Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230-8407 [LINKING]

Metformin's role in the treatment of breast fibrocystic illness

Zainab Mohammed Salih[1], Dezhwar Yahya Ghazi[2], Hasan Muhsin Hasan[3], Sabah A. Mohammed[4]

[1] General Surgeon, University of Duhok College of Medicine, Duhok, Kurdistan Region Iraq
[2] General Surgeon, University of Duhok College of Medicine, Duhok, Kurdistan Region Iraq
[3] General Surgeon, University of Duhok College of Medicine, Duhok, Kurdistan Region Iraq
[4] General Surgeon, University of Duhok College of Medicine, Duhok, Kurdistan Region Iraq

How to cite: Zainab Mohammed Salih, Dezhwar Yahya Ghazi, Hasan Muhsin Hasan, Sabah A. Mohammed. **Metformin's role in the treatment of breast fibrocystic illness**. International Research Journal of Pharmacy. 2025; 16:11: 52-60.

DOI: http://doi.org/10.56802/irjp.2025.v16.i11.pp52-60

==========

Abstract

Background and Objectives: - Fibrocystic Disease of the Breast is one of the commonest benign breast diseases associated with hormonal disturbance. Thus, this study aims to assess the role of Metformin in treating the presenting complains of Fibrocystic Disease of the Breast compared to Placebo.

Methodology: A prospective double-blind Randomized clinical trial among cases with Fibrocystic disease of the Breast. The cases were collected from the Breast assessment clinic in Azadi Teaching Hospital and a privet clinic in Duhok City, Kurdistan region, Iraq. The study took a total duration of 12 months. A total of 100 cases were fit and were enrolled in the study, 50 cases on placebo with watchful waiting and 50 cases on metformin 500 mg twice daily; 2 cases were excluded due to adverse effects from the treatment.

Results: Nearly 2/3 of the cases showed response were on metformin compared to 1/3 on Placebo; indicating clinically the superiority of Metformin in reducing the cyst size, P = 0.002. Metformin was associated with 8.4% reduction in Nipple discharge and 54.0% reduction in Mastalgia vs 18% and 54%, respectively for Placebo, both showing significant impact, P < 0.001, with a higher Odd for Placebo in both symptoms, 1.7 vs 3.5 and 11.7 vs 23.5.

Conclusion: Compared to Placebo, Metformin is associated with a significant reduction in the size of the cysts. While there is no significant difference in pain management and decreasing nipple

discharge in both groups, with higher odds for Placebo over Metformin in the latter symptoms. Additionally, both Metformin and Placebo were associated with nearly 54% reduction in Mastalgia.

Keywords: Metformin; Fibrocystic Disease of the Breast; Breast Cancer; Benign Breast Lesions.

Introduction

According the Women's Health Initiative Study (WHI), the risk of benign breast diseases increased by 74% among females who were receiving combined estrogen and progesterone while 28% reduction in prevalence of benign proliferative breast disease was seen among those on anti-estrogen [1] indicating the role of hormone exposure in Benign breast disease, one of which is the commonest worldwide is the Fibrocystic disease of the breast which [2] that is commonly encountered among females aging 30- 50 years of age [3].

The disease is typically seen due to several important risk factors including; Hormonal imbalance with prolonged estrogen exposure and progesterone deficiency that lead to the proliferation of the connective tissue and cyst formation [4-6], age and menstrual status which is commonly seen in premenopausal and decrease after [4, 6-7], and caffeine and the intake of methylxanthine [8]. In the Literatures, several studies show the link between Fibrocystic disease of the breast and breast cancer; those with atypical epithelial hyperplasia increase the risk of breast cancer by 2 to 4 folds [2, 4-7].

According to the histological background, several types of Fibrocystic disease of the breast present, some which are highly associated with cancer, these include; Cystic change which consist of fluid filled cysts [4, 9-10], Fibrotic changes with increased fibrous tissue [9, 11], and Apocrine metaplasia with change in cell type [9, 12] which all three have a low risk of carcinoma. While those with a higher risk of cancer include; Epithelial Hyperplasia, Sclerosing adenosis and Papillary hyperplasia [5, 9, 13].

Patients typically present with breast pain and tenderness, breast nodules and cysts that could be unilateral or bilateral that worsen premenstrual and could persist throughout the cycle [4-5, 8]. Sonographic assessment of the breast is a useful method for the diagnosis, assessment and size measurement [14].

So far, there has no effective management strategy for the disease [15], however, researchers are assessing the role of metformin, oral hypoglycemic agent, for treatment purpose [15-17] which acts via anti-proliferative effect and induction of cell cycle arrest at the G1 phase and anti-estrogen effect [15]. Thus, this study aims to assess the role of Metformin in treating the presenting complains of Fibrocystic Disease of the Breast compared to Placebo.

Methodology

This study was conducted as a prospective double-blind Randomized clinical trial among cases with Fibrocystic disease of the Breast. The cases were collected from the Breast assessment clinic in Azadi Teaching Hospital and a privet clinic in Duhok City, Kurdistan region, Iraq. The study took a total duration of 12 months to collect the data.

Inclusion criteria included: all female patients between age of 18-50 Years with fibrocystic breast disease were enrolled in the study. Exclusion criteria included: patient with diabetes mellitus, and those who cannot tolerate therapy or develop side effect of drug, also patient who refuses to participate in study, all of them were excluded.

Permissions were obtained from the ethical committee at the general directorate of health in the city and the scientific committee of the college of medicine.

The study was conducted as a double-blind randomized clinical trial. Women who were diagnosed with Fibrocystic disease of the Breast through a thorough clinical assessment and ultrasonographic assessment who has shown a measurable microcyst clusters on ultrasound, were enrolled. The cases were divided into two groups, cases who were placed on metformin 500 mg twice daily for 6 months and controls who were only followed up for 6 months with watchful waiting. Prior the initiation of the study and after 6 months, the size of microcystic clusters were measured using a well-trained radiologist on ultrasound and the subjective symptoms were well documented for comparison. A total of 100 cases were fit according to the criteria and were enrolled in the study, 50 cases on placebo with watchful waiting and 50 cases on metformin 500 mg twice daily. Each case was re-assessed at least twice after that; once after 3 months and then after 6 months. Those who developed side-effects were assessed earlier and were assigned to discontinue metformin, then were excluded from the study.

Patients Risk: After taking the consent from participants/responsible relatives. All subjects were assured of the privacy of their information that they will not be disclosed and only results of the study will be published and presented in Journals and possible conferences and symposiums.

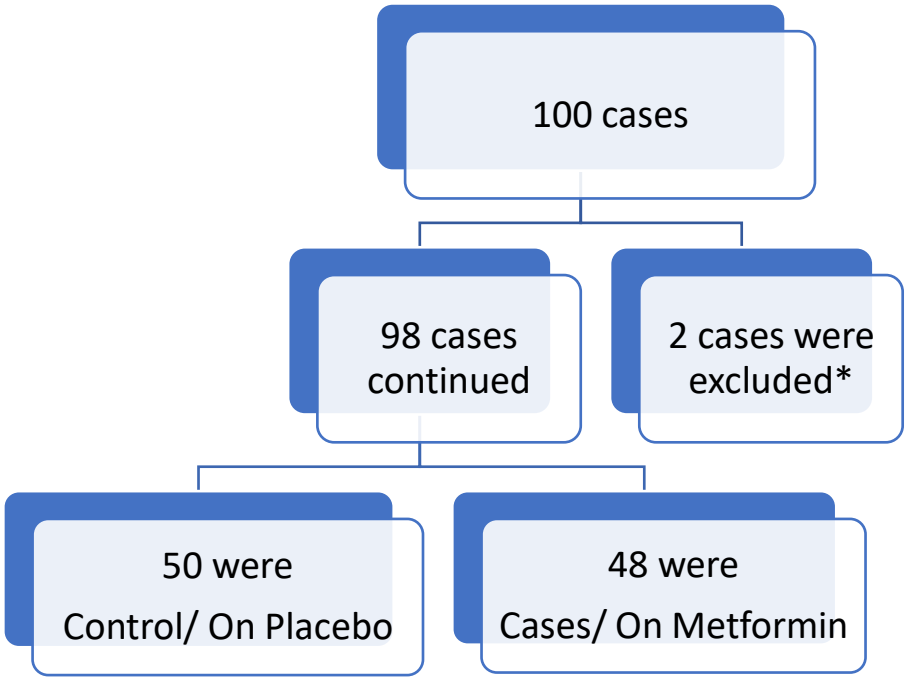

*Figure 1: The road map of cases enrolled in the study. * Two cases were excluded due to medication side-effect.*

The data were analyzed using SPSS version 26. The frequency of each character was analyzed using descriptive statistics. Fisher Chi-square test was used to assess the alteration in the size of the cyst and Mastalgia. Paired T test and Odd ratios were used to assess the Nipple discharge and Mastalgia. All were regarded statistically significant at $P < 0.05$

Results

Table (1) describes some basic information on the sociodemographic features of the participants. The vast majority of the participants were married 74.0% vs 26.0% who were single. Smoking was almost neglectable among cases 4.0% compared to non-smokers 96.0%. among the participating females, 37.0% have had no pregnancy, 15.0% had 1-2 pregnancies, while 31.0% had 3 to 5 pregnancies, and 17.0% have had at least 6 pregnancies. Mastalgia was a common symptom among those participants accounting for 88.0%. nearly 29% of the cases had nipple discharge on presentation and 47.0% had breast lumpiness.

Table 1. Socio-demographic features of the participants initially

Character		No	%
Number of Pregnancies	0	37	37.0%
	< 3	15	15.0%
	3 to 5	31	31.0%
	> 5	17	17.0%
Marital Status	Married	74	74.0%
	Single	26	26.0%
Smoking Status	No	96	96.0%
	Yes	4	4.0%
Mastalgia	Present	88	88.0%
	Absent	12	12.0%
Unilateral	Yes	41	41.0%
	No	59	59.0%
Bilateral	Yes	48	48.0%
	No	52	52.0%
Nipple Discharge	Present	29	29.0%
	Absent	71	71.0%
Breast Lumpiness	Yes	47	47.0%
	No	53	53.0%

Table 2 demonstrates the clinical response difference between control on Placebo and the cases group on Metformin 500 mg twice daily for 6 months. After 6 months of treatment and follow-up, a total of 42 cases showed clinical response with reduction of the cyst sizes on sonographic assessment. Of them 28 cases were on metformin while 14 were on placebo; 2/3 of the cases which showed response were on metformin rather on placebo and that accounted for 58.3% of

the Cases, while 1/3 of the response were from Control group and that accounted for 28% of the sample. Furthermore, the use of metformin was significantly associated with reduction in cyst size with a P value of 0.002 with 3.6 Odd ratio.

Table 2. Alteration in the size of the cysts.

		Decrease	Increase or no Change	Total
Interventional Group	**Count**	28	20	48
	% within Response	66.70%	35.70%	49.00%
Control Group	**Count**	14	36	50
	% within Response	33.30%	64.30%	51.00%
Total	**Count**	42	56	98
	% within Response	100.00%	100.00%	100.00%

P value = 0.002, Odd ratio = 3.6

Table 3 demonstrates the nipple discharge response among cases comparing cases and control before and after 6 months of follow-up. Among cases on Metformin, the percentage of complain of Nipple Discharge reduced from 29.2% to 20.8% with a P value < 0.001 and an OR = 1.7 while for Control group, a higher reduction was seen 28% to 10% with a P value < 0.001 and an OR of 3.5. Yet, there was no significant difference in both group in decreasing nipple discharge with P value =0.253 using Fisher test.

Table 3. Nipple discharge and response between Case and Control using Paired T test

			Discharge	No Discharge	Total	T- test P value	OR
Metformin	**Before**	**Count**	14	34	48	< 0.001	1.7
		% within Discharge	29.20%	70.80%	100.00%		
	After	**Count**	9	38	48		
		% within Discharge	20.80%	79.20%	100.00%		
Placebo	**Before**	**Count**	14	36	50	< 0.001	3.5
		% within Discharge	28.00%	72.00%	100.00%		
	After	**Count**	5	45	50		
		% within Discharge	10.00%	90.00%	100.00%		

P value of Fisher test = 0.2531

Paired T test calculated the importance of Metformin vs Placebo in controlling patients Mastalgia with both treatment approach showing significant decrease with the pain experienced P value < 0.001, yet a higher Odd Ratio for Placebo than Metformin, 23.5 vs 11.7, respectively.

In metformin group, Mastalgia decreased from 81.25% to 27.08%, while in Placebo group Mastalgia decreased from 94.0% to 40.0%. Furthermore, despite these results, it can be seen in table 5 that there was no significant difference in the management of Mastalgia between both groups using Fisher Exact test, P value = 0.204.

Table 4. Mastalgia and response between Case and Control using Paired T test

			Mastalgia	No Mastalgia	Total	T- test P value	OR
Metformin	**Before**	**Count**	39	9	48	< 0.001	11.7
		% within Mastalgia	81.25%	18.75%	100.00%		
	After	**Count**	13	35	48		
		% within Mastalgia	27.08%	72.92%	100.00%		
Placebo	**Before**	**Count**	47	3	50	< 0.001	23.5
		% within Mastalgia	94.00%	6.00%	100.00%		
	After	**Count**	20	30	50		
		% within Mastalgia	40.00%	60.00%	100.00%		

Table 5. Mastalgia response to treatment

		Decrease	Increase or no Change	Total
Metformin Group	**Count**	35	13	48
	% within Response	72.91%	27.08 %	48.98%
Control Group	**Count**	30	20	50
	% within Response	60.00%	40.00%	51.02%
Total	**Count**	65	33	98
	% within Response	100.00%	100.00%	100.00%

P value = 0.204

Discussion

Fibrocystic Breast Disease is the commonest benign disease of the breast encountered mainly among females in the premenopausal period, mainly between 30 – 50 years of age [3] that is believed to be caused due to hormonal imbalance between estrogen and progesterone; estrogen predominance and progesterone deficiency [4-6]. Patients typically present with breast lumpiness, Mastalgia and nipple discharge of some duration [5, 8]. Other than the symptoms, the disease gain a relatively more concern due to the potential malignancy association; despite that most of the cases are benign, those with atypia has a significant increase risk of cancer [4-5, 8]. Most of the

cases undergo medical therapy with recent studies signifying the use of Metformin; particularly for reduction of cyst size and number in addition for pain relief [15-16, 18]. Thus, this study was conducted to analyze the effectiveness of Metformin for management of Mastalgia, and reduction of cyst size compared to Placebo.

In this study, the use of Metformin 500 mg twice daily was significantly associated with decrease in the size of fibrocystic disease of the breast. In which after 6 months of follow-up the reduction in the size of the cyst was seen in 58.3% of the cases on Metformin compared to 28.0% of the control group on Placebo. This study is in line with previous studies [16, 18]; Metformin is associated with reduction of cyst size compared to Placebo and this mechanism is believed to act through antiproliferative properties through reducing adenosine mono phosphate kinase (AMPK) [19-20].

Furthermore, one of the main complain of these patients is Nipple discharge. In this study, both groups showed clinically significant reduction in the complain of nipple discharge; 8.4% among cases and 18% among control group, yet the response was more significant among control; OR 3.5 for control vs 1.7 for cases. Indicating improvement in the symptoms. Talaei and colleagues [16], reported similar findings.

This study further describes Mastalgia response in both groups. It was seen that Mastalgia tends to decrease in both groups, Metformin and Placebo, with 6 months of follow-up with a more significant reduction in Placebo group compared to Metformin group; Odd ratio 23.5 vs 11.7, respectively. Furthermore, in Placebo group Mastalgia decreased from 94.0% to 40.0% while in Metformin group from 81.25% to 27.08%; indicating a 54.17% reduction in Metformin group vs 54.0% reduction in placebo group. Similarly, in another study conducted by Alipour and colleagues, at least 50% reduction was seen in metformin group compared to placebo [15]. Nevertheless, no significant difference was seen in Pain reduction in this study compared to Alipour and colleagues [15], indicating both approaches' can be used regardless, yet with higher chances with Placebo group.

Strengths and Limitations

This study has several important strength points from being a case-control study to reporting similar findings to other studies or near results and last but not least, to the best of the knowledge is the only article in the region which describes these findings. The only limitation was the small sample size.

Conclusion

Metformin despite acting as an oral hypoglycemic agent it can be used for the management of other disease one of which is trending is Fibrocystic Disease of the breast. Compared to Placebo, Metformin is associated with a significant reduction in the size of the cysts. While there is no significant difference in pain management and decreasing nipple discharge in both groups, with higher odds for Placebo over Metformin in the latter symptoms. Additionally, both Metformin and Placebo were associated with nearly 54% reduction in Mastalgia. Nevertheless, Metformin is an

important consideration since it reduces the cysts sizes and significantly reduce the symptoms of pain and nipple discharge.

Funding

None.

Conflict of Interest

None to declare.

Clinical Trail

Not applicable

Ethical Approval

The ethical approval was obtained from the university college.

Contribution

Z.M.S. was the sole author behind the idea conception, data collection and case assessment, operation and post-operative evaluation. The first and final draft was written and assessed by Z.M.S.

References

1. Kour, A., Sharma, S., Sambyal, V., Guleria, K., Singh, N. R., Uppal, M. S., Manjari, M., Sudan, M., & Kukreja, S. (2019). Risk Factor Analysis for Breast Cancer in Premenopausal and Postmenopausal Women of Punjab, India. Asian Pacific journal of cancer prevention : APJCP, 20(11), 3299–3304. https://doi.org/10.31557/APJCP.2019.20.11.3299
2. Malherbe K, Khan M, Fatima S. Fibrocystic Breast Disease. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551609/
3. Gopalani, S. V., Janitz, A. E., Martinez, S. A., Gutman, P., Khan, S., & Campbell, J. E. (2020). Trends in Cancer Incidence Among American Indians and Alaska Natives and Non-Hispanic Whites in the United States, 1999-2015. Epidemiology (Cambridge, Mass.), 31(2), 205–213. https://doi.org/10.1097/EDE.0000000000001140.
4. Vorherr, H. (1986). Fibrocystic breast disease: pathophysiology, pathomorphology, clinical picture, and management.. *American journal of obstetrics and gynecology*, 154 1, 161-79 . https://doi.org/10.1016/0002-9378(86)90421-7.
5. Greenblatt, R., Samaras, C., Vasquez, J., & Nezhat, C. (1982). Fibrocystic "disease" of the breast.. The New England journal of medicine, 308 12, 722-3 . https://doi.org/10.1097/00003081-198206000-00019.
6. Myhre, E. (1984). Is fibrocystic breast disease a pre-malignant state?. Acta Obstetricia et Gynecologica Scandinavica, 63. https://doi.org/10.3109/00016348409157009.
7. Molina, R., Filella, X., Herranz, M., Prats, M., Velasco, A., Zanón, G., Martinez-Osaba, M., & Ballesta, A. (1990). Biochemistry of Cyst Fluid in Fibrocystic Disease of the

Breast. Annals of the New York Academy of Sciences, 586. https://doi.org/10.1111/j.1749-6632.1990.tb17786.x.

8. Scott, E. (2003). Fibrocystic breast disease. Postgraduate Medicine, 114, 79 - 80. https://doi.org/10.1080/00325481.2003.11445761.
9. Bh, D., & Wc, D. (1987). Fibrocystic change and fibrocystic disease of the breast.. *Obstetrics and Gynecology Clinics of North America*, 14, 685-702.
10. Faguy, K. (2022). Fibrocystic Breast Changes.. Radiologic technology, 93 3, 303M-315M .
11. Malherbe, K., & Fatima, S. (2019). Fibrocystic Breast Disease. . https://doi.org/10.1007/springerreference_44259.
12. Scott, E. (2003). Fibrocystic breast disease. Postgraduate Medicine, 114, 79 - 80. https://doi.org/10.1080/00325481.2003.11445761.
13. Robertson, K., Kazmi, S., & Jordan, L. (2009). Female-type fibrocystic disease with papillary hyperplasia in a male breast. Journal of Clinical Pathology, 63, 88 - 89. https://doi.org/10.1136/jcp.2009.071043.
14. Gumus, I. I., Koktener, A., Dogan, D., & Turhan, N. O. (2009). Polycystic ovary syndrome and fibrocystic breast disease: is there any association?. Archives of gynecology and obstetrics, 280(2), 249–253. https://doi.org/10.1007/s00404-008-0889-8.
15. Alipour, S., Rastad, H., Saberi, A., Faiz, F., Maleki-Hajiagha, A., & Abedi, M. (2021). Metformin in the management of fibrocystic breast disease: a placebo-controlled randomized clinical trial. Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences, 29(2), 389–396. https://doi.org/10.1007/s40199-021-00424-6
16. Talaei, A., Moradi, A., & Rafiei, F. (2017). The evaluation of the effect of metformin on breast fibrocystic disease. Breast disease, 37(2), 49–53. https://doi.org/10.3233/BD-160256
17. Dr Prashant Dhannur, Dr Mamata Rathod, Dr Sunil Telkar, Dr Ganesh Bhavikatti. Metformin as a new treatment option in medical management of Benign Breast disease - A randomised clinical trial. Journal of Surgery and Research. 7 (2024): 501-505.
18. Musina, E., & Kogan, I. (2018). The effect of Metformin on fibrocystic breast disease in women with insulin resistance. Tumors of female reproductive system. https://doi.org/10.17650/1994-4098-2018-14-3-19-24.
19. Liu, B., Fan, Z., Edgerton, S. M., Yang, X., Lind, S. E., & Thor, A. D. (2011). Potent anti-proliferative effects of metformin on trastuzumab-resistant breast cancer cells via inhibition of erbB2/IGF-1 receptor interactions. Cell cycle (Georgetown, Tex.), 10(17), 2959–2966. https://doi.org/10.4161/cc.10.17.16359
20. Hardie, D. G., Ross, F. A., & Hawley, S. A. (2012). AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nature reviews. Molecular cell biology, 13(4), 251–262. https://doi.org/10.1038/nrm3311.