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Original Research Article

A Placebo Control Double Blind Randomized Clinical Evaluation of the Effect of Metformin on Breast Fibrocystic Disease

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Abstract

Aim: The aim of the present study was to evaluate the effects of metformin on Fibrocystic changes of breast changes.

Methods: This was a placebo control double blind randomized clinical trial in the Department of General Surgery. Among women of age group 18 to 40 years with FCD who were visited to Surgery OPD with presenting complaint of breast lump and cyclic mastalgia or breast pain for at least one week during every monthly for six months were selected.

Results: The mean age of participants in metformin, vitamin E and control groups was 30.4 ±3.91, 30±3.17 and 30.2±2.92 years respectively that based on variance analysis there was not a significant difference between the three groups (p-value >0.05). Based on analysis variance, the mean of the number of cysts, cyst size, tenderness and breast pain at the basal had no significant difference between the groups, but they had a significant difference between the groups at the end of the study ($p < 0.05$). The frequency of cyst location at the basal was not different between the groups, but at the end of the study, in situation when there were unilateral in metformin, vitamin E and control groups showed there is a meaningful difference between the groups after the intervention ($p < 0.5$).

Conclusion: The present study showed that metformin is effective to relief the clinical symptoms and imaging items of FCC. Although, more high quality researches are needed in different ethnic populations to confirm these results.

Keywords: Fibrocystic changes of breast, metformin.

Introduction

Fibrocystic disease (FCD) affects premenopausal women, more commonly between the ages of 30 and 40 years. [1] The incidence of the disorder cannot be evaluated correctly due to the inconsistent definitions in various studies. FCD deserves specific attention to reduce the incidence of unnecessary breast biopsy and surgery, avoid confusion with more important breast problems, including cancer, and lessen patients' symptoms and anxiety. [2] The presentation of FCD consists mainly of breast pain, tenderness, swelling, nodularity, and breast lumps. [2,3] Breast ultrasound (US) is useful for the detection of FCD and reveals heterogeneous nodular and fibrous breast tissue containing anechoic cysts with a posterior acoustic enhancement of variable sizes. [4]

Dependency to sex steroid hormones is a definite characteristic of FCD [3,5,6] and is documented by its cyclical alterations, association with estrogen replacement therapy [7] and consumption of oral contraceptives. [8] However, no effective

management strategy for FCD has been introduced so far. Traditionally, reassurance, dietary restrictions, vitamin supplements, and hormonal manipulations have been used in the management of FCD. [2] Nonetheless, none of these options is completely efficient. Metformin (MF), an anti-hyperglycemic biguanide used in various non-diabetes-related clinical settings, has shown positive effects on fibroadenoma of the breast [9] and has been used in FCD with favorable outcomes in a previous study. However, the sample size has been small, and the study suggested further researches to confirm their results. [10]

Metformin belongs to biguanids and is the most common drug used for type two diabetes mellitus and metabolic syndrome. [11] Obesity and its association with hyperinsulinemia and glucose intolerance and type two diabetes mellitus increase the risk of breast disease including breast cancer. [12] Metformin reduce hyperinsulinemia and insulin resistance through reducing adenosine mono phosphate kinase (AMPK) that has a key role in cell energy and hemostasis. [13] The activation of this pathway lead to decreasing of cell proliferation. In fact, metformin has anti proliferative properties. [11] Metformin strongly inhibits dose dependently prostate cell proliferation. [14] In addition, it has been documented that metformin can reduce colon and breast cell proliferation. Oral and parenteral taking of metformin in rats inhibited 55% and 35% tumor growth respectively. [15] Phonix showed that metformin suppressed significantly, estrogen positive receptor breast cells proliferation, but it had a minimal effect on negative estrogen receptor breast cells. [16]

The aim of the present study was to evaluate the effects of metformin on Fibrocystic changes of breast changes.

Materials and Methods

This was a single center placebo-control double blind randomized clinical trial conducted in the department of general surgery. Among women who were visited to general surgery out patient department, 200 women with FCD between age of 18 and 40 years, with unilateral or bilateral breast lump and cyclical breast pain or mastalgia for at least one week during every month for six months were selected.

The inclusion criteria were the women in pre-menopausal age group and breast FCD or breast mass and having imaging and clinical criteria of FCD. Malignancy ruled out by core biopsy, lump FNA (fine needle aspiration biopsy) and also by cytology examination of breast discharge. Mamography and ultra-sonography were performed for all patients. Patients who were having metabolic syndrome, known case of diabetes mellitus and already on oral hypoglycemic agents, allergic to biguanids, on therapy with oral contraceptive pills and history of breast cancer, and patients having hypothyroidism, hyperthyroidism, galactorrhea, severe iron deficiency anaemia, hyperlipidemia, renal, cardiac and pulmonary diseases were excluded from the study.

This research was done in accordance with the Declaration of Helsinki and informed consent was received from all subjects before registering to the study group.

Randomization:

After fulfilment of the inclusion and exclusion criteria, patients were randomized into 3 groups. Patients in Group A were treated with Vitamin E 400 mg daily. Patients in Group B were treated with Metformin 500 mg twice a day. The patients in Group C didn't receive any treatment and given placebo during six months and considered as control group. Questionnaire was filled out for all participants based on clinical history and physical examination. The sample size was calculated. 200 sample size was taken and randomized into 3 groups *i.e.* Group A, Group B and Group C and therapy was given as per methodology. (Fig. 1)

Data analysis was done by SPSS version 20. Frequency percent and charts and mean of variables were used to describe the data. One-way variance analysis, student t test, pried t test and Chi- square were used to compare the variables between the groups. P value less than 0.05% was considered significant. Data of continuous variables were analyzed as mean ± standard deviation and for categorical variables it was presented as number with percentages. Two groups were compared as analyzed by Student t-test and Chi-square test. In the same group pre and post treatment was analyzed by Paired-t-test.

Results

In this study, 222 patients were enrolled, out of which 64 patients were in Group A (Vitamin E), 75 patients were in Group B (Metformin) and 83 patients were in Group C (control). Twenty two patients (4 patients from Group A, 5 patients from Group B and 13 patients from Group C) were excluded from analysis due to poor adherence to treatment (8 patients) and loss to follow up (14 patients).

The mean age of participants in different groups are 30.4±3.91, 30±3.17 and 30.2±2.92 years in Group A, Group B and Group C respectively ($p>0.05$). Mean ages of patients in all three groups were comparable.

Table 1: Comparison of age between groups

	Age in years				
Group	Number	Mean	SD	Least	Most
A (Vitamin E)	60	30.4	3.91	25	39
B (Metformin)	70	30	3.17	24	39
C (Control)	70	30.2	2.92	27	38

At the beginning of study and before intervention, there were no significant difference in different groups in terms of the means number of cysts, mean cyst size, tenderness and breast pain. But after intervention, significant differences were noted in mean number of cysts, mean size of cyst and tenderness over the breast (p-value <0.05).

Table 2: Comparison of clinical symptoms before and after intervention in the groups

Variables	Vitamin E		Metformin		Control		P Value
	Before	After	Before	After	Before	After	
Number of cysts	8.8±3.9	3.5±3.5	5.7±3.1	6.9±3.7	7.5±2.9	6.2±2.7	0.001
Size of cysts (mm)	8.8±4.9	7.3±5.5	5.7±1.9	5.4±2.0	5.6±2.1	4.5±2	0.001
Unilateral Cyst	8	20	17	23	30	23	0.890
Bilateral Cyst	35	25	28	40	30	32	0.952
Tenderness	34	16	28	38	32	40	0.001
Mild pain	20	45	28	40	27	15	0.743
Moderate pain	65	10	70	35	40	20	0.650

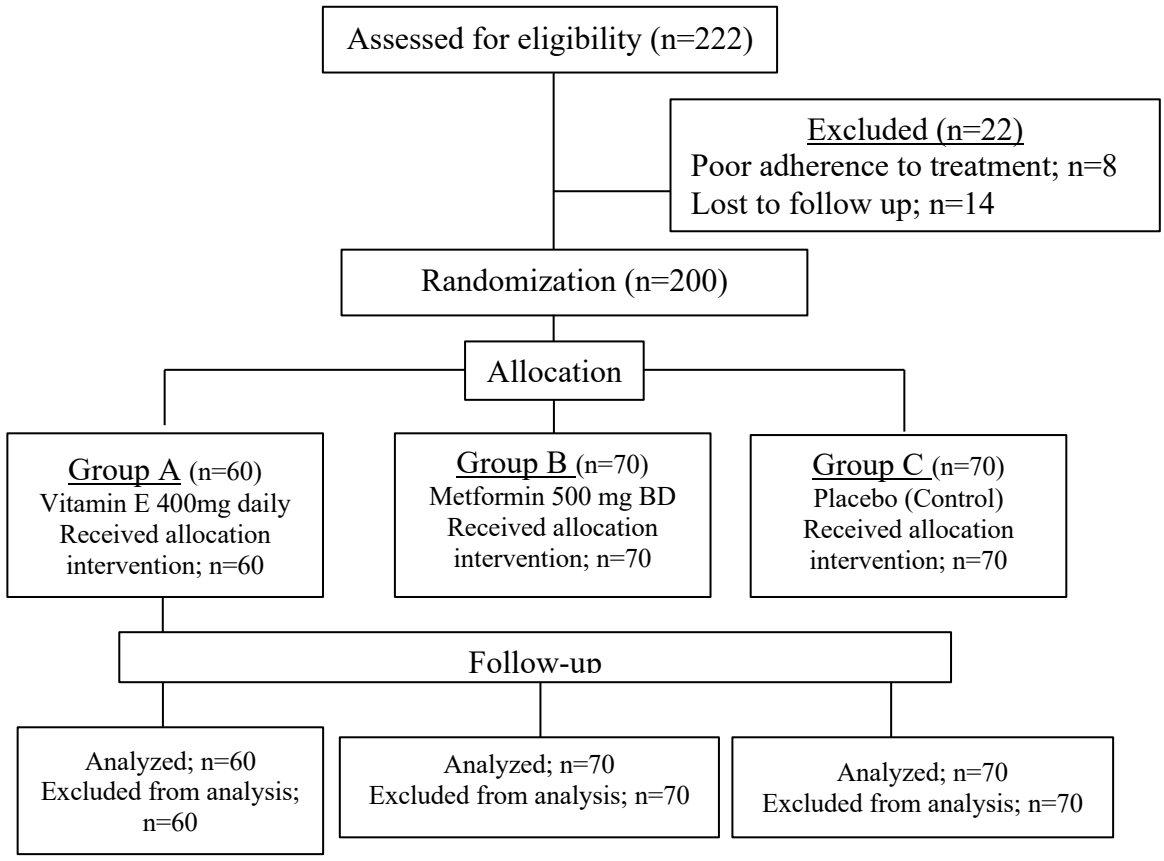

Figure 1: Summary of CONSORT flowchart

Discussion

Fibrocystic disease is a common breast disorder that affects women in their active years of life. The nodularity and lumpiness that accompany FCD may interfere with the correct detection of breast masses, and mastalgia may be significant enough to affect the patient's activities and quality of life or cause concern and worry about breast health. Appropriate suppression of FCD that could control the symptoms and modify the physical breast

changes would ease the breast exam and the detection of actual breast disease and soothe the patient discomfort. Management protocols that have been proposed for FCD are centered on the probable mechanisms that lead to its development. Prolactin has been mentioned to play a role in the pathogenesis of FCD, and inhibitors of prolactin have been used for its treatment with acceptable results. [17]

The mean age of participants in metformin, vitamin E and control groups was 30.4 ±3.91, 30 ± 3.17 and 30.2 ±2.92 years respectively that based on variance analysis there was not a significant difference between the three groups ($p>0.05$). Metformin is the first step drug for diabetes and has antitumoral properties. Several studies have shown that among whom take metformin, the risk of cancer and also the mortality rate of cancer has been reduced.[11] Also, metformin intake has been associated with the better response to chemotherapy. [18] The effects of metformin on breast cancerous cells are induced in two ways; direct and indirect. Indirect effects of metformin that are insulin dependent and are on both cells and whole organism include; decreasing of serum insulin level, reduced IGF-1 and mTOR suppression. [19]

Based on analysis variance, the mean of the number of cysts, cyst size, tenderness and breast pain at the basal had no significant difference between the groups, but they had a significant difference between the groups at the end of the study ($p < 0.05$). The frequency of cyst location at the basal was not different between the groups, but at the end of the study, in situation when there were unilateral in metformin, vitamin E and control groups showed there is a meaningful difference between the groups after the intervention ($p < 0.5$). Direct effects of metformin are due to the activation of AMPK (Activated Protein Kinase) through mitochondrial breating suppression. This protein kinase has a key role in homeostasis and metabolism and it is sensitive to increasing intracellular AMP to ATP ratio. [20] AMP acts as an energy sensor and cause the phosphorilation of effectors that stimulate ATP producing signals and suppress ATP consuming pathways. [13]

Insulin by binding to insulin receptor induces mitogenic and antiapoptosis effects in breast cancer and high serum insulin level is associated with the increased risk of cancer and worse prognosis. [12] Metformin intake cause weight loss and reduce BMI, FBG, HOMA-IR (Homeostatic Model Assessment insulin Resistance), cell proliferation and its marker Ki-67, and increase cell apoptosis and its marker TUNEL (Terminal deoxynucleatidyl transferase (TdT) dUTP Nick End Labeling) and it also reduce insulin receptors in tumor cells. [21] Hadad showed that metformin 500 mg daily for one week and then 1 g for second week reduced significantly cancer biomarker of Ki-67. [22] However, all studies don't confirm these effects. For example, Kanlinsykevin conclude that metformin intake had no effect on proliferative markers in breast cancer but it caused weight loss and reduced serum insulin level. [23]

Conclusion

The present study showed that metformin is effective to relief the clinical symptoms and imaging signs of FCC. Although, it needs larger study and researche in different ethnic populations to confirm these results.

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