**Inhibitory role of Metformin for tamoxifen induced uterine cell proliferation in diabetic patients with ER-positive Breast cancer**

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**ABSTRACT**

The objective of the current work to evaluate the role of metformin in inhibiting the tamoxifen induced endometrial changes in diabetic patients with ER-positive breast cancer, a case-control study, carried out between December 2018 to May 2019, forty diabetic women in postmenopausal phase with ER+ breast cancer on tamoxifen (20mg/day), metformin (1700 mg/day) GROUP A, and 40 diabetic patients with ER+ breast cancer on the same dose of tamoxifen, but other hypoglycemic agent GROUP B, were selected as controls. Uterine thickness was assessed by ultrasonography imaging at the beginning of treatment with tamoxifen and after 2 years of treatment. Hysteroscopy was done, and pathological findings also recorded. Mean uterine thickness of diabetic patients on other hypoglycemic was significantly higher than diabetic patients on metformin (14.79±3.6 vs 4.37±1.8). Uterine thickness >5mm were 2 (5%) vs 36 (85%) reported with the diabetic patient on metformin and the diabetic patient on other oral hypoglycemic group. Three cases (7.5%) of the diabetic patients on other hypoglycemic agent were developed uterine polyps, and one case (2.5%) of diabetic patients on metformin were developed uterine polyps. One case (2.5%) of uterine carcinoma was reported with diabetic patients on other hypoglycemic group. In conclusions metformin significantly inhibit tamoxifen-induced endometrial changes and offers favorable endometrium protection.

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**INTRODUCTION**

Patients with breast cancer have a higher risk of endometrial proliferative conditions, as indicated by the high prevalence of these pathological conditions identified at the beginning of tamoxifen administration (Garuti et al., 2005). Tamoxifen is a first-line adjuvant hormonal therapy for premenopausal breast cancer patients with estrogen receptor α (ERα) positive tumors and is frequently given to postmenopausal females with ERα+ tumors. Tamoxifen functions as an antagonist to ERα and blocks its signaling pathway in ERα+ breast cancer cells (Davies et al., 2013). One of the most important side effects of postmenopausal tamoxifen treatment is its...
ability to increase a patient’s chance of developing endometrial lesions, including hyperplasia, polyps, carcinomas, and sarcoma (Jones et al., 2012). The estrogen agonist properties of tamoxifen reflect on the increased risk of gynecologic pathologies and include the development of endometrial pathologies and ovarian cysts (Nasu et al., 2008).

The link between insulin resistance and cell proliferation offers an intriguing potential therapeutic target to reverse uterine cell proliferation and prevent endometrial carcinoma. Some early trials have corroborated this link, showing the efficacy of metformin in inducing endometrial atrophy in benign endometrial proliferative disorders; one reported atrophy and therefore a reversal of endometrial hyperplasia in 96% of women treated with metformin (Tabrizi et al., 2015; Mohammed et al., 2018). The role of metformin in minimizing the side effects of tamoxifen is not well investigated, we hypothesized that metformin decreases the genital side effect of tamoxifen concerning increasing the uterine thickness, so the aim of this study is to explore the role of metformin in inhibiting the increases of uterine thickness in patients with breast cancer receiving tamoxifen.

MATERIALS AND METHODS

The study was conducted at Oncology Teaching Hospital at the Medical City Compus, Baghdad, Iraq, during the period from December 2018 to May 2019. Forty diabetic patients in postmenopausal phase with breast cancer of ER+ receptor on tamoxifen therapy (20mg/day) and metformin (1700mg/day) and 40 diabetic patients with ER+ breast cancer on other hypoglycemic agent with the same dose of tamoxifen were selected as controls. The hormonal level and menstrual history were used for assessment of menopausal phase. The women with amenorrhea for >12 months or serum FSH levels >40 mIU/mL were defined as a postmenopausal phase. The data were extracted from medical records of the patients, which included; patient’s Sociodemographic characteristics, used medications, findings of ultrasonography imaging and the result of histopathological examination. Uterine thickness was evaluated by the US after 2 years of treatment with tamoxifen. The assessment of the endometrial lining was done by calculating the maximum thickness from the outermost limits of endometrial myometrial juncature. The data entry and analysis was carried out by using SPSS version 23. Number and percentage were used to express the categorical data while the mean and standard deviation was used with numerical data. Appropriate tests were used to confirm significance. Statistical significant considered whenever the P-value was less than 0.05.

RESULTS AND DISCUSSION

The findings showed there was no significant difference in the mean value of age for the diabetic patients on metformin (GROUP A) and the diabetic patients on other hypoglycemic agent (GROUP B) with ER+ breast cancer (51.02±7 vs 52.65±10.2). The uterine thickness of GROUP B was significantly higher than GROUP A (14.79±3.6 vs 4.37±1.8), and this finding reflects the inhibitory role of metformin concerning uterine proliferation, as seen in Table 1. Only 2 cases (5%) of GROUP A had a uterine thickness of >5 mm, and 36 (85%) cases of GROUP B were had a uterine thickness of >5 mm. Three cases (7.5%) of GROUP B and one case (2.5%) of GROUP A were developed uterine polyp. Uterine carcinoma was reported with one case (2.5%) of GROUP B only. Metformin, which is generally used in the treatment of type 2 diabetes, has low toxicity and is considered a safe medicine with known pharmacokinetics. The inhibitory effect of metformin for cell proliferation and anticancer effect have been cited in several studies (Goodwin et al., 2011).

Our data indicated that the metformin in a dose of 1700 mg per day had an a significant inhibitory role concerning tamoxifen induced uterine cell proliferation as the results showed that the uterine thickness of a control group (B) who do not use metformin, was significantly increased or higher in comparison to diabetic patients on metformin therapy. These findings in line with Davis et al. (2018) who were studied 112 women with breast cancer on tamoxifen therapy and found the median endometrium thickness after 52 weeks of therapy with metformin was significantly lower for the metformin (n = 36) group than for the placebo group (n = 45) (2.3 mm (ranged from 1.4 to 7.8) vs 3.0 (ranged from 1.2 to 11.3), as well as they, found that 13.3% who were assigned to placebo had an endometrium thickness greater than 4 mm vs 5.7% for metformin. (Erdemoglu et al., 2009), (Zhao et al., 2018) and (Hanawa et al., 2018), reported substantial evidence that metformin may protect the endometrium against risk factors by local inhibition of mTOR (Target of rapamycin) which is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, cellular energy, and stress either through activation of the human tumor suppressor LKB1/AMPK pathway and indirectly via targets associated with insulin resistance. The relationship between cell proliferation and insulin resistance offers a potential therapeutic goal to in-
verse hyperplasia and prevent carcinoma of the endometrium. Some early trials have verified this link, showing the effectiveness of metformin in inducing endometrial atrophy in benign endometrial proliferative disorders; one reported atrophy and, therefore, a reversal of endometrial hyperplasia in 96% of women treated with metformin (Tabrizi et al., 2015).

Many studies reported the protective effects of metformin in the endometrium, with observational studies reporting metformin causing reversal of endometrium hyperplasia to normal endometrium (Meireles et al., 2017; Clement et al., 2016; Shen et al., 2008).

The inhibition of cell proliferation by metformin also supported by Ma et al. (2014) were they stated that metformin had synergistic effect with tamoxifen where metformin enhanced tamoxifen-mediated inhibition of proliferation, DNA replication activity, colony formation, soft-agar colony formation, and induction of apoptosis in ER-positive breast cancer cells (Ma et al., 2014).

There was a shortage in studied that examine the endometrial effects of metformin in women with breast cancer taking tamoxifen and this the first study in our country which highlights the role of metformin in reduction or prevention of tamoxifen induced uterine cell proliferation.

**CONCLUSIONS**

Metformin significantly inhibit tamoxifen-induced endometrial changes and offers favorable endometrium protection.

**REFERENCES**


