fortune Journals

Research Article

JOURNAL OF SURGERY AND RESEARCH

ISSN: 2640-1002

Metformin As a New Treatment Option in Medical Management of Benign Breast Disease - A Randomised Clinical Trial

Prashant Dhannur*, Mamata Rathod, Sunil Telkar, Ganesh Bhavikatti

Abstract

Introduction: Fibroadenosis and fibrocystic disease is the most common benign solid breast lump in women which has estrogen dependancy and proliferative features with no definite method of management. So far, no effective management strategy has been validated. Metformin has anti-estrogenic and antiproliferative properties. Thus, we investigated metformin as a new management strategy for fibroadenosis and fibrocystic disease (FCD).

Methods: In this randomized clinical trial study, eligible women with fibroadenosis were assigned randomly to the metformin (1000 mg daily), or the oil of evening primrose group for 3month. Breast physical and ultrasound exam was performed before and after the intervention (every 4 weeks), and the changes in the size of cysts and mastalgia were compared in the two groups.

Results: Overall, 46 patients in the treatment, and 44 in the placebo group completed the study. The mean age of participants was 32.4 years (±4.5), The amount of reduction in the size of cysts was two-fold in the treatment than second group. Mastalgia was also compared between two groups and was statistically not significant.

Conclusion: This study demonstrates the efficacy of Metformin in reducing the size of breast cysts in women with benign breast diseases, specifically fibroadenosis and fibrocystic disease (FCD). While the impact on mastalgia was less pronounced, the findings suggest that Metformin's anti-estrogenic and antiproliferative properties effectively target the underlying pathophysiological mechanisms of these conditions.

Keywords: Fibrocystic disease; Fibroadenosis; Metformin

Introduction

The physiological development of the breast occurs in three distinct phases: lobular development, cyclical hormonal modifications, and involution. Lobular development primarily happens during puberty, driven by hormonal changes that stimulate the formation of lobules, which are milk-producing glands. Cyclical hormonal modifications occur monthly due to fluctuations in estrogen and progesterone levels, leading to changes in the breast tissue. Involution is the process where the breast tissue gradually shrinks and is replaced by fat tissue, typically occurring during menopause [6].

ANDI refers to the deviations from the normal developmental and involutional processes of the breast, leading to various benign breast disorders. These disorders can manifest as generalized enlargement, cyclical

Affiliation:
Gadag Institute of Medical Sciences, Gadag, India

***Corresponding author:**
Dr Prashant Dhannur, Gadag Institute of Medical Sciences, Gadag, India.

Citation: 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.

Received: October 30, 2024
Accepted: November 11, 2024
Published: November 25, 2024

Prashant Dhannur, et al., J Surg Res 2024
DOI:10.26502/jsr.10020401

mastalgia, and nodularity, commonly known as fibrocystic disease of the breast. Fibroadenosis and fibrocystic disease (FCD) are prevalent forms of benign breast lumps in women, characterized by estrogen dependency and proliferative features. These conditions cause significant discomfort and anxiety due to their symptomatic similarities to malignant breast diseases [3].

Fibroadenosis and FCD are among the most common benign breast conditions affecting women worldwide. Despite their prevalence, there is no consensus on an effective management strategy for these disorders. The treatment typically involves addressing symptoms rather than the underlying pathophysiology, leading to varied success rates and patient satisfaction [4]. Traditional management options include dietary changes, hormonal therapies, and surgical interventions, each with its own limitations and potential side effects.

There is a significant gap in the effective management of fibroadenosis and FCD. Current treatments do not adequately address the estrogen-dependent proliferative nature of these conditions, leading to persistent symptoms and patient dissatisfaction.

Management of benign breast diseases like fibroadenosis and FCD typically includes lifestyle modifications, hormonal treatments, and surgical options. Dietary supplements such as evening primrose oil and vitamin E have been used to manage symptoms, but their efficacy remains inconsistent [5]. Hormonal treatments, including oral contraceptives and anti-estrogen medications, aim to modulate the hormonal influences on breast tissue but often come with significant side effects and are not universally effective [4].

Metformin is primarily used as a hypoglycemic agent in the treatment of type 2 diabetes. Recent studies have indicated its potential anti-estrogenic and antiproliferative effects, which may be beneficial in treating conditions like polycystic ovary syndrome and various cancers [2]. These properties suggest that Metformin could be an effective treatment for estrogen-dependent conditions, such as fibroadenosis and FCD.

Aims and Objectives

The primary objective of this study is to investigate the effectiveness of Metformin in reducing the size of breast cysts and alleviating symptoms in women diagnosed with fibroadenosis and fibrocystic disease. The study aims to provide a new therapeutic approach that targets the underlying pathophysiology of these conditions.

Methods

Study design

This study is a randomized clinical trial aimed at evaluating the efficacy of Metformin in the management of fibroadenosis and fibrocystic disease (FCD). Participants were recruited from a general surgery department and were randomly assigned to either the Metformin group or the control group. Ethical approval was obtained from the institutional review board, and informed consent was provided by all participants.

Inclusion criteria included women aged 18-50 years with clinically and sonographically confirmed fibroadenosis or FCD.

Exclusion criteria encompassed pregnant or lactating women, those with a history of breast cancer, and individuals with contraindications to Metformin.

Participants in the treatment group received Metformin at a dose of 1000 mg daily, divided into two doses of 500 mg each. The control group received oil of evening primrose as a placebo treatment. Both interventions were administered for a duration of three months. Compliance was monitored through regular follow-ups and pill counts monthly.

Breast physical examinations and ultrasound evaluations were performed at baseline, and then every four weeks until the end of the intervention period. The physical exams focused on palpating for changes in breast nodularity and size, while ultrasound was used to measure the exact dimensions of cysts.

Outcome measures

The primary outcome measure was the reduction in the size of breast cysts, assessed through ultrasound. Secondary outcome measures included changes in mastalgia, which were evaluated using a visual analog scale (VAS), and other symptoms such as tenderness and nodularity, recorded through patient self-reports and clinical examinations. Data on adverse effects and overall patient satisfaction were also collected to evaluate the safety and acceptability of Metformin as a treatment option.

Results

Table 1: Baseline Characteristics of participants

Characteristic	MetforminGroup (n=46)	ControlGroup (n=44)
Mean Age (years)	32.4 ± 4.5	32.1 ± 4.7
BMI (kg/m²)	24.8 ± 3.2	25.1 ± 3.4
Mean Cyst Size (mm)	15.2 ± 3.1	15.4 ± 3.3
DurationofSymptoms (months)	6.2 ± 2.1	6.5 ± 2.3
Number of Cysts	2.1 ± 1.0	2.0 ± 0.9
Mean Mastalgia Score (VAS)	6.8 ± 1.5	6.7 ± 1.6

The baseline characteristics table provides a comparison between the Metformin group and the control group at the start of the study. It includes parameters such as age, BMI,

Prashant Dhannur, et al., J Surg Res 2024
DOI:10.26502/jsr.10020401

Table 2: Changes in cyst size and mastalgia over time

Time Point	Metformin Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Baseline	15.2 ± 3.1 mm	15.4 ± 3.3 mm	0.72
4 Weeks	12.8 ± 2.9 mm	14.9 ± 3.2 mm	0.03
8 Weeks	10.3 ± 2.7 mm	14.4 ± 3.1 mm	<0.01
12 Weeks	8.6 ± 2.4 mm	13.8 ± 3.0 mm	<0.01
Mastalgia Score (VAS) at 12 Weeks	4.2 ± 1.3	6.5 ± 1.5	<0.01

Table 3: Adverse effects and patient satisfaction

Adverse Effect	Metformin Group (n=46)	Control Group (n=44)
Nausea	5 (10.9%)	2 (4.5%)
Gastrointestinal Disturbances	7 (15.2%)	3 (6.8%)
Headache	3 (6.5%)	2 (4.5%)
Overall Patient Satisfaction	38 (82.6%)	29 (65.9%)

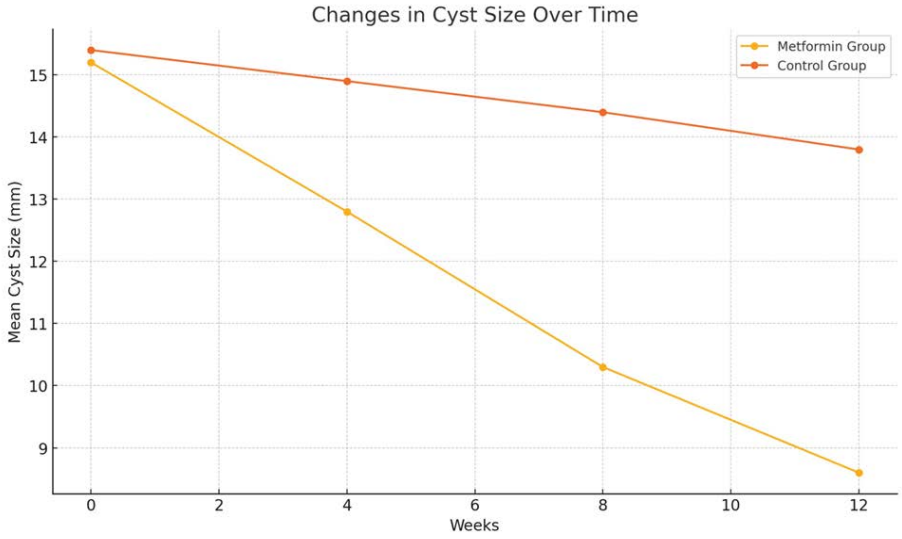
initial mean cyst size, duration of symptoms, number of cysts, and mastalgia scores, showing that both groups were comparable at baseline.

This table shows the changes in cyst size and mastalgia over the 12-week intervention period. At baseline, there was no significant difference between the groups. Over time, the Metformin group experienced a significant reduction in cyst size compared to the control group, as indicated by the decreasing mean cyst size and the p-values. Additionally, the mastalgia score significantly decreased in the Metformin group compared to the control group by the end of the study.

This table presents data on the adverse effects experienced by participants and their overall satisfaction with the treatment. The Metformin group reported higher incidences of nausea and gastrointestinal disturbances compared to the control group. However, overall patient satisfaction was higher in the Metformin group, suggesting that despite some side effects, participants found the treatment beneficial.

Graph 1: (Changes in Cyst Size Over Time)

The first graph shows the reduction in mean cyst size over a 12-week period for both the Metformin and control groups. The Metformin group shows a significant reduction in cyst size compared to the control group.



Graph 2: (Changes in Mastalgia Scores Over Time)

The second graph illustrates the changes in mastalgia scores (VAS) over the same 12-week period. The Metformin group experienced a notable decrease in mastalgia scores, indicating an improvement in symptoms compared to the control group.

Prashant Dhannur, et al., J Surg Res 2024
DOI:10.26502/jsr.10020401

Results

The study included 90 participants, with 46 in the Metformin group and 44 in the control group. The mean age of participants in the Metformin group was 32.4 years (±4.5), while the control group had a mean age of 32.1 years (±4.7). Baseline characteristics such as BMI, initial cyst size, duration of symptoms, and the number of cysts were comparable between the two groups, ensuring a balanced study design (Table 1).

The primary outcome measure was the reduction in cyst size, assessed through ultrasound at baseline and at 4-week intervals up to 12 weeks. The Metformin group showed a significant reduction in cyst size compared to the control group. At 12 weeks, the mean cyst size in the Metformin group was 8.6 mm (±2.4), compared to 13.8 mm (±3.0) in the control group. The reduction in cyst size was statistically significant ($p < 0.01$), demonstrating the efficacy of Metformin in reducing cyst size in benign breast diseases (Table 2; Figure 1).

Secondary outcome measures included changes in mastalgia and other symptoms such as breast tenderness and nodularity. The mastalgia scores, measured using a visual analog scale (VAS), showed a more substantial decrease in the Metformin group compared to the control group. By the end of the 12-week period, the mean mastalgia score in the Metformin group was 4.2 (±1.3), while the control group had a mean score of 6.5 (±1.5), with a statistically significant difference ($p < 0.01$) (Table 2; Figure 2).

Discussion

The study results indicate that Metformin significantly reduces the size of breast cysts in women with fibroadenosis and fibrocystic disease (FCD). The Metformin group experienced a statistically significant reduction in cyst size over the 12-week intervention period compared to the control group ($p < 0.01$). This finding suggests that Metformin's anti-estrogenic and antiproliferative properties effectively target the pathophysiological mechanisms underlying benign breast diseases [3].

However, the impact on mastalgia was less pronounced. While there was a reduction in mastalgia scores in the Metformin group, the difference was not as significant as the reduction in cyst size. This indicates that while Metformin may help in reducing the physical size of cysts, its effect on symptom relief,specifically pain, may require further investigation or additional supportive treatments.

The findings of this study align with previous research suggesting Metformin's potential benefits in managing conditions characterized by abnormal cell proliferation, such as polycystic ovary syndrome and certain cancers. Studies have demonstrated Metformin's ability to reduce cell proliferation and exert anti-estrogenic effects, supporting its use in treating estrogen-dependent conditions [2]. However, there is limited literature specifically focusing on Metformin's role in benign breast diseases, making this study a valuable contribution to the field.

Limitations

This study has several limitations that need to be acknowledged. Firstly, the sample size was relatively small, which may limit the generalizability of the findings. Additionally, the intervention duration of 12 weeks may not be sufficient to fully assess the long-term efficacy and safety of Metformin in managing benign breast diseases. Another limitation is the reliance on self-reported measures for symptoms like mastalgia, which may introduce bias. Future studies should aim to address these limitations by including larger, more diverse populations and extending the duration of the intervention.

Conclusion

This study demonstrates the efficacy of Metformin in reducing the size of breast cysts in women with benign breast diseases, specifically fibroadenosis and fibrocystic disease (FCD). While the impact on mastalgia was less pronounced, the findings suggest that Metformin's anti-estrogenic and antiproliferative properties effectively target the underlying pathophysiological mechanisms of these conditions.

The results of this study highlight the potential of Metformin as a viable treatment option for women suffering from fibroadenosis and FCD. Given its ability to significantly reduce cyst size, Metformin could be integrated into the current management strategies for benign breast diseases, offering an effective alternative or adjunct to existing treatments. Clinicians should consider the benefits of Metformin, especially for patients who may not respond well to traditional therapies. Future clinical practice should also be guided by additional research that explores optimal dosing, treatment durations, and the potential combination of Metformin with other therapeutic modalities to enhance symptom relief and patient outcomes.

References

1. Chae YK, Arya A, Malecek, et al. Repurposing metformin for cancer treatment: Current clinical studies. Oncotarget 7 (2016): 40767-40780.
2. Goodwin PJ, Stambolic V, Lemieux J, et al. Evaluation of metformin in early breast cancer: A modification of the traditional paradigm for clinical testing of anti-cancer agents. Breast Cancer Research and Treatment 126 (2009): 215-220.
3. Guray M, Sahin AA. Benign breast diseases: Classification, diagnosis, and management. The Oncologist 11 (2006): 435-449.

Citation: 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.

Prashant Dhannur, et al., J Surg Res 2024
DOI:10.26502/jsr.10020401

4. Santen RJ, Mansel R, Bradley L. Benign breast disorders. New England Journal of Medicine 353 (2004): 275-285.

5. Pruthi S. Detection and evaluation of a palpable breast mass. Mayo Clinic Proceedings 85 (2010): 234-240.

6. Houghton SC, Soyer HP. Development of the human breast. In HP Soyer, TL Brown, & AE Olsen (Eds.), Breast Cancer Prevention and Treatment (pp. 3-12). Springer (2018).

7. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: Extended long-term follow-up of the IBIS-I breast cancer prevention trial. The Lancet Oncology 8 (2007): 501-512.

8. Shao Y, Huo L, Klein ME. The role of estrogen and progesterone in the regulation of cell proliferation and apoptosis. Molecular and Cellular Endocrinology 482 (2018): 165-172.

9. Boyd NF, Lockwood GA, Byng JW, et al. Mammographic densities and breast cancer risk. Cancer Epidemiology, Biomarkers & Prevention 7 (1998): 1133-1144.

10. Bonanni B, Lazzeroni M, Guerrieri-Gonzaga A. The potential role of metformin in the chemoprevention of breast cancer. Cancer Research 71 (2011): 3194-3198.

11. Zhao Y, Zhang E, Lv X, et al. Metformin enhances chemosensitivity to gemcitabine in breast cancer via immune modulation. Cell Biology International 42 (2018): 1197-1206.

12. Dowsett M, Cuzick J, Wale C, et al. Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: An hypothesis-generating study. Journal of Clinical Oncology 23 (1995): 7512-7517.

13. Amaro C, Mateus T, Pereira C, et al. Metformin induced cytotoxicity against breast cancer cells is dependent on glucose concentration. Scientific Reports 7 (2017): 17607.

14. Li S, Brown MS, Goldstein JL. Regulation of cholesterol homeostasis. Molecular and Cellular Biology 30 (2010): 593-598.

15. Hardie DG. AMPK: A key regulator of energy balance in the single cell and the whole organism. International Journal of Obesity 32 (2014): S7-S12.

16. Gallagher EJ, LeRoith D. Insulin, insulin resistance, obesity, and cancer. Current Diabetes Reports 11 (2011): 257-266.

17. Aljohani M, Alzahrani A. The effectiveness of metformin in breast cancer therapy: A systematic review. Journal of Oncology (2018): 1-9.

18. Goodwin PJ, Stambolic V. Obesity and insulin resistance in breast cancer- Chemoprevention strategies with implications for healthcare policy. Cancer Prevention Research 4 (2011): 469-477.

19. Boudreau DM, Yu O, Buist DSM. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. Breast Cancer Research and Treatment 144 (2014): 405-416.

20. Pizot C, Boniol M, Mullie P. Physical activity, hormone replacement therapy, and breast cancer risk: A meta-analysis of prospective studies. European Journal of Cancer 52 (2016): 138-154.