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RESEARCH ARTICLE

Metformin in the management of fibrocystic breast disease: a placebo-controlled randomized clinical trial

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Abstract

Background and Purpose Fibrocystic disease (FCD) of the breast as a very common health problem in women has estrogen-dependent and proliferative features. No effective management strategy has been validated for this disorder, so far. The anti-hyperglycemic agent metformin has both anti-proliferative and estrogen-suppressing effects. Thus, we investigated metformin as a management strategy for FCD.

Methods The study was a double-blind placebo-controlled randomized clinical trial. Premenopausal women with FCD according to history, physical exam and ultrasound, who had measurable microcyst clusters on ultrasound (US) were entered the study. Oral placebo and metformin tablets (500 mg) were used twice daily by participants in the intervention and control groups. Size and number of microcyst clusters on US and the subjective pain score were recorded before and after the intervention.

Results 154 participants were randomly allocated into two groups of 77 interventions and 77 controls. The decrease in size of the largest microcyst cluster in each patient and the mean decrease in number of microcyst clusters were not statistically significant ($P=0.310$ and $P=0.637$, respectively). However, those microcyst clusters which were ≥ 14 mm became significantly smaller after metformin use ($P=0.006$). Additionally, in the subset of participants with pain at baseline, a larger proportion in the intervention group experienced at least 50% reduction in pain score (63.8% (30/47) in the intervention vs. 44.2% (19/43) in the placebo groups, $P=0.031$).

Conclusion Our study showed that metformin might be effective in the management of FCD. Further studies are proposed for confirmation of this subject.

Introduction

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

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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].

Regarding the proliferative characteristics and estrogen-dependency of FCD on the one hand, and anti-proliferative [11–13] and estrogen-suppressing features [14–16] of MF on the other hand, we aimed to investigate the effects of this medicine in controlling the disorder.

Material and methods

Design and setting

This study has been held in the breast clinic of Arash Women's Hospital, affiliated with Tehran University of Medical Sciences, from October 2018 to January 2020. The study was approved by the Institutional Research Board (Proposal Code: 97–01–218-37,719) and the Ethics Committee (Approval ID: IR.TUMS.VCR.REC.1397.358) of Tehran University of Medical Sciences, Tehran, Iran. The protocol was registered at the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT20100706004329N6). The study was designed as a double-blind, randomized placebo-controlled clinical trial, and the study population included patients attending the clinic for breast complaints or breast cancer screening from March 2019 to December 2019.

The research protocol and aims of the research were first described for all the participants, and they all signed a written informed consent at the first step.

Inclusion and exclusion criteria

We considered premenopausal female patients above 18 years of age who were diagnosed with FCD according to history, physical exam, and the US; and had measurable clusters of microcyst on the US.

Criteria that were defined for excluding patients from the study were diabetes or use of hypoglycemic medication; history of metabolic syndrome; previous history of allergy to biguanides; consumption of medicines containing estrogen, progesterone or GnRH analogs, agonists or antagonists; consumption of Danazol, or analgesics; renal, hepatic or heart failure; hyper- or hypothyroidism; severe iron deficiency anemia and hyperlipidemia; BMI more than 29.9; vegetarianism; pregnancy or lactation state; history of breast cancer; and non-compliance with use of MF or placebo during the intervention.

Sample size calculation, random allocation, concealment and blinding

The sample size was calculated to compare our main outcome, i.e., the change in the size of the largest cluster of microcyst, between groups. G-power 3.1 for a two-tailed independent t-test and using effect size (d) of 0.5 and power of 0.80 revealed 63 patients in each group. Considering a dropout rate of 20%, the ultimate sample size was calculated to be 76 patients in each group.

Women were entered into the study by surgeons of the breast clinic according to the inclusion criteria. An independent investigator randomly allocated participants to intervention and control groups by using a random number sequence, according to the block randomization method. The size of the blocks was six. The randomization list was concealed from all research staff involved in enrollment and assessment by using sealed envelopes.

MF and completely identical placebo tablets were placed in identical bottles that were coded. The identities of the codes were only available to one of the research members; therefore, the outcome investigators (surgeon, radiologist, clinic nurse, and interviewer), participants, and the statistician were unaware of the type of intervention until the end of the study.

Intervention

Metformin 500 mg oral tablets and placebo tablets, made by the same company (Osveh Pharmaceutical Company, Iran), were used twice a day for six months by the intervention and control groups, respectively. Also, as a routine of our clinic, recommendations about dietary considerations and supportive management were offered to all patients; and pearls containing 400 International Units of Vitamin E (Zahravi Pharmaceutical Company, Iran) were prescribed for every participating woman twice weekly, consumed at 3–4 days intervals. Participants marked the daily use of the medicines in an aide-mémoire form.

Primary outcome

The largest diameter of the largest cluster of microcyst and the number of clusters detected on the US were the main measures assessed before and after the intervention and were defined as the primary outcome.

Secondary outcome

A reduction of at least 50% in pain score at follow-up compared to the baseline, adverse drug reactions according to the patient's report, and body mass index (BMI) were evaluated as secondary outcomes.

Tests and measurements

Laboratory tests

Blood tests comprising blood sugar, complete blood count, liver and renal function tests were performed at the first entrance, and renal function tests were repeated at the end of the study.

Breast ultrasound

All US exams were performed by one radiologist expert in breast US before and after the intervention. Clusters of microcyst were detected and measured separately for each breast and reported in the defined US form.

Questionnaires and forms

A questionnaire including demographic variables, reproductive information, and self and family history of disease were filled in by the patient at the entrance. The patients were asked to score their pain, if they had any, using the visual analog scale (VAS) for pain [17]. A trained staff measured and recorded the anthropometric dimensions of all participants before and after the intervention.

Statistical methods

The baseline characteristics of participants in each study group were summarised using mean ± (Standard Deviation (SD)) or median (Interquartile Range (IQR)) for continuous variables and frequency (%) for categorical variables. The change in the size of the largest cluster of microcyst was compared between two groups using a two-tailed t-test. Median (Inter quartile range (IQR)) of the size of the largest cluster of microcyst, before and after the intervention, was compared between groups by using the Mann-Whitney U test. As most participants in both groups had 1 (before intervention) or zero (after intervention) cluster of microcyst on the US, we treated the number of clusters of microcyst, before and after the intervention, as a categorical variable (0, 1, 2, ≥3). All categorical variables were compared between the two groups before and after the intervention by using Chi2 or Fisher exact tests, as appropriate.

Statistical significance was defined as a two-tailed P value <0.05. All statistical analyses were conducted using SPSS Version19.0 (SPSS, Chicago, IL, USA).

Results

As shown in Fig. 1, 77 women were enrolled in the intervention group, and 77 in the control group at the beginning of the study. During the intervention, one woman from the intervention group left the study due to pregnancy. Also, five participants out of this group and nine from the control group were excluded from the study because of the irregular use of medicines. Four in each group also were lost to follow-up due to COVID-19 restrictions. Therefore, the total number of participants at the final analysis was 131, including 67 in the intervention and 64 in the control group.

Overall, the mean age (±SD) of the participants was 43.25 ± 8.27 years. Baseline characteristics of women in the two groups are shown in Table 1; there was no substantial difference between the two study groups.

Findings consistent with the number of clusters of microcyst and the size of the largest cluster of microcyst in the US, as well as nodularity and tenderness in clinical breast exam, all before and after the intervention, are demonstrated in Table 2. The results showed no significant difference between the intervention and control groups regarding the US and clinical exam variables.

We assessed the alterations in the number of clusters by categorizing changes as increase or decrease in number or no change. Table 3 shows the results, and the classification showed no significant benefit for the intervention group. We also assessed the amount of size decrement of the largest cluster of microcyst in every patient. Results showed that there was a greater decrease in the intervention group; however, the difference between the two groups was not statistically significant.

We also performed subgroup analysis by the size of clusters of microcyst (cut point: 14 mm). As displayed in Table 4, in the subset of patients with cluster size ≥14 mm, patients receiving metformin experienced a greater reduction in size of cluster compared to others (Median (Interquartile range (IQR): −18.0 (−28,-3.4) vs. -3.0 (−14.5, 1.3), respectively; effect size: 0.48, P value = 0.006). However, there was no significant difference between groups in the subgroup of patients with cluster size <14 mm.

Change in pain score was assessed in the subset of participants with pain at baseline. Patients with either cyclical or noncyclical breast pain were included, as the management is the same for the two categories. The median (IQR) of the pain score at baseline was similar between treatment

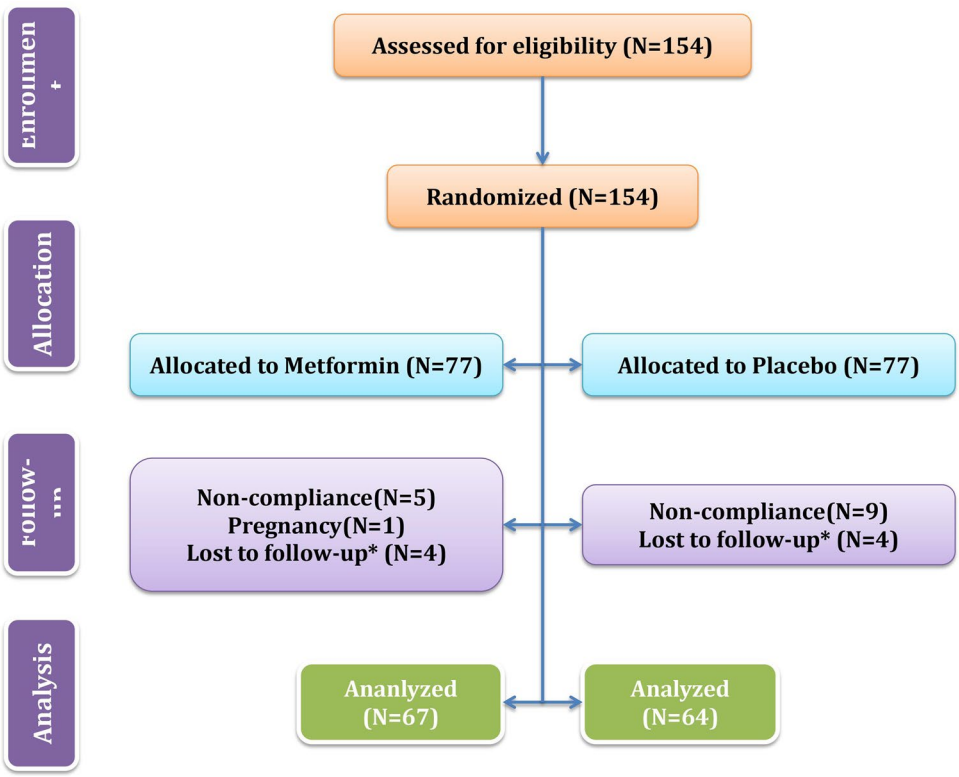

Fig. 1 Summary of patients flow, *Due to COVID restrictions

Table 1 Baseline characteristics of participants in the two study groups at enrollment

Variables		Intervention Group, n = 67	Control Group, n = 64
Mean Age ± SD (years)		42.8 ± 8.0	43.7 ± 8.6
Mean BMI ± SD (Kg/m^2)		27.0 ± 5.0	26.9 ± 5.1
Gravidity (Mode)		2	2
History of Breastfeeding, N (%)	Yes	56 (83.6%)	57(89.1%)
	No	11 (16.4%)	7 (10.9%)
History of OCP consumption, N (%)	Yes	20 (29.9%)	14 (21.9%)
	No	47 (70.1%)	50 (78.1%)

BMI = Body Mass Index, N = Number, SD = Standard Deviation, OCP = oral contraceptives

and control groups (5 (3, 7) vs. 5 (4, 7), respectively; P value = 0.569). At follow-up, the intervention group showed a greater decrease in the pain score than the control group, but their difference was statistically non-significant (3 (0, 5) vs. 1 (0, 5), respectively; P value = 0.226). Compared to patients receiving placebo, a larger proportion of participants in the intervention group experienced at least 50% reduction in the pain score at follow-up (63.8% (30/47) in the intervention group vs. 44.2% (19/43) in the placebo group, P value = 0.031).

During the study, three patients complained of bloating in the intervention group, which was easily tolerated and disappeared after two to three weeks of MF use after meals. Renal function tests (blood urea nitrogen and serum creatinine) were normal in all participants of the two groups before and after the intervention (data not shown). Mean BMI had a slight increase (from 26.9 to 27.4) among the controls and a minimal decrease (from 27 to 26.7) in those who received MF; however, this difference was not significant (P value = 0.563).

Discussion

In this study, we have investigated whether MF can control the clinical and US presentation of FCD; and found favorable results in patients who had clusters of microcyst larger than 14 mm on the US. We also found that metformin can reduce the breast pain associated with FCD. However, our sample size might be small for supporting the clinical

Table 2 Main findings in breast physical exam and ultrasound before and after the intervention

Variables		Intervention Group		Control Group		P- value
		Before	After (at 6 months)	Before	After (at 6 months)	
Ultrasound features	Number of clusters of microcyst (%)					
	0	–	33 (49.3%)	–	31 (48.4%)	Before: 0.833 After: 0.997
	1	47 (70.1%)	22 (32.8%)	46 (71.9%)	22 (34.4%)	
	2	18 (26.9%)	10 (14.9%)	15 (23.4%)	9 (14.1%)	
	≥ 3	2 (3.0%)	2 (3.0%)	3 (4.7%)	2 (3.2%)	
	Largest cluster* (mm), median (IQR)*	10.0 (8.0–13.5)	5.3 (0.0–11.0)	11.0 (8.0–14.0)	5.0 (0.0–12.9)	Before: 0.435 After: 0.929
	Change in largest cluster size*, mean (SD)	−6.02 (9.7)		−4.42 (8.25)		0.310
Breast exam features	Tenderness (%)	9 (15.5%)	10 (17.5%)	7 (12.5%)	7 (12.5%)	0.477
	Nodularity (%), missing data = 10 in each group					
	0	18 (31.6%)	15 (25.9%)	21 (37.5%)	20 (35.7%)	0.989
	1	23 (40.4%)	27 (46.6%)	30 (53.6%)	31 (55.4%)	
	2	16 (28.1%)	16 (27.6%)	5 (8.9%)	5 (8.9%)	

IQR = interquartile range; *in each patient

Table 3 Alteration in the number of clusters of microcyst within categories

		Changes in the number of clusters*			Total
		Decrease	Increase	Constant	
Intervention group	Count	35	3	29	67
	% within group	52.2%	4.5%	43.3%	100.0%
Control group	Count	35	5	24	64
	% within group	54.7%	7.8%	37.5%	100.0%
Total	Count	70	8	53	131
	% within group	53.4%	6.1%	40.5%	100.0%
P value = 0.637					

*Before and after the intervention

Table 4 Alterations in the size of clusters of microcyst within categories

Cluster size before the intervention	Group	Number	Mean	Standard deviation	P value
13 mm or less	Intervention	52	−2.83	6.38	0.258
	Control	47	−4.17	5.27	
14 mm or more	Intervention	15	−17.09	11.13	0.011
	Control	17	−5.09	13.71	

significance of these findings, and it might be better to interpret these findings with caution.

FCD 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 [18]. Danazol is a weak androgen with antigonadotropin effects and has been widely used in previous years as the main therapy of FCD and breast pain, with encouraging results regarding pain control and suppression of cyst formation and breast nodularity. Selective estrogen receptor modulators (SERMs) like tamoxifen and Ormeloxifene have been shown to improve the signs and symptoms of FCD. Other types of hormonal agents that have been considered for control of FCD include analogs of luteinizing hormone-releasing

hormone, Gestrinone tablets, and different forms of progestin [19, 20]. Also, evening primrose oil, Vitamin B6 [21], and Vitamin E [22] have caused moderate improvement in FCD.

All of these forms of therapeutic interventions have shown some levels of effectiveness; however still, no one modality or specific protocol of treatment has been assigned to the management of FCD. This is either due to the bothering adverse effects, like for Danazol, prolactin antagonists, and SERMs, or the small proportion of patients who show improvement, as with Vitamin E, Vitamin B6, and evening primrose oil. Therefore, we investigated MF as a treatment modality for FCD.

MF is the most commonly used anti-hyperglycemic agent in the first-line treatment of diabetes type II all over the world; its potential for management of other disorders has been proved or is being investigated [23]. One of the major advantages of MF over the other anti-hyperglycemic agents is that it is not associated with hypoglycemia. Also, the frequency of adverse effects, including nausea, diarrhea, and abdominal cramps, is low and usually subsides gradually with the continuation of the medicine. Lactic acidosis is the main drawback but occurs rarely.

Overall, less than 5% of patients do not tolerate MF. In our study also, no serious adverse effect occurred in the intervention group, and no patient withdrew from the study because of drug intolerance.

Studies on the effect of metformin on breast diseases have been more focused on malignant lesions so far. Metformin can exert anti-proliferative effects through inhibition of cell proliferation and induction of cell cycle arrest at the G1 phase, probably via reducing the expression of the cyclin D1 and E2F1. Metformin can also inhibit MAPK, Akt, and mTOR activity in all the cell lines [24, 25].

In a review article, Del Barco S, et al. have mentioned that metformin can even have preventive effects against breast cancer development by regulating the rate of tumor progenitor cell proliferation in premalignant lesions [26].

In terms of the antiestrogenic effects of metformin, there are some studies that have shown that metformin can reduce the blood levels of estrogen and testosterone [14, 27, 28]. The mechanism of lowering the serum sex hormone levels by metformin remains unclear. However, it has been suggested that metformin may inhibit aromatase activity. In Pimentel I, et al. study, metformin has caused the ER-positive breast cancer cells and breast adipose stromal cells to exhibit reductions in aromatase mRNA through suppression of promoter (PII) and P1.3-specific transcripts and activation of AMPK [27].

According to our comprehensive searches, the effect of metformin on benign breast diseases has been less addressed in previous studies. We found only one study that investigated the effect of MF and compared it with vitamin E and no medical treatment in 186 otherwise healthy women with FCD. They detected a significant difference regarding the decrease in the number and size of cysts as well as breast tenderness in the MF group in comparison with the other two groups [10].

We also found two studies that evaluated the effect of MF on FCD disorder in insulin-resistive and non-insulin-resistive patients that showed the positive effect of MF in the management of FCD in these patients [29, 30].

In our study, the statistically significant efficacy of MF in reducing the size of the larger clusters of microcyst and the pain score and the absence of significant adverse effects may be in favor of the effectiveness of MF in the management of FCD. However, the dose of MF prescribed in this study was low, and gradual dose increments or higher doses might lead to more favorable results regarding the number of clusters and the breast nodularity and tenderness.

One of the strengths of our study was that we only included FCD cases that had definite, measurable clusters of microcyst in their ultrasound. The reason for this selection was that we wanted to consider only definite FCD cases and not women with single or multiple cysts without FCD; we also wanted to define a US-based variable that was more specific to FCD and could easily be measured and followed by the US.

The main limitations of our study were the small sample size and the lack of evaluation of the effects of the treatment after discontinuation of the drug.

We believe that studies with larger sample sizes, comprising higher doses of MF (e.g., 1500 or 2000 mg daily in divided doses), and including only cases with large clusters of microcyst would be helpful in order to more efficiently assess the benefits of MF in the management of FCD.

Conclusion

In this study, metformin was not effective in reducing either the number of microcyst clusters or the size of small clusters. Yet our study showed partial beneficial effects of MF in the management of pain and large microcyst clusters in FCD patients and no serious adverse effects. So, we think that MF could be valuable as a safe management strategy for FCD. However, further clinical trials with larger sample sizes and using higher doses of MF should be carried out to confirm this point before suggesting MF for FCD patients.

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Data availability All data analyzed during this study are included in this published article and row-data are available from the corresponding author on reasonable request.

Authors' contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mahboubeh Abedi, Hadith Rastad, Azin Saberi, Firoozeh Faiz, and Arezoo Maleki-Hajiagha. The first draft of the manuscript was written by Sadaf Alipour and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors have no conflicts of interest.

Consent for publication Not applicable.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Research Board (Proposal Code: 97–01–218-37,719) and the Ethics Committee (Approval ID: IR,TUMS.VCR.REC.1397.358) of Tehran University of Medical Sciences, Tehran, Iran.

Consent to participate Written informed consent was obtained from all participants.

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