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Research Article

Effect of Metformin on Endometrial Thickness in Postmenopausal Breast Cancer Patients Receiving Tamoxifen

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Abstract

Background: Adjuvant hormonal therapy with tamoxifen reduces recurrence rate, morbidity, and mortality. Tamoxifen increases endometrial thickness, resulting in relevant gynecological complications. Several studies revealed the benefits of co-administering metformin with tamoxifen to avoid endometrial hyperplasia, but the available clinical data are still limited. ***Objective***: To evaluate the effect of metformin on endometrial thickness in a sample of postmenopausal Iraqi ER+ breast cancer patients on adjuvant tamoxifen therapy. ***Methods***: A total of 63 postmenopausal breast cancer patients on adjuvant Tamoxifen therapy were enrolled in a double-blinded randomized control trial (RCT). Patients were randomly allocated to two groups in a 1:1 ratio, with one group receiving Metformin along with tamoxifen and the other group receiving Placebo along with tamoxifen for a 12-month duration. Baseline endometrial thickness was obtained using ultrasound, and follow-up visits were scheduled in 3,6,9, and 12-month periods to evaluate the ultrasound changes in endometrial thickness as well as related adverse events. ***Results***: Over 12 months, the placebo group exhibited a significant ET increase (6.32mm), while the metformin group showed minimal change (4.13mm) (p<0.001). ANOVA confirmed a significant time effect and time × group interaction (p<0.001). PMB occurred in 6.7% of the metformin group *vs*. 26.7% in the placebo group (p=0.038). ***Conclusions***: Metformin significantly ameliorates tamoxifen-associated endometrial thickness and the incidence of postmenopausal bleeding in postmenopausal women with estrogen receptor-positive breast cancer.

Keywords: Breast cancer; Endometrial hyperplasia; Metformin; Postmenopausal bleeding; Tamoxifen.

تأثير الميتفورمين على سمك بطانة الرحم لدى مريضات سرطان الثدي بعد سن اليأس اللواتي يعالجن بالتاموكسيفين

الخلاصة

الخلفية: العلاج الهرموني المساعد بالتاموكسيفين يقلل من معدل الانتكاس، والمراضة، والوفيات. يزيد تاموكسيفين من سمك بطانة الرحم، مما يؤدي إلى مضاعفات نسائية ذات صلة. كشفت عدة دراسات عن فوائد إعطاء الميتفورمين المشترك مع التاموكسيفين لتجنب فرط تنسج بطانة الرحم، لكن البيانات السريرية المتاحة لا تزال محدودة. **الهدف**: تقييم تأثير الميتفورمين على سمك بطانة الرحم في عينة من مرضى سرطان الثدي العراقيين بعد انقطاع الطمث ER+ الذين تلقوا العلاج المساعد بالتاموكسيفين. **الطرائق**: تم تسجيل ما مجموعه 63 مريضا من سرطان الثدي بعد انقطاع الطمث الذين تلقوا علاجا مساعدا بالتاموكسيفين في تجربة عشوائية مزدوجة التعمية (RCT). تم توزيع المرضى عشوائيا إلى مجموعتين بنسبة 1:1، حيث تلقت مجموعة واحدة الميتفورمين مع التاموكسيفين، وتلقت المجموعة الأخرى الدواء الوهمي مع التاموكسيفين لمدة 12 شهرا. تم الحصول على سماكة بطانة الرحم الأساسية باستخدام الموجات فوق الصوتية، وتم جدولة زيارات متابعة على فترات 3، 6، 9، و12 شهرا لتقييم تغيرات الموجات فوق الصوتية في سمك بطانة الرحم بالإضافة إلى الأحداث الجانبية ذات الصلة. **النتائج**: خلال 12 شهرا، أظهرت مجموعة الدواء الوهمي زيادة ملحوظة في التيار الكهرومغناطيسي (6.32 ملم)، بينما أظهرت مجموعة الميتفورمين تغيرا طفيفا (4.13 ملم) (p<0.001). أكد تحليل التنفس العميق تأثيرا زمنيا كبيرا وتفاعل زمني × المجموعة (ص<0.001). حدث PMB في 6.7٪ من مجموعة الميتفورمين مقابل 26.7٪ في مجموعة الميتفورمين (*p=0.038*). **الاستنتاجات**: الميتفورمين يحسن بشكل كبير من سماكة بطانة الرحم المرتبطة بالتاموكسيفين وحدوث النزيف بعد انقطاع الطمث لدى النساء بعد انقطاع الطمث المصابات بسرطان الثدي الإيجابي لمستقبلات الإستروجين.

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INTRODUCTION

Breast cancer is still the most common cancer among women around the world. Estrogen-receptor-positive (ER+) breast cancers are one type of breast cancer that responds very well to adjuvant hormonal therapy [1]. This is because estrogen receptors on the tumor can be blocked, which creates a chance for treatment, as this blocking can be done with a non-invasive medication-based approach to anti-hormones [2]. Tamoxifen, a selective estrogen receptor modulator (SERM), remains the standard adjuvant hormonal therapy for ER+ breast cancer. It has this effect by competitively binding to and blocking estrogen receptors in breast cells. This stops the growth and transcription of cells that are controlled by estrogen. This mechanism leads to a significant reduction in the recurrence, morbidity, and cancer-specific mortality in women with ER+ breast cancer [3]. The role of tamoxifen as a selective estrogen receptor modulator (SERM) is characterized by tissue-specific estrogenic and anti-estrogenic effects, while it acts as a competitive antagonist to estrogen receptors in the breast tissue. In other organs, tamoxifen-bound estrogen receptors tend to

recruit coactivators rather than co-repressors, resulting in a partial agonist activity [2,3]. This exact mechanism carries several therapeutic advantages and disadvantages for Tamoxifen. Compared to aromatase inhibitors like Anastrozole (Arimidex), which potentially inhibits the synthesis of estrogen, lowering its systemic level, Tamoxifen offers a more protective effect in regard to bone mineral density and lipid metabolism, especially in postmenopausal women [4]. However, tamoxifen's effect as a partial agonist, particularly on the uterine estrogen receptors "alpha" (ERα), results in stimulation of stromal and glandular growth, ultimately leading to endometrial hyperplasia and increased endometrial thickness (ET), which can manifest as polyps, postmenopausal bleeding, or, rarely, endometrial carcinoma [5]. Metformin, a biguanide used as a first-line agent in treating type 2 Diabetes Mellitus (DM), has a theoretical potential in decreasing Tamoxifen-related endometrial hyperplasia by means of lowering systemic insulin, which in turn indirectly suppresses and downregulates endometrial hyperplasia by decreasing the insulin/IGF activity, as well as direct intracellular effects in activating AMP-activated protein kinase (AMPK), which in turn inhibits the mTOR (a central growth-promoting kinase), which results in decreased estrogen-driven cellular growth and proliferation in the endometrium [6-8]. Metformin also has a role in potentially suppressing ERα phosphorylation, which generally decreases the expression of several estrogen-responsive genes [8,9]. Despite being readily proven in vitro [10,11], there is limited clinical evidence supporting the role of metformin as a potential adjunct to tamoxifen to prevent tamoxifen-related endometrial complications while preserving tamoxifen's advantages over using aromatase inhibitor therapy. For instance, a randomized placebo-controlled trial by Davis et al. investigated the effect of coadministering metformin with tamoxifen and reported positive outcomes regarding endometrial thickness and insulin sensitivity [12]. Despite such promising data, many clinical studies in this regard are limited in sample sizes, do not focus on the postmenopausal female population, and have poor follow-up data. The current study aims to evaluate the effect of metformin on endometrial thickness in a sample of postmenopausal Iraqi ER+ breast cancer patients on adjuvant tamoxifen therapy in the context of a well-designed randomized control trial to support and enrich the worldwide evidence on this matter of interest.

METHODS

Study design and setting

The current study is a two-arm double-blind randomized clinical trial (RCT). The study was conducted between January 2nd in 2024, and July 1st in 2025, in the breast clinic and radiology unit of a specialized oncology center. Written and informed consent was obtained from the patients to participate in the study and undergo all the follow-up procedures.

Study sample

One-hundred postmenopausal female patients with histologically confirmed estrogen receptor-positive (ER+) breast cancer with > 1 year on adjuvant Tamoxifen therapy were assessed for eligibility. A total of 63 patients were eligible and randomly allocated into two groups in a 1:1 ratio. Group I (n=32) was designated to be the experimental group, and the patients in this group were assigned to administer their prescribed Tamoxifen in addition to Metformin 500mg twice daily, titrated to tolerance, for the upcoming 12 months. Group II (n=31) was designated to be the placebo comparator group, and the patients in this group were assigned to administer their prescribed Tamoxifen in addition to a placebo tablet matching the shape, size, and color of Metformin twice daily for the upcoming 12 months. Patients were then assigned to undergo a transabdominal ultrasound exam to determine the baseline endometrial thickness (in millimeters). A follow-up ultrasound was performed at 3, 6, 9, and 12 months after initiating the allocated intervention to examine changes in endometrial thickness over time. The primary outcome of this study is to evaluate the effect of metformin in preventing/halting tamoxifen-induced endometrial hyperplasia in comparison to placebo. Secondary outcomes included monitoring postmenopausal bleeding events as well as reporting any possible adverse effects. Three participants were lost to follow up leaving 60 participants for analysis (30+30). Figure 1 demonstrates the study design in a flowchart.

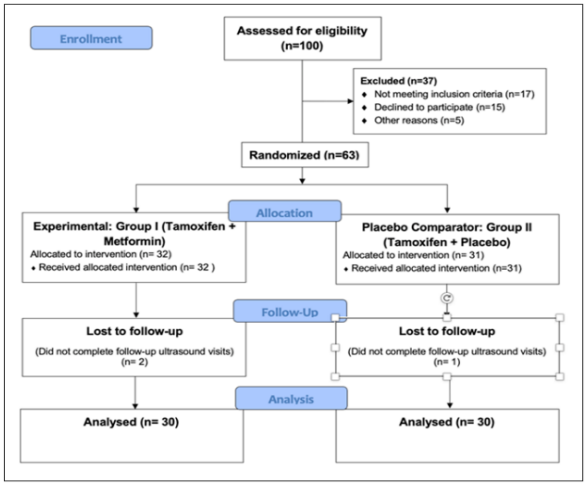

Figure 1: Flow chart of the study.

Blinding and randomization

The current study is double-blind, in which neither the participant nor the outcome assessor performing the transabdominal ultrasound is aware of the study group's allocation. The patients' sequence was prelabeled in

numbers, and the randomized allocation was done in a 1:1 ratio using the computer software (randomizer.org).

Drug intervention

Both study groups continued receiving tamoxifen as per their prescribed dose under the supervision of the responsible oncologist. Group I (Tamoxifen + Metformin) received an addition of Metformin 500 mg (Glucophage™ 500 mg, Merck Serono, Darmstadt, Germany) twice daily, titrated to tolerance. Group II (Tamoxifen + Placebo) received an inert, film-coated tablet that identically matches Metformin 500mg (Glucophage™ 500mg) in shape, size, coloring, coating, weight, and dosing regimen, manufactured with no biologically active ingredient utilizing standard excipients (e.g., microcrystalline cellulose, starch/croscarmellose, povidone, magnesium stearate) and an identical film coat (e.g., hypromellose, polyethylene glycol, titanium dioxide). Packaged in sealed blisters to minimize odor/taste cues. Dispensed by the investigational pharmacy per randomization; to be taken twice daily.

Ultrasound measurement

The transabdominal uterine ultrasound was performed by the radiology team under the supervision of an experienced radiologist while the patient was lying comfortably in the supine position with a full bladder. Multiple uterine sweeps were performed to obtain a true midsagittal plane view. Total endometrial thickness was reported in millimeters (mm), either as a double-layer measurement or as the sum of single-layer measurements when there were intracavitary fluids or intracavitary lesions separating the two layers. The measurement was taken using the ACUSON Juniper™ ultrasound device (Siemens Healthineers, Erlangen, Germany) with a suitable curvilinear 5C1 probe with a frequency of 1.4–5 MHz. Patients in both groups underwent ultrasound to evaluate baseline endometrial thickness before intervention, and follow-up visits were scheduled at 3,6,9, and 12 months after initiation of intervention.

Inclusion criteria

Postmenopausal Female patients (amenorrhea ≥ 12 months). Histologically confirmed estrogen receptor-positive (ER+) breast cancer. Completed all required surgery and/or chemotherapy (if indicated). On adjuvant tamoxifen therapy for at least 1 year. Accepts to enroll in the study.

Exclusion Criteria

Patients refusing to enroll in the study. Ongoing or history of endometrial or ovarian malignancy. Concurrent hormonal therapy that might affect endometrial thickness. Concurrent Diabetes mellitus in which Metformin is already prescribed. Known hypersensitivity or severe intolerance to metformin.

Sample Size Calculation

The sample size per group (n) was calculated using the following formula for an independent sample t-test with a continuous outcome (endometrial thickness in mm) [13]:

$$n = \frac{2 \cdot (Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \cdot \sigma^2}{\Delta^2}$$

Where: n: Sample size per group, $Z_{1-\frac{\alpha}{2}}$: Z-score corresponding to the significance level (α) for a two-sided test equals 1.96 $\alpha = 0.05$, $Z_{1-\beta}$: Z-score corresponding to the desired power 80% (1-β) equals 0.84, σ: Standard deviation of the change in endometrial thickness, assumed to be 3 mm, based on a previous study [14], Δ: Expected difference in mean change in endometrial thickness between the treatment and placebo groups (effect size), assumed to be 2 mm based on a previous study [15]. Thus, approximately 36 participants per group are required, with a total of 72, accounting for an allocation ratio of 1:1. In the present study, a total of 63 eligible participants were enrolled (32 and 31 per group), which was comparable to the calculated sample and reasonably powered for analysis.

Trial registration

This clinical trial is registered and published by clinicaltrials.gov (NCT07145827).

Statistical analysis

Data were analyzed using SPSS software (version 26.0). Independent samples t-tests for continuous variables and chi-square tests for categorical variables were used to compare baseline demographic and clinical characteristics between the intervention and control groups. A p-value greater than 0.05 meant that there were no meaningful differences. A repeated measures ANOVA was used to look at changes in endometrial thickness over time (baseline, 3, 6, 9, and 12 months) in both groups. Wilks' Lambda was used to look at the main effect of time and the time × group interaction. Secondary outcomes (incidence of postmenopausal bleeding and adverse events) were summarized descriptively and analyzed using chi-square tests. The significance level was set at $p < 0.05$.

RESULTS

A total of 60 postmenopausal women with estrogen receptor-positive breast cancer, who had been receiving tamoxifen for at least one year, were enrolled between January 2024 and July 2025. Participants were randomly assigned to two groups: Tamoxifen + Metformin (n = 30) and Tamoxifen + Placebo (n = 30). Baseline demographic and clinical characteristics, as presented in Table 1, were comparable between the two groups ($p > 0.05$ for all variables), confirming randomization. Endometrial thickness (ET) was measured at baseline, 3, 6, 9, and 12 months.

Table 1: Baseline demographic and clinical characteristics (n=30 in each group)

Variable	Tamoxifen + Metformin	Tamoxifen + Placebo	*p*-value
Age (year)	57.7±6.382	57.61±4.765	0.949
BMI (kg/m²)	27.9±3.448	26.633±3.145	0.143
Years since menopause (year)	6.90±4.27	6.67±3.304	0.814
Baseline endometrial thickness (mm)	3.387±0.436	3.339± 0.624	0.731

Values are presented as mean±SD.

Table 2 displays the ET values over time for both groups. At baseline, ET was similar between the Tamoxifen + metformin (3.39 mm) (ranging between 2.64 and 4.63 mm with a median of 3.355 mm) and tamoxifen + Placebo (3.34 mm) (ranging between 2.11 and 4.57 mm with a median of 3.26 mm) groups. At 3 months, ET ranged between 2.84 and 4.73 mm with a median of 3.505 mm for tamoxifen + metformin compared to 3.29 to 5.61 mm with a median of 4.195 mm for the tamoxifen + placebo group. At 6 months, ET ranged between 2.86 and 5.42 mm with a median of 3.76 mm for tamoxifen + metformin compared to 3.44 to 7.05 mm with a median of 4.985 mm for the tamoxifen + placebo group. At 9 months, ET ranged between 2.79 and 5.25 mm with a median of 4.01 mm for tamoxifen + metformin compared to 4.09 to 7.62 mm with a median of 5.82 mm for tamoxifen + placebo group.

Table 2: Endometrial thickness (mm) over time

Time Point	Tamoxifen + Metformin		Tamoxifen + Placebo		Mean difference	95% CI of the Difference	*p*-value
Baseline	3.387±0.435	3.355 (2.64-4.63)	3.339±0.624	3.26 (2.11-4.57)	0.048	[-0.23016, 0.32616]	0.731
3 months	3.593±0.475	3.505 (2.84-4.73)	4.27±0.653	4.195 (3.29-5.61)	-0.677	[-0.97168, -0.38166]	<0.0001
6 months	3.886±0.625	3.76 (2.86-5.42)	5.035±0.833	4.985 (3.44-7.05)	-1.149	[-1.52813, -0.76920]	<0.0001
9 months	3.999±0.561	4.01 (2.79-5.25)	5.751±0.927	5.82 (4.09-7.62)	-1.752	[-2.14804, -1.35596]	<0.0001
12 months	4.133±0.551	4.095 (3.16-5.26)	6.319±1.022	6.3 (4.54-8.42)	-2.186	[-2.60980, -1.76153]	<0.0001

Values are expressed as mean±SD.

Over the 12 months, a progressive and statistically significant divergence was observed throughout follow-up. The tamoxifen + placebo group exhibited a marked increase in ET, reaching 6.32 mm (ranging between 4.54 and 8.42 mm with a median of 6.3 mm), while the tamoxifen + metformin group showed minimal change, with a mean ET of 4.13 mm (ranging between 3.16 and 5.26 mm with a median of 4.095 mm). This resulted in a mean increase of +0.74 mm in the metformin group compared to +2.98 mm in the placebo group ($p < 0.001$). Repeat measures ANOVA revealed a significant main effect of time, Wilks' Lambda = 0.096; F(4, 55) = 129.335; p-value < 0.001, indicating a substantial change in ET over time. The time × group interaction was also significant (Wilks' Lambda = 0.215; F(4, 55) = 50.260; $p < 0.001$), suggesting that the change in ET over time differed between the groups. Figure 2 illustrates this trend, with the tamoxifen + metformin curve remaining nearly flat, while the tamoxifen + placebo curve shows a progressive upward slope. PMB was reported in 2 patients (6.7%) in the tamoxifen + metformin group, compared to 8 patients (26.7%) in the tamoxifen + placebo group.

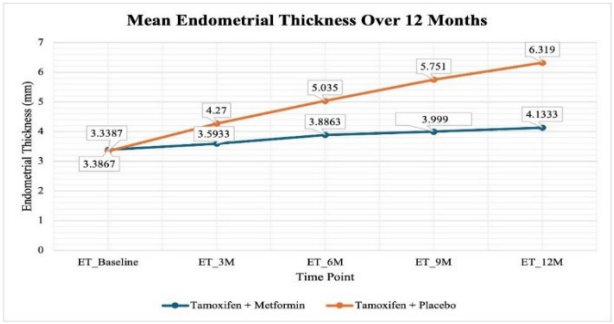

Figure 2: Endometrial thickness (y-axis, mm) versus time points (x-axis: baseline, 3, 6, 9, and 12 months).

This difference showed a trend toward a lower incidence in the metformin group ($\chi^2 = 4.320$; $p = 0.038$), as illustrated in Table 3.

Table 3: PMB and adverse events (n=30 in each group)

Adverse Event		Tamoxifen + Metformin	Tamoxifen + Placebo	*p*-value
Postmenopausal Bleeding (PMB)	PMB	2(6.67)	8(26.67)	0.038
	No PMB	28(93.33)	22(73.33)	
GI Symptoms	Mild	10(33.33)	3(10)	
	Moderate	2(6.67)	0(0)	0.023
	None	18(60)	27(90)	
Fatigue	Mild	5(16.67)	6(20)	
	Moderate	5(16.67)	3(10)	0.735
	None	20(66.67)	21(70)	

Values are expressed as frequency and percentage.

Adverse events were monitored throughout the study, with results summarized in Table 3. Gastrointestinal (GI) symptoms were more frequent in the tamoxifen + metformin group, occurring in 12 patients (40%), compared to 4 patients (13.3%) in the tamoxifen + placebo group. These symptoms were predominantly mild to moderate and transient, resolving within the first three months, with no participants requiring

discontinuation. Fatigue was reported in 10 patients (33.3%) in the tamoxifen + metformin group, compared to 11 patients (36.67%) in the tamoxifen + placebo group ($p = 0.735$). No severe adverse events, hypoglycemia, or lactic acidosis were reported.

DISCUSSION

The literature on metformin co-administration with tamoxifen for patients with breast cancer to ameliorate endometrial hyperplasia (EH) is scarce, with only one prior randomized controlled trial (RCT) addressing this specific combination [12]. Tamoxifen, a selective estrogen receptor modulator (SERM), is a cornerstone endocrine therapy for estrogen receptor-positive (ER+) breast cancer patients [16]. Although it is an estrogen antagonist in the breast, tamoxifen is an estrogen agonist in the endometrium [17]. But its estrogen-agonistic effects on the endometrium raise the chances of endometrial hyperplasia (EH), polyps, and cancer. The risk of endometrial cancer is two to seven times higher after two to five years of use [17–19]. The mean endometrial thickness (ET) has been reported to increase, on average, 5-6 mm in the first year of tamoxifen use [18, 20]. The current double-blind, randomized controlled trial (RCT) looked at the effects of giving metformin and tamoxifen together to make tamoxifen's effects on endometrial thickening in women who have ER+ breast cancer and who are past menopause better. The results showed that metformin (500 mg twice daily) lowered endometrial thickness (ET) much more than a placebo did. Over 12 months, the ET increase was 0.75 mm in the metformin group and 2.98 mm in the placebo group, a mean difference of 2.23 mm ($p < 0.001$). Additionally, metformin reduced the incidence of postmenopausal bleeding (PMB) in the metformin groups versus the placebo group (6.7% *vs*. 26.7%, respectively, with a *p*-value of 0.038), which is a clinical indicator of EH and potential malignancy [21]. These findings align with the only prior RCT by Davis *et al*. [12], which reported a 2.3 mm reduction in ET with metformin (850 mg twice daily) versus a 3.0 mm increase in controls over 52 weeks (p-value = 0.05). The consistency across these studies reinforces metformin's potential as an adjunct therapy to counteract tamoxifen's proliferative effects on the endometrium. Upon reviewing the literature, a noteworthy finding reported in addition to the ability of tamoxifen to induce pathological endometrial changes, as it appeared to differ between premenopausal and postmenopausal women receiving this medication. However, the current study focuses on postmenopausal women. It has been reported that there was no difference in endometrial cancer rates between women treated with tamoxifen and those in the placebo group in women aged ≤ 49 years; however, in women aged ≥ 50 years, the risk ratio was 4.01 for those treated with tamoxifen versus those receiving placebo [22, 23]. Tamoxifen induces endometrial cell growth via the mammalian target of rapamycin (mTOR) pathway and exacerbates insulin resistance (IR), a risk factor for endometrial proliferation [24-27]. On the other hand, metformin exerts antiproliferative effects through direct and indirect mechanisms [25, 28-32]. Directly, it activates the LKB1/AMP-activated protein kinase (AMPK) complex, inhibiting mTOR signaling and inducing G0-G1 cell cycle arrest via reduced cyclin D1 expression and enhanced tumor suppressor activity (p27, FOXO3a) [25,28-33]. Indirectly, metformin lowers circulating insulin and insulin-like growth factor-1 (IGF-1) levels, attenuating tumorigenic pathways such as PI3K/Akt/mTOR and MEK/ERK1/2, which are related to tamoxifen-induced EH [28, 31] . Routine endometrial thickness screening by transvaginal ultrasound (TVUS) has been used for many years for the early detection of endometrial hyperplasia and endometrial cancer (EC) during tamoxifen treatment. However, is not recommended due to poor correlation with abnormal pathology and increased risk of unnecessary interventions [21,22,34]. Thus, the clinical significance of these findings lies in metformin's potential to reduce the need for invasive procedures, such as endometrial biopsies, often prompted by increased ET or PMB in tamoxifen-treated patients. Concerning the safety profile of metformin, adverse events were predominantly gastrointestinal (GI) with mild to moderate symptoms reported in 12 of 30 participants during the initial three months; only two of them had moderate GI adverse events, yet no discontinuations were necessary. This tolerability profile is consistent with metformin's established safety in non-diabetic populations, as noted by Hadad *et al*. [35], who reported transient GI side effects in 20-25% of non-diabetic breast cancer patients, with all cases resolving without intervention and no severe events like lactic acidosis. The absence of severe adverse events such as hypoglycemia or lactic acidosis in the current study further corroborates metformin's safety profile, aligning with guidelines from the American Diabetes Association 2024 [36] that emphasize its low risk in non-diabetic populations when titrated appropriately. Compared to alternatives like aromatase inhibitors (AIs), which are reported to provide a potential protective effect on the endometrium in postmenopausal breast cancer patients previously treated with tamoxifen. However, they are associated with serious side effects due to a hypoestrogenic state that results in a strong association with the development of adverse musculoskeletal symptoms such as joint pain, stiffness, decreased grip strength, and decreased exercise tolerance in up to 50% of patients [37,38], thus, metformin could offer a well-tolerated option. Progestin -another alternative- while effective in reducing EH in estrogen-treated patients, lacks evidence for safety in tamoxifen-treated breast cancer patients and is not recommended [22]. A meta-analysis by Yao *et al*. [39] in 2022 linked metformin to improved survival in gynecologic cancers, potentially through reduced proliferative events, supporting its role in EH prevention. The findings of this

study extend the mechanistic insights into clinical settings, showing a practical reduction in ET that could probably reduce the concerns regarding tamoxifen-induced EH. Future research should prioritize multicenter RCTs with larger cohorts, extended follow-up, and inclusion of premenopausal women to validate these findings and establish clinical treatment protocols.

Limitations of the study

Limitations of this study include the relatively small sample size (n=30) for each arm of the study and a single-center design. The exclusion of premenopausal women and the lack of long-term follow-up beyond 12 months also prevent assessment of sustained effects or late-onset adverse events. Furthermore, evaluating weight and BMI after metformin co-administration could further elicit the relation between obesity, metabolic factors, and EH.

Conclusion

Metformin co-administration with tamoxifen significantly reduces endometrial thickening and PMB incidence in postmenopausal women with ER+ breast cancer. GI symptoms were mild and self-limiting, confirming good safety and tolerability. These findings, consistent with emerging evidence, support the potential preventive role of metformin against tamoxifen-induced endometrial proliferation in postmenopausal breast cancer patients.

Conflict of interests

The author declared no conflict of interest.

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Data sharing statement

Supplementary data can be viewed at Zenodo: Effect of Metformin on endometrial thickness in postmenopausal breast cancer patients receiving Tamoxifen doi: https://doi.org/10.5281/zenodo.17478948

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