	**AI Group**	**TX Group**	**AI Group**	**TX Group**	**Med:**	**Mom:**	**Inter:**
HbA1C (%)	5.83 ± 0.81 (6)	7.94 ± 2.83 (7)	6.38 ± 0.97 (6)	6.40 ± 1.64 (7)	0.150	0.494	0.157
TG (mg/dL)	139.07 ± 37.28 (4)	138.16 ± 55.57 (8)	89.75 ± 10.34 (4)	135.44 ± 43.11 (8)	0.256	0.189	0.238
HDL (mg/dL)	48.15 ± 2.36 (4)	72.40 ± 61.97 (7)	64.75 ± 3.86 (4)	76.36 ± 63.38 (7)	0.440	0.656	0.784
VLDL (mg/dL)	27.80 ± 7.45 (4)	25.51 ± 10.12 (7)	18.15 ± 1.95 (4)	25.57 ± 8.00 (7)	0.484	0.198	0.192
LDL (mg/dL)	171.21 ± 21.35 (4) [a]	116.91 ± 19.11 (7) [b]	175.60 ± 31.62 (4) [a]	114.38 ± 28.20 (7) [b]	<0.001 *	0.934	0.759
AST/ALT ratio	1.04 ± 0.66 (11)	0.90 ± 0.41 (13)	1.25 ± 0.52 (11)	1.14 ± 0.52 (13)	0.394	0.147	0.921
GGT (U/L)	95.67 ± 94.08 (3)	33.00 ± 10.70 (5)	43.00 ± 19.05 (3)	102.80 ± 95.73 (5)	0.968	0.811	0.107
ALP (U/L)	98.71 ± 22.06 (7) [a]	68.00 ± 13.87 (7) [b]	97.71 ± 37.41 (7) [a]	72.71 ± 36.99 (7) [b]	0.019 *	0.868	0.799

The table shows the mean and standard deviation and number of participants.
*: there was a significant difference. Mom: moment (influence of time on the dependent variables, regardless of the medication used). Med: medication (influence of the medication on the dependent variables, regardless of the time elapsed). Inter: interaction (influence of independent variables—time and medication—on dependent variables). HbA1C: Glycated hemoglobin; TG: Triglycerides; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein; LDL: Low-density lipoprotein; AST/ALT ratio: Aspartate aminotransferase / alanine aminotransferase; GGT: Gamma-glutamyl transferase; and ALP: Alkaline phosphatase. Two-way repetitive ANOVA with Bonferroni correction was performed.
Source: Prepared by the authors

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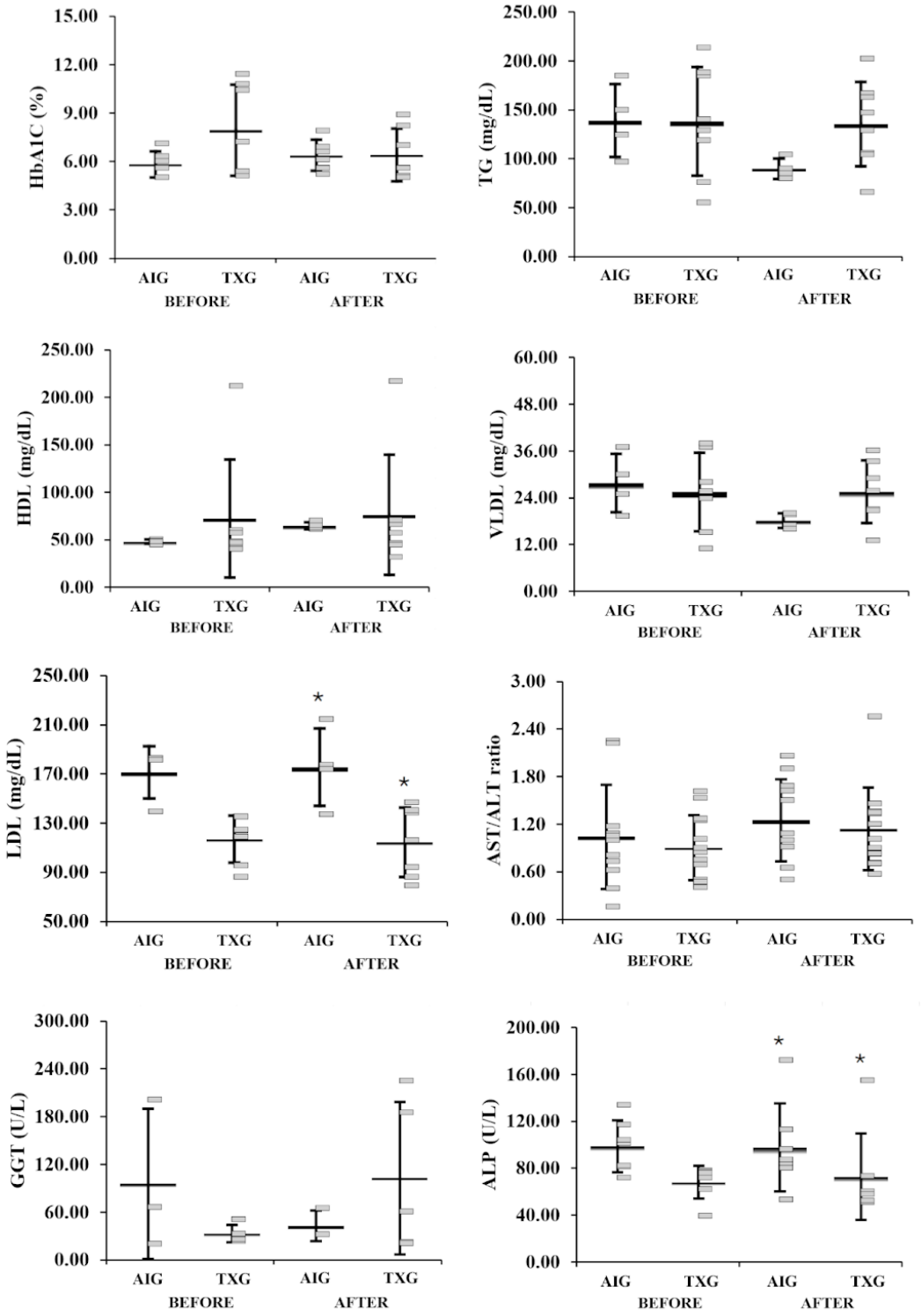
Figure 3. Lipid profile values and liver damage markers before and after breast cancer treatment using aromatase inhibitors and tamoxifen.



The figure shows the mean, standard deviation, and participants.
***:** there was a significant difference, as shown in Table 3. AIG: Aromatase Inhibitors Group. TXG: Tamoxifen Group.
Source: Prepared by the authors.

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3.4 ULTRASOUND LIVER IMAGING REPORTING

In the US examination, the number of women with steatosis was the same before and after the treatment, and there was no statistical significance in the results obtained. Additionally, the diameter of the portal vein was measured and was normal in all participants (p = 0.874) (Table 4).

Table 4. Data on hepatic steatosis and portal vein diameter in patients in Group AI and TX, determined based on US at different times.

Variable	AI Group	TX Group	p-value
US steatosis before (%)			
No	37.5 (6)	44.4 (8)	0.919
Yes	56.3 (9)	50.0 (9)	
Does not apply	6.3 (1)	5.6 (1)	
US steatosis after (%)			
No	40.0 (6)	47.1 (8)	0.688
Yes	60.0 (9)	52.9 (9)	
Does not apply	0	0	
US portal vein diameter (%)			
Normal	81.3 (13)	83.3 (15)	0.874
No data	18.8 (3)	16.7 (3)	

US: Ultrasonography. Pearson's chi-square test was performed. There were no significant data.
Source: Prepared by the authors.

3.5 PATIENTS' PREVIOUS MEDICAL HISTORY

With regard to the patients' previous medical history, DM and dyslipidemia were not present in most participants and were not statistically significant. Family history of obesity was not predominant among the patients and was not statistically significant in both groups (Table 5).

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Table 5. Data regarding the previous medical history of patients in Groups IA and TX.

Variable	AI Group	TX Group	p-value
Diabetes mellitus			
No	75.0 (12)	83.3 (15)	0.549
Yes	25.0 (4)	16.7 (3)	
Dyslipidemia			
No	68.8 (11)	88.9 (16)	0.147
Yes	31.3 (5)	11.1 (2)	
Family history of obesity			
No	68.8 (11)	61.1 (11)	0.897
Yes	31.3 (5)	38.9 (7)	

Pearson's chi-square test was performed. There were no significant data.
Source: Prepared by the authors.

4 DISCUSSION

AIs, predominantly used to treat ER^+ breast cancer in postmenopausal women, may cause vaginal dryness, low libido, hot flushes, and ischemic heart disease (Derzko; Elliott; Lam, 2007; Boszkiewicz; Piwowar; Petryszyn, 2022), as well as increased bone loss (Tenti *et al.*, 2020). The use of TX to treat ER^+ breast cancer can lead to the development of uterine cancer, vaginal dryness, hot flushes (Osborne, 1998), loss of libido (Barni; Mondin, 1997), leukopenia, thrombocytopenia, thromboembolic events (Mintzer; Billet; Chmielewski, 2009), and hepatic steatosis in >30% of women (Murata *et al.*, 2000; Nishino *et al.*, 2003; Bilici *et al*., 2007).

In this study, obesity was present in 12.50% of patients in Group AI and in 21.88% of patients in Group TX. Dyslipidemia and DM were more prevalent in Group AI, with no statistically significant difference. The number of patients with steatosis, assessed using US, did not change with the use of the medications. Studies have shown a relationship between the use of TX (82 out of 156 patients) (Liu *et al*., 2006) and AIs (26 out of 178 patients) (Lin *et al.*, 2014) and the development of hepatic steatosis. Other studies have not found similar evidences regarding TX (Braal *et al*., 2022) and AIs (Cheung *et al.*, 2023); however, both medications may be associated with dyslipidemia (Sahebkar *et al.*, 2017). The relationship between the socioeconomic characteristics of a population and obesity is also discussed in the literature (Carmichael; Bates, 2004; Dinsa *et al.*, 2012). In this study, steatosis was investigated using US, and no relationship was

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found between the use of any of the medications and hepatic steatosis because the number of patients with and without steatosis did not change over the course of the treatments. This finding can be explained by the study's small sample size. In addition, both groups had risk factors that may have affected the tests, such as dyslipidemia, obesity, DM, increased body mass, dysfunctional eating patterns, and a sedentary lifestyle. Considering the target population of the study, the health-related risk factors may be linked to the socioeconomic conditions of the participants, which is an important bias.

In this study, LDL increased significantly in Group AI compared with Group TX ($p < 0.001$); however, it was above the upper reference limit in both groups. HDL increased and TG decreased in both groups compared with the baseline, and VLDL decreased in Group AI and increased in Group TX, without statistical significance. Trials have shown that prolonged use of TX (2 years) increases TG and HDL levels ($p = 0.001$ and $p = 0.02$, respectively) and decreases LDL levels ($p < 0.001$) (Braal *et al.*, 2022). Hong *et al.* (2017) compared the use of TX and AIs over 5 years and showed a similar increase in HDL for both, compared to baseline ($p < 0.05$), and a greater decrease in LDL and total cholesterol with the use of TX compared with AIs ($p < 0.001$), whereas TG remained unchanged. Estrogen contributes positively to the lipid profile in women (Naessen; Rodriguez-Macias; Lithell, 2001), partly through its adjuvant role in the production of the ApoB100/ApoE (apolipoprotein B-100 / apolipoprotein E) receptor (Bérczi *et al.*, 2024). In this context, studies have shown an increase in serum lipids in postmenopausal women treated using AIs (Franchi *et al*., 2021; Chlebowski *et al*., 2006). In the present study, there was a relationship between LDL elevation and the use of AIs compared with the use of TX. Despite this, it was not possible to prove the association between LDL and hepatic steatosis. Given the difference between the samples, five of the nine patients diagnosed with steatosis based on US had no data on LDL. Additionally, the increased LDL at baseline in patients from Group AI may be associated with the characteristics of the women in this group. A higher mean age (60.32 ± 14.84) compared to the TX Group (53.43 ± 8.90) may contribute to this result but obesity; abdominal circumference; and BMI

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were more altered in the TX Group. Finally, the N for the LDL sample was reduced, and some patients were taking statins.

With regard to the patients' blood count, MCV and NEU were higher in Group AI than in Group TX ($p = 0.033$ and 0.044, respectively). A study in rats (Panchal *et al.*, 2014) showed that TX reduces RBC, Hb, and MCV ($p < 0.05$). In relation to AIs, two studies (Iyengar; Sheppard, 2013; Yeruva *et al.*, 2015) discuss the possibility of elevated androgen levels being correlated with erythrocytosis and increased MCV, and another study suggests the relationship of AIs with increased neutrophils (Zarkavelis *et al.*, 2016). The present study indicated a relation between high levels of NEU and MCV and the use of AIs. In contrast, in the study by Panchal *et al.* (2014) there was an increase in MCV in the TX Group compared to baseline, albeit not significant.

In addition, with regard to the parameters measuring liver and bile duct damage (GGT, ALP, AST/ALT ratio), ALP increased in the TX Group compared with the AI Group ($p = 0.019$). The AST/ALT ratio and GGT showed no significant changes in both groups. These results contrast with an Italian chemoprevention trial comparing TX with placebo (Bruno *et al.*, 2005) conducted with 5,408 women in which 232 of the 5,087 women had at least one altered AST and ALT result throughout the study. The study by Lin *et al.* (2014) compared the effect of TX and anastrozole on liver enzymes (AST, ALT, ALP, GGT, and total bilirubin) and showed that 29 women (16.6%) in the TX Group and 36 women (20.2%) in the anastrozole group had altered liver function, with no statistically significant difference between the results, and no direct relationship between abnormal liver function and hepatic steatosis.

In this study, it was not possible to clearly conclude whether about a relationship between changes in transaminases and GGT and hepatic steatosis, given the small number of laboratory tests. In addition, there may be no relationship between the two because there is disagreement between the number of patients with steatosis and the values of the biochemical parameters of liver damage. In the analyses, there was no direct relationship between TX or AIs and changes in transaminases and GGT. Although high GGT values suggest liver

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damage, it was not possible to establish a relationship because of the small number of GGT samples.

In fact, elevated GGT and ALP have a strong relationship with liver dysfunction (Martin; Goldber, 1986). However, elevated ALP alone can originate outside the liver (Sharma; Pal; Prasad, 2014), including bones, placenta, and intestine (Stigbrand, 1984). Studies show that AIs can cause bone demineralization, which leads to an increase in ALP (Perez *et al.*, 2006; Eastell *et al.*, 2006, 2008; Gaillard; Stearns, 2011; Cheng *et al.,* 2023). Thus, in the present study, the increase in ALP in Group AI could indicate bone dysfunction rather than liver disease, caused by the drug itself or by the decrease in plasma estrogen levels related to postmenopause in the women of this group.

This study had limitations that need to be addressed. First, some practical issues, like missing data in electronic health records and the absence of women in medical consultation, made it difficult to collect data properly and obtain a larger sample. Second, we included women who were taking medications (carbamazepine, sodium divalproate, paracetamol, and amitriptyline) that may induce hepatotoxicity as well as statins, teas, and herbal medicines that may have influenced the results (Chang; Schiano, 2007). Third, US was used to diagnose steatosis, instead of CT or other highly sensitive methods, which are more advantageous than US. According to Stern and Castera (2017), US has lower specificity than CT and MRI. Fourth, women with steatosis at baseline and with risk factors like obesity and DM were not excluded from the study. Finally, the length of follow-up varied among the participants.

5 CONCLUSIONS

In this study, adjuvant therapy for ER^+ breast cancer in women using TX or AIs was not associated with increase in steatosis or liver enzymes, except for ALP. Conversely, the use of AIs worsened the patients' lipid profile, especially LDL, when compared with TX. Given the potential risk of high LDL levels for women with long-term cardiovascular and liver health, this is an important

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adverse effect to consider when choosing the medication to be used (AIs or TX), especially in women with previous risk factors, such as obesity, DM, and dyslipidemia. It is also important to advise patients on how to adopt healthy lifestyle habits, such as regular physical activity and a balanced diet. Finally, randomized clinical trials with large samples on the subject are scarce, especially in the Latin American population, and more studies are needed to understand the exact role of these medications in liver, blood, and lipid profile.

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