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The benefits of adding metformin to tamoxifen to protect the endometrium- a randomized placebo-controlled trial

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ABSTRACT

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Background: We investigated whether metformin prevents tamoxifen-induced endometrial changes and insulin resistance (IR) after a diagnosis of breast cancer.

Methods: This was a single centre, randomized, double-blind, placebo-controlled, parallel group trial. Postmenopausal women with hormone receptor-positive breast cancer taking tamoxifen were randomly allocated to metformin 850mg or identical placebo, twice daily, for 52 weeks. Outcome measures included double endometrial thickness (ET) measured by transvaginal ultrasound, fasting insulin, glucose and IR estimated by the homeostasis model of assessment (HOMA-IR).

Results: 112 women were screened and 102 randomized. Results are presented as median (range). The 101 women who took at least one dose of medication were aged 56 (43-72) years, 5(0.5-28) years post menopause and had taken tamoxifen for 28.9 (0-367.4) weeks. The baseline ET was 2.9mm (1.4-21.9) for the placebo group (n=52) and 2.5mm (1.3-14.8) for the metformin group (n=50). At 52 weeks, the median ET was statistically significantly lower for the metformin (n=36) than the placebo group (n=45), (2.3 mm (1.4-7.8) vs 3.0 (1.2-11.3); p=0.05). 13.3% allocated to placebo had an ET greater than 4mm vs 5.7% for metformin (p=0.26). There was no endometrial atypia or cancer. Compared with placebo, metformin resulted in significantly greater baseline adjusted reductions in weight (p<0.001), waist circumference (0.03) and HOMA-IR (p<0.001).

Conclusions: Metformin appears to inhibit tamoxifen-induced endometrial changes and has favourable metabolic effects. Further research into the adjuvant use of metformin after breast cancer and to prevent, EH and cancer is warranted.

Introduction

Tamoxifen, as endocrine therapy for women with estrogen and /or progesterone receptor positive (hormone receptor; HR+) breast cancer, may be taken for up to 10 years ¹. Although an estrogen antagonist in the breast, tamoxifen is an estrogen agonist in the endometrium ². The mean endometrial thickness (ET) measured by transvaginal ultrasound (TVU) has been reported to increase, on average, 5-6 mm in the first year of tamoxifen ^{3,4}, and tamoxifen has been associated with endometrial polyps, endometrial hyperplasia (EH) and endometrial cancer ^{2,4}. There is a 2 to 7-fold increase in the risk of endometrial cancer after 2 and 5 years of tamoxifen treatment respectively compared with non-use after breast cancer⁵.

Tamoxifen stimulates endometrial cell growth and proliferation by activation of the protein mammalian target of rapamycin (mTOR) pathway ^{6,7}. Tamoxifen also causes hepatic steatosis and insulin resistance (IR)⁸, with the latter a risk factor for endometrial proliferation ⁹. Metformin is a widely used oral anti-diabetic agent. In vitro and in animal models, metformin stimulates the

LKB1/AMP-activated protein kinase (AMPK) complex which in turn inhibits mTOR signalling resulting in anti-proliferative effects in the endometrium^{7, 10, 11}. A reduction in IR by metformin would provide a complementary anti-proliferative effect on the endometrium. The effects of metformin on endometrial proliferation have not been studied in women in a prospective clinical trial.

The primary aim of the study was to determine whether metformin inhibits the endometrial effects of tamoxifen by assessment of ET and presence of new abnormalities such as polyps and, with the expectation that the majority of the study participants would have an ET that would warrant endometrial sampling at week 52^{3, 4}, the impact of metformin on activation of the mTOR pathway in the endometrium assessed by gene expression. The effects of metformin on clinical characteristics and clinical biochemistry were also explored as pre-determined secondary outcomes.

Study Methods

Participants

Women were eligible to participate if they were postmenopausal, aged < 75 years and had been prescribed tamoxifen 20mg/day for the treatment of HR+ breast cancer, either as their first endocrine therapy or after switching from an aromatase inhibitor. Women were required to be non-hysterectomized. Women were excluded if they had used any systemic hormone therapy in the prior 6 months, had a serious endocrine disorder or other systemic disease, consumed more than 3 standard alcoholic drinks per day, had insulin dependent diabetes mellitus or took an oral hypoglycemic agent. Women with advanced breast cancer and likely to have progression of their disease within the study period, as assessed by their treating oncologist, were excluded.

Women were referred by their oncologist, recruited through the Breast Cancer Network of Australia, the National Breast Cancer Foundation (Register 4), or from the community, via advertisements in health bulletins and the Women's Health Research Program website. The study was approved by the Monash University Human Research Ethics Committee (Clayton, Victoria, Australia) and all participants provided written, informed consent.

Study Design and Treatment

This was a single centre, randomized, double-blind, placebo-controlled, parallel group trial. It consisted of a 4-week screening period plus a 52-week treatment phase involving 4-6 study visits, depending on the need for endometrial biopsy, and telephone contacts at weeks 2, 6 and 40. Participants attended the Monash University Women's Health Research Program in Melbourne, Australia for their study visits, had their TVU at Malvern Ultrasound for Women, Melbourne and,

when indicated, were seen by a study gynecologist as described below. All participants underwent a physical examination, including vital signs, at screening. Women who met the eligibility criteria were allocated a study number, had blood drawn and had a TVU. Endometrial sampling was not performed if the ET was 4mm or less, with no abnormalities, as biopsy would be unlikely yield tissue for histology. Women with an ET $\leq$ 4mm were randomized and sent study medication. Women with a double ET greater than 4mm and/ or an abnormality that warranted investigation, were seen by a study gynecologist (JMcN, JW) for endometrial sampling (by office biopsy or hysteroscopy and curettage). A finding of EH with atypia or endometrial cancer at this point resulted in exclusion. Otherwise, women were randomized and commenced on study medication. The same procedure, with respect to referral for endometrial sampling, was followed when women had their TVU at the end of the 52-week treatment period.

Randomization and treatment

Women were randomly allocated, in a 1:1 ratio to metformin or identical placebo tablets, provided by Activa Pty Ltd, The Rocks, NSW, Australia. The computer-generated randomization schedule was created in random blocks of 4 and 6 with separate schedules for women with a body mass index below 30 and greater than 30 kg/m². The randomization schedules were generated and held by PJR, who was not involved in the day-to-day conduct of the study. The schedules remained concealed until data analysis was complete. The study medication boxes were numbered and participants were sequentially assigned to the next unassigned treatment code at randomization. All study participants, study staff, including outcome assessors, remained blind to the intervention until the end of the analysis.

The metformin dose was titrated over three weeks from 425mg at night to 850mg twice a day. Participants were asked to return all unused tablets. Treatment compliance was checked by counting returned tablets at 26 weeks and at the final visit. A participant was considered to be compliant if she used at least 75% of the study drug that would be expected for the duration of her participation.

Outcomes Measures

Weight and body mass index (BMI)

BMI was calculated as height in weight (kg)/ height (m)². Abdominal circumference was taken as the greatest measure between the lowest rib and the top of the pelvis.

Endometrial thickness

TVUs were performed by gynecological sonographers (SP or AE) using a Philips iu22 with a vaginal probe c8-4v or GE Voluson E8 with a 3D vaginal probe RIC5-9-D. If the endometrial thickness was difficult to measure, if there were irregularities or thickness was >4mm, saline

infusion sonohysterography (SIS) was performed¹². ET was distinguished by the sonographers from observable subendometrial cystic changes¹³. A second TVU was not performed after endometrial sampling before commencement of study medication as the sampling procedure would have resulted in a thin endometrium.

Biochemical variables

All biochemical analyses were performed by the Department of Biochemistry at the Alfred Hospital, Melbourne, Australia. Fasting glucose was measured by the Abbott Architect ci16200 instrument (Abbott Diagnostics, Illinois, USA) and fasting insulin was measured by chemiluminescent microparticle immunoassay with CVs of 4.3% at low concentration and 2.9% at high concentrations. HOMA-IR, as an estimate of insulin resistance, was calculated using the formula $\text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/l)} / 22.5$ ¹⁴.

Study power calculations and statistical analyses

The study power calculation assumed that at least 60% of the women allocated to placebo would have an ET > 4mm at week 52 and undergo sampling^{3,4}. Based on a mean increase in ET with tamoxifen of 5.41mm (SD3.78) compared with exemestane of 2.94 (SD1.91) over 12 months reported by Kieback et al⁴, 25 women per group would provide a power of 80% to find a difference of this magnitude ($\alpha=0.05$). In an observational study, hyper-proliferative and hyperplastic endometrial tissue from women receiving tamoxifen exhibited higher phosphorylation levels at specific amino residues of AKT in the order of (2.6-3.5 fold) and for mTOR (10-20 fold) compared with benign endometrial tissue from non-treated patients¹⁵. Thus, the effect sizes anticipated in the molecular pathways to be studied in the endometrial samples were large (minimum changes of 2 to 3-fold). Taking a pragmatic approach, we aimed to recruit 130 women and randomize half to each treatment. Allowing for a conservative 25% non-completion rate and 20% unevaluable samples, we aimed to have evaluable endometrial tissue and study data for 40 women in the placebo arm, and potentially fewer in the metformin arm if it inhibited proliferation. Without available information about the variability of the effects, we estimated that our relatively modest study size would be adequately powered for both ET and examination of the mTOR pathway gene expression. The sample size calculation could not be based on EH, polyps or endometrial cancer, as in their own right these are not sufficiently common. Recruitment to the study was unexpectedly challenging and took nearly 2 years. Therefore, recruitment was ceased once we achieved randomization of over 100 women, with the expected completion of a sufficient number of women to meet statistical power.

Statistical analysis was performed using the program Stata Version 12.1 (Stata Corp, College Station, Texas, USA) and SPSS (version 20; SPSS Australasia Pty Ltd, North Sydney, Australia). Modelling was performed for each outcome using a linear regression approach with the outcome

variable being the change between the week 52 assessment and baseline. The independent variables were treatment group and baseline result. Non-normal variables were log transformed. All except one of the 25 women who had endometrial sampling at baseline had hysteroscopy and curettage, and hence restoration of a thin endometrium. We could not baseline-adjust the 52 week ET measure as a TVU was not performed post curettage, although all women were considered to have had a ET of 4mm or less at randomization.

Results

112 potential participants were screened for eligibility between July 2014 and June 2016. One woman with an endometrial ablation and another with a progestin intra-uterine device in situ were excluded (Figure 1A). One woman had just undergone TVU and endometrial curettage and therefore satisfied the requirement of having an ET less than 4mm, and was randomized. 109 women were referred for a TVU and 106 of these women had a baseline TVU that provided a measure of ET. Two of the 109 women withdrew, one who needed a SIS refused the procedure and for the other, SIS could not be performed because of cervical stenosis. A third woman with indeterminate ET was referred for endometrial biopsy and was subsequently randomized.

Baseline TVU findings

81 women had a baseline ET of 4mm or less. Of these, 4 women had an endometrial polyp and underwent endometrial sampling. Of the 25 women with an ET greater than 4mm, 20 underwent hysteroscopy and curettage, one had office endometrial sampling and four women (3 from interstate) withdrew and pursued private follow-up. Endometrial histopathology at baseline was available for 28 women, including the four women with an ET of ≤ 4 mm and a polyp, and 3 women with a thickened endometrium who withdrew after their TVU. There was no EH, atypia or cancer. Fifteen women had an endometrial polyp, four not having been identified by TVU. Microglandular hyperplasia was reported in one sample and proliferative endometrium in another from a woman who also had an endometrial polyp. Hysteroscopy resulted in no curettings in 3 women, and atrophic or inactive endometrium in the remainder.

Intervention phase

102 women were randomised and 101 took at least one dose of study medication (Figure 1B). Their median age (range) was 56 years (43-72), they were a median of 5 years (0.5-28) post menopause and had been on tamoxifen for a median duration 28.9 weeks (0 to 367.4) at screening (Table 1). One woman (participant X) randomized to metformin had an abnormal endometrial cavity with uncertainty about an endometrial or myometrial lesion, but no evidence of increased ET. This was

found to be a large intra-uterine polyp at hysterectomy after study completion. The baseline TVU-reported ET was similar for the treatment groups: median (range) for the placebo group 2.9 mm (1.4-21.9) and 2.5mm (1.3-14.8) for the metformin group.

Study outcomes

Thirty-six of the 50 women randomized to metformin and 45 of the 51 women randomized to placebo had a TVU at 52 weeks. The median ET was significantly lower for the 35 women in the metformin group (ET of participant X could not be measured at 52 weeks) than the 45 women in the placebo group (2.3 mm (range 1.4-7.8) vs 3.0 (1.2-11.3); $p=0.05$) (Table 2). At 52 weeks, a TVU-measured ET > 4mm was found in 6 of the 45 women on placebo (13.3%, range 5-11.3mm) and 2 of the 36 women taking metformin (5.6%, range 5-7.8mm) ($p=0.26$). One woman in each group had an indeterminate ET and both had a hysteroscopy with no curettings. New endometrial polyps were found in another 2 of the 45 women on placebo and after gynaecological review one had a hysteroscopy. Overall 10 women had endometrial sampling, 3 in the metformin group and 7 in the placebo group. Apart from one woman randomized to placebo who had a baseline ET of 3.5mm and an ET of 11.3 mm at 52 weeks who had disordered endometrial proliferation, all of the women who had endometrial sampling had either no curetting or inactive endometrial tissue. Consequently, no proliferative endometrial tissue was available for gene expression analysis.

Of the 46 women in the placebo group, 13 (28%) lost weight compared with 27 of the 37 (73%) randomized to metformin ($p<0.001$). Compared with the placebo group, the metformin group had significantly greater reductions in weight ($p<0.001$), BMI ($p<0.001$), fasting glucose ($p<0.001$), insulin ($p=0.004$) and HOMA-IR ($p<0.001$). The statistical significance for each of these variables was unchanged in an analysis of change adjusted for baseline. For waist circumference, adjustment for baseline resulted in a significant between-group difference of -2.3cm (95% CI -4.4 to -0.25, $p=0.03$).

Adverse events

Nine women treated with metformin and one woman treated with placebo withdrew because of gastrointestinal symptoms in the first 6 months. The other causes for withdrawal were unrelated to study drug. No women experienced vaginal bleeding during the course of the study.

Discussion

Metformin, at a dose of 1700mg/day, may prevent endometrial thickening, and development of new polyps, associated with standard dose tamoxifen, indicated by TVU over 12 months. Metformin treatment resulted in weight loss, reduction in waist circumference and improved insulin sensitivity.

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Not only was the mean ET at 52 weeks significantly less for the metformin group, but a smaller proportion of women in the metformin group had endometrial changes that justified hysteroscopy and curettage. Overall this is strongly indicative of a clinically meaningful effect of metformin on the endometrium.

Major risk factors for endometrial hyperplasia and cancer include obesity, IR, unopposed estrogen and tamoxifen therapy^{16-18 5, 19}. There is substantial evidence that metformin may protect the endometrium against these risk factors by local inhibition of mTOR either through activation of the LKB1/AMPK pathway^{11, 20-22} and indirectly via targets associated with IR²³. Added to this there has been mounting clinical evidence of the protective effects of metformin in the endometrium, with observational studies reporting metformin causing reversion of EH to normal endometrium²⁴⁻²⁶. Yet no randomized clinical trials have been undertaken. This is because, despite endometrial cancer being the most common gynaecological cancer, it is not sufficiently common to study the endometrial effects of metformin in any other than the most high-risk group, such as women being treated with tamoxifen. This, taken together with the increasingly large number of women with breast cancer requiring treatment with tamoxifen for up to 10 years, underpinned the design of this study.

The perfect study design would have been for every woman to have undergone pre-randomization endometrial sampling by hysteroscopy and curettage. However, hysteroscopy is an invasive procedure that can only be justified if an evaluable endometrial tissue sample is to be obtained. This is unlikely with an ET of 4mm or less²⁷. We set the threshold for endometrial sampling at an ET thickness above 4mm, with the expectation that the majority of the participants in the placebo arm would have TVU findings that would justify sampling^{4, 28, 29}. Surprisingly few women in our study had sufficient ET to warrant biopsy after 52 weeks, and when sampling was undertaken, it resulted in either no tissue or inactive endometrium in all but one of the samples. In contrast, in another study, tamoxifen treatment of 61 women, with a mean baseline ET similar to our study participants, resulted in 34 women having an ET of over 5mm by 12 months of therapy, with a mean increase in ET of 6mm, and 13 women had confirmed histological abnormalities on sampling⁴. In the endometrial sub-study of the Arimidex, Tamoxifen, Alone or in Combination adjuvant breast cancer trial, 7 of the 69 women treated with tamoxifen who had endometrial biopsies, developed endometrial pathology in the first year of treatment, including one case of atypical EH²⁹.

The link between obesity, IR, EH and cancer risk suggests that factors produced by fat tissue not only influence metabolic pathways involved in IR, but also pathways involved in endometrial cancer development. Obesity is also associated with a greater risk of breast cancer recurrence, even

in women with stage I disease, independent of age and treatment³⁰. Furthermore, tamoxifen use is associated with a more than 2-fold increase in risk of diabetes³¹. Over half of our study participants were overweight or obese, but none were diabetic. Metformin resulted in weight-loss in over 70% of the women, and statistically significant reductions in waist circumference and improved insulin sensitivity compared with placebo, similar to our prior study of obese, non-diabetic midlife women³². Therefore, metformin offers several clinical benefits to women taking tamoxifen. The significant reduction in weight and IR may protect against breast cancer recurrence, although this remains to be established³³. Tamoxifen causes hepatic steatosis and non-alcoholic liver disease, mostly through increased visceral fat accumulation and IR³⁴⁻³⁶. Co-treatment with metformin may prevent hepatic steatosis and therefore ameliorate the long term adverse metabolic effects of tamoxifen therapy³⁷.

The main limitation of this study was few women having sufficient ET to prompt endometrial tissue sampling at baseline and following a year of tamoxifen therapy, and therefore being unable to study endometrial gene expression pertaining to the biochemical pathways of interest. The withdrawal of women due to gastro-intestinal side-effects in the metformin group was unavoidable, with nausea and diarrhoea being common with metformin.

In summary, this study is the first to examine the endometrial effects of metformin in women taking tamoxifen in a randomized placebo-controlled clinical trial. The study did not demonstrate the anticipated prevalence of adverse endometrial effects of tamoxifen that would prompt an endometrial biopsy after 52 weeks of exposure, which in itself is an important finding. Nonetheless, there are no drugs available for the prevention of abnormal endometrial proliferation, EH or cancer. Metformin offers favourable metabolic protection and the endometrial protection suggested by this study, provides a strong basis for the conduct of a larger clinical trial. With our increasingly overweight and ageing population, the incidence of EH is expected to rise such that the availability of a safe nonsurgical therapeutic intervention to prevent or treat EH associated with tamoxifen, and in the broader community, is of clinical importance.

Figure legend

Figure 1 Participant flow- pre-treatment assessment (A) and progression after randomization (B).

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The principal investigators, SRD and RJB, designed the trial and supervised its conduct. The investigators collected the study data, which were analysed by PJR and RJB. The manuscript was prepared and submitted for publication by the authors, who vouch for the accuracy and completeness of the reported analyses. Activa Pty Ltd had no role in the planning or conduct of the study or the data analyses, and the manuscript did not require Activa's approval prior to submission

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Table 1 Descriptive statistics of the 101 women randomised who took at least one dose of study medication

	Placebo n = 51 Median (Range)	Metformin n = 50 Median (Range)	Total n = 101 Median (Range)
Age	60 (42 to 75)	56 (43 to 72)	56 (42 to 75)
Weight (kg)	71.2 (49.8 to 125.7)	73.5 (53.0 to 113.7)	72.4 (49.8 to 125.7)
Height (cm)	162.0 (151.5 to 174.0)	164.3 (147.5 to 180.0)	162.5 (147.5 to 180.0)
Body mass index (kg/m ²)	27.2 (19.8 to 49.1)	27.0 (20.2 to 43.7)	27.1 (19.8 to 49.1)
Waist circumference (cm)	95 (74 to 123)	94.5 (72 to 121)	95 (72 to 123)
Years since menopause n = 100 (Placebo missing 1)	6.0 (0.6 to 28)	5.0 (0.5 to 25)	5.0 (0.5 to 28)
Time on tamoxifen (weeks)	50 (0 to 367.4)	27.9 (0 to 219.1)	28.9 (0 to 367.4)
Glucose (mmol/L)	5.1 (4.4 to 6.2)	5.1 (4.4 to 6.5)	5.1 (4.4 to 6.5)
Insulin (μU/ml)	6.7 (3.0 to 17.9)	6.0 (3.0 to 16.8)	6.5 (3.0 to 17.9)
HOMA-IR	1.53 (0.64 to 4.69)	1.42 (0.63 to 4.85)	1.48 (0.63 to 4.85)
Endometrial thickness (mm) (Metformin missing 1)	2.9 (1.4 to 21.9)	2.5 (1.3 to 14.8)	2.7 (1.3 to 21.9)
Endometrial thickness > 4 mm, n (%)	12 (23.5%)	8 (16.3%)	20 (20.0%)
Chemotherapy yes, n (%)	32 (62.8%)	30 (60.0%)	62 (61.4%)
Switch from AI yes, n (%)	16 (31.4%)	21 (42.0%)	37 (36.6%)

Table 2: Descriptive statistics of women who took at least 1 dose of medication at 12 months, and the difference between 52 weeks & baseline.

	52 weeks			Change from baseline		
	Placebo n = 46 median (range)	Metformin n = 37 median (range)	p-value	Placebo n = 46 median (range)	Metformin n = 37 median (range)	p-value
Waist circumference (cm)	97.5 (74 to 119)	93 (70 to 116)	0.19	1 (-12 to 14)	-1 (-13 to 5)	0.056
Weight (kg)	73.0 (50.0 to 123.9)	73.2 (50.1 to 106.4)	0.42	1.5 (-6.1 to 7.4)	-1.7 (-8.4 to 3.7)	<0.001
BMI (kg/m ²)	28.4 (19.9 to 48.4)	27.0 (20.2 to 44.0)	0.11	0.52 (-2.27 to 2.90)	-0.58 (-2.96 to 1.37)	<0.001
Glucose mmol/L	5.2 (4.3 to 6.6) n = 45	4.9 (4.2 to 5.7) n = 36	0.01	0.0 (-0.5 to 0.7) n = 45	-0.25 (-1.3 to 0.6) n = 36	<0.001
Insulin	8.1 (2.6 to 16.6) n = 45	6.0 (3.2 to 12.2) n = 36	<0.001	0.5 (-2.7 to 9.8) n = 45	-0.5 (-7.9 to 4.5) n = 36	0.004
HOMA-IR	1.73 (0.55 to 4.87) n = 45	1.32 (0.63 to 2.87) n = 36	<0.001	0.14 (-0.71 to 2.48) n = 45	-0.17 (-2.07 to 0.96) n = 36	<0.001
Endometrial thickness (mm)	3.0 (1.2 to 11.3) n = 45	2.3 (1.4 to 7.8) n = 35	0.05			
Endometrial thickness >4 mm, n (%)	6 / 45 (13.3 %)	2 / 36 (5.6%)	0.26			

Endometrial thickness indeterminate	1	1				
Women with new endometrial polyps (n)	2	0				
Hysteroscopy and curettage/office biopsy (n/n)	6/1	3/0				
Histology- inactive endometrial tissue or no tissue (n)	6	3				
Disordered proliferation on biopsy (n)	1	0				

p-value => Kruskal Wallis for the difference between groups

Note: 1 woman (metformin) had unmeasurable endometrium at baseline and 12 months due to a polyp but thin endometrium

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