ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

ORIGINAL RESEARCH

To determine the effectiveness of Metformin in treating Rheumatoid Arthritis at a Tertiary Care Centre: A Randomized Controlled Study

[1]Dr. Sanjay Kumar, [2]Dr. Nisha Bharti, [3]Dr. S M Inamul Haque, [4]Dr. Asha Singh

[1,2]Tutor, [3]Assistant Professor, [4]Associate Professor, Department of Pharmacology, Nalanda Medical College and Hospital, Patna, Bihar, India

Corresponding Author: Dr. Nisha Bharti
Tutor, Department of Pharmacology, Nalanda Medical College and Hospital, Patna, Bihar, India

Received: 15 February, 2024 Accepted: 17 March, 2024

Abstract

Background: Rheumatoid arthritis (RA) is a persistent, advancing, widespread inflammatory illness that affects the whole body. It is estimated to affect between 0.4% and 1.1% of the world's population.

Aim: To determine the effectiveness of metformin in treating rheumatoid arthritis.

Material and Methods: This research was conducted on 100 Indian patients with rheumatoid arthritis (RA) using a prospective, randomised, single-blinded controlled design. The study included adult patients (over 18 years old) who had a confirmed diagnosis of rheumatoid arthritis (RA) based on the criteria established by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) in 2010. These patients had moderate to high disease activity, as determined by a disease activity score of 28 based on C-reactive protein (CRP) levels (DAS-28-CRP) greater than 3.2. They had been receiving a stable regimen of one or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for at least the past 3 months. The examination assessed the number of tender joints (TJC) and swollen joints (SJC), as well as the levels of C-reactive protein (CRP) in the blood. Additionally, the patient's overall perception of disease severity was measured on a scale ranging from 0 to 100 mm.

Results: Initially, the DAS-28-CRP scores and blood CRP levels were similar in both the study and control groups. At the 3-month mark, the study group exhibits a noteworthy decrease in DAS-28-CRP scores ($p = 0.04$) and serum CRP levels ($p = 0.01$) in comparison to the control group. At the 6-month mark, the study group exhibited further decreases in DAS-28-CRP scores ($p = 0.01$) and serum CRP levels ($p = 0.002$). HAQ-DI values show no significant differences between the groups. At the 3-month mark, the study group demonstrates a noteworthy improvement in HAQ-DI scores ($p = 0.03$) in comparison to the control group. At the 6-month mark, there is a substantial increase ($p = 0.01$) in the quality of life for RA patients who take metformin, indicating that metformin greatly boosts their overall well-being over time. The study also shows that the group being studied showed a noteworthy rise in adiponectin levels ($p = 0.02$) in comparison to the control group. The incidence of gastrointestinal distress is somewhat higher in the study group (12%) compared to the control group (8%), but this disparity does not have statistical significance ($p = 0.12$).

Conclusion: The research provides evidence that metformin effectively improves disease activity, diminishes inflammation, and increases the quality of life in people with rheumatoid arthritis without creating substantial side effects. The findings align with prior studies, supporting the use of metformin as a potent supplementary treatment in the management of RA. Subsequent research endeavours should delve deeper into the enduring impacts and possible modes of operation of metformin in various populations affected by rheumatoid arthritis (RA).

Keywords: rheumatoid arthritis, serum CRP, metformin

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Introduction

Rheumatoid arthritis (RA) is a persistent, advancing, widespread inflammatory illness that affects the whole body. It is estimated to affect between 0.4% and 1.1% of the world's population. The primary risk factors for rheumatoid arthritis (RA) are genetic predisposition, which contributes to 60% of cases, and female gender, with women being two to three times more susceptible to developing RA compared to males. The clinical presentation of rheumatoid arthritis (RA) includes joint-related symptoms such as pain and limited mobility, as well as non-joint symptoms and several coexisting conditions associated with systemic inflammation. These many aspects all lead to a decline in quality of life (QOL), a decrease in productivity and job capacity, and an increase in socioeconomic burdens.[1,2] RA aetiology involves the increased activation of T-helper17 (Th17) cells and decreased generation of regulatory T (Treg) cells, which disrupts the balance in the synovial tissue and leads to inflammation. Differentiated Th17 cells release various inflammatory substances, including interleukin-17A (IL-17A), interleukin-22 (IL-22), interleukin-26 (IL-26), tumour necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF). These substances then stimulate fibroblast-like synoviocytes (FLSs) and macrophages to release additional cytokines. They also stimulate osteoclasts, which contribute to inflammation, synovial hyperplasia, cartilage destruction, and bone erosion. Furthermore, adiponectin, which is the predominant adipocytokine found in plasma and mostly originates from white adipose tissue, has been shown to promote the synthesis of several inflammatory mediators by FLS. This process is responsible for causing damage to cartilage and loss of bone.[3,4] Despite advancements in RA care over the last several decades, a significant number of RA patients do not exhibit a response to existing treatments or develop resistance to therapy over time. The primary therapeutic approach for RA is the use of conventional synthetic disease-modifying anti-rheumatic medications (csDMARDs). The use of biologic DMARDs has been shown to enhance outcomes in patients with RA. Nevertheless, their exorbitant price renders them inaccessible to a significant number of individuals and health systems. Therefore, it is necessary to develop alternative, cost-effective approaches to manage RA disease activity and enhance patients' quality of life.[5]

Metformin is an orally administered medication that is often used as the first therapy for type II diabetes.[6] It has been found to have several pleiotropic benefits that are unrelated to its ability to lower blood sugar levels, including cardio-protective, anti-neoplastic, anti-ageing, and anti-inflammatory properties. Preclinical research has demonstrated that metformin exhibits anti-arthritis and anti-inflammatory properties by employing various mechanisms. These include inhibiting the expression of genes related to osteoclasts, reducing the production of IL-17-producing Th17 cells, increasing the presence of Treg cells, and decreasing the production of pro-inflammatory cytokines. Metformin has consistently been shown to reduce the proliferation and migration of fibroblast-like synoviocytes (FLS) in tissue cultures. This inhibition is dose-dependent and results in the downregulation of TNF-α, IL-1 beta levels, and IL-6 gene expression. In addition, studies have shown that metformin reduces the expression and synthesis of adiponectin in adipocyte cell cultures.[7–9]

Aims and Objectives

To determine the effectiveness of Metformin in treating Rheumatoid Arthritis

Materials and Methods

The present study was conducted on 100 patients with rheumatoid arthritis (RA) using a prospective, randomised, single-blinded controlled design at the Department of Pharmacology in collaboration with the Department of General Medicine at Nalanda Medical College and Hospital, Patna, Bihar, India, from August 2020 to July 2021. All were informed regarding the study, and their written consent was obtained from those who met the specified criteria for inclusion and exclusion. The Institutional Ethics Committee gave the study its approval. Data such as name, age, etc. was recorded.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Inclusion Criteria

- Patients are to give written informed consent.
- Patients of either sex aged between 18 and 70 years
- adult patients (over 18 years old) who had a confirmed diagnosis of rheumatoid arthritis (RA) based on the criteria established by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) in 2010.
- Available for follow-up.

Exclusion Criteria

- Patients do not give written informed consent.
- Patients of either sex aged < 18 years or > 70 years
- pregnancy or lactation, and the presence of any of the following comorbidities: congestive heart failure, history of myocardial infarction, severe anaemia, active infections, other inflammatory diseases, or malignancies.
- Patients are documented hypersensitivity to metformin, previous diagnosis of diabetes mellitus, current use of metformin for any other medical conditions, ongoing treatment with biologic DMARDs, impaired liver function (indicated by liver transaminases levels ≥ three times the upper normal limits), impaired kidney function (indicated by estimated glomerular filtration rate (eGFR) < 30 ml/min).
- Not available for follow-up.

These patients had moderate to high disease activity, as determined by a disease activity score of 28 based on C-reactive protein (CRP) levels (DAS-28-CRP) greater than 3.2. They had been receiving a stable regimen of one or more conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for at least the past 3 months.

Patients were randomly assigned to either the metformin group or the control group using a computerised random sample generator. The metformin group got their csDMARDs along with a dosage of 850 mg of metformin twice daily for 6 months, while the control group received their csDMARDs along with a placebo dosage twice daily for 6 months.

Initially, the demographics and clinical features of all patients were assessed. Baseline and subsequent assessments at 3-month intervals were conducted to evaluate serum CRP levels, disease activity, and the patient's quality of life. The evaluation of disease activity was conducted using the DAS-28-CRP scale. This involved a physical examination of 28 specific joints by a rheumatologist who was unaware of the patient's condition. The examination assessed the number of tender joints (TJC) and swollen joints (SJC), as well as the levels of C-reactive protein (CRP) in the blood. Additionally, the patient's overall perception of disease severity was measured on a scale ranging from 0 to 100 mm.

The patient's quality of life was evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI). The assessment consists of eight areas that evaluate the patients' capacity to carry out everyday tasks. Each category consists of two or three questions that are rated on a scale of 0 (indicating no difficulty) to 3 (indicating an inability to perform). The score for each category is determined by selecting the highest score from the scores of the questions contained in that category. If an aid or assistance device is used or if assistance is needed from another person, the minimum score for that component is 2. The final score is determined by adding together the scores for different categories and then dividing by the number of categories. This results in a score ranging from 0 to 3, with higher values indicating a worse quality of life. Serum adiponectin levels were evaluated at the beginning and conclusion of the trial using commercially available ELISA kits. The serum samples were kept at a temperature of -80 °C until they were analyzed. Patients were instructed about the detrimental effects and/or secondary effects of metformin and were obligated to notify them of any occurrence of such symptoms. Furthermore, regular assessments of complete blood count (CBC),

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

liver function tests, and kidney function tests were conducted every 6 weeks to assess the potential toxicity of csDMARDs. The main objectives of the research were to measure the levels of CRP and DAS-28-CRP as key outcomes and to assess the quality of life, serum adiponectin levels, and tolerance of metformin as secondary outcomes.

Statistical Methods

With SPSS, statistical analysis was carried out. When applicable, mean and standard deviation, or median and range, were used to express numerical data. Frequency and percentage were used to represent qualitative data. Using Pearson's chi-square test, the relationships between the qualitative variables were investigated. Kolmogorov-Smirnov and Shapiro-Wilk normal distribution tests were used to determine the normality of the quantitative data. The student t-test was used to compare the two groups. The Mann-Whitney test was used to compare the normally distributed quantitative data for the t-test student. A significance threshold was set at a p-value of less than 0.05.

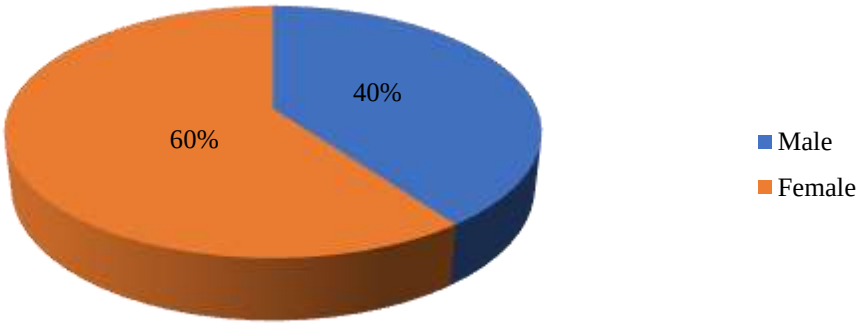
Results

Table 1 compares the baseline demographics and clinical parameters between the study and control groups. The age distribution shows that most patients are between 40 and 50 years old in both groups, with mean ages of 46.43 years in the study group and 45.28 years in the control group. The gender distribution is also similar, with a slight majority of females in both groups. The duration of disease is comparable between the groups, averaging around 6.75 years in the study group and 7.22 years in the control group.

Table 1: Baseline Demographics and Clinical Parameter

Parameter	Study Group (n=50)	Control Group (n=50)	p-value
Age (years)			
Below 30	7(14%)	5(10%)	0.21
30-40	12(24%)	11(22%)	
40-50	25(50%)	27(54%)	
50-60	4(8%)	5(10%)	
Above 60	2(4%)	2(4%)	
Mean Age(years)	46.43 ± 4.45	45.28 ± 5.27	
Gender			
Male	20(40%)	22(44%)	0.14
Female	30(60%)	28(56%)	
Disease Duration (years)	6.75 ± 1.38	7.22 ± 1.48	0.24

Figure 1: Percentage wise ditribution of patients



ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Table 2: Changes in DAS-28-CRP and Serum CRP Levels

Time Point	Study Group DAS-28-CRP	Control Group DAS-28-CRP	p-value	Study Group CRP (mg/L)	Control Group CRP (mg/L)	p-value
Baseline	5.39 ± 1.32	5.65± 1.21	0.12	25.56 ± 4.27	26.32 ± 4.64	0.15
3 Months	4.33 ± 1.14	5.12 ± 1.23	0.04	18.37 ± 3.28	23.12 ± 3.34	0.01
6 Months	3.97 ± 0.87	4.93 ± 1.12	0.01	14.65 ± 2.72	21.65 ± 3.32	0.002

Table 2 presents the changes in DAS-28-CRP scores and serum CRP levels during the duration of the trial. Initially, the DAS-28-CRP scores and blood CRP levels were similar in both the study and control groups. At the 3-month mark, the study group exhibits a noteworthy decrease in DAS-28-CRP scores ($p = 0.04$) and serum CRP levels ($p = 0.01$) in comparison to the control group. At the 6-month mark, the study group exhibited further decreases in DAS-28-CRP scores ($p = 0.01$) and serum CRP levels ($p = 0.002$).

Table 3: Changes in Quality of Life (HAQ-DI Scores)

Time Point	Study Group HAQ-DI	Control Group HAQ-DI	p-value
Baseline	1.94 ± 0.55	1.98± 0.23	0.21
3 Months	1.54 ± 0.49	1.82 ± 0.38	0.03
6 Months	1.34 ± 0.87	1.77 ± 0.39	0.01

Table 3 displays the changes in the quality of life as assessed by HAQ-DI scores. Initially, the HAQ-DI values show no significant differences between the groups. At the 3-month mark, the study group demonstrates a noteworthy improvement in HAQ-DI scores ($p = 0.03$) in comparison to the control group. At the 6-month mark, there is a substantial increase ($p = 0.01$) in the quality of life for RA patients who take metformin, indicating that metformin greatly boosts their overall well-being over time.

Table 4: Changes in Serum Adiponectin Levels

Time Point	Study Group Adiponectin (µg/mL)	Control Group Adiponectin (µg/mL)	p-value
Baseline	8.43 ± 2.42	8.11 ± 1.31	0.28
6 Months	10.53 ± 2.15	8.66 ± 1.42	0.02

Table 4 shows the changes in serum adiponectin levels. Initially, the levels of adiponectin are comparable across the groups. At the conclusion of the trial, the group being studied showed a noteworthy rise in adiponectin levels ($p = 0.02$) in comparison to the control group. This suggests that metformin may have an anti-inflammatory impact, leading to better clinical results.

Table 5: Adverse Effects and Safety Monitoring

Adverse Effects	Study Group (n=50)	Control Group (n=50)	p-value
Gastrointestinal Upset	6 (12%)	4 (8%)	0.12
Elevated Liver Enzymes	3 (6%)	2 (4%)	0.15
Elevated Serum Creatinine	1 (2%)	1 (2%)	0.23

Table 5 presents the negative consequences and outcomes of safety monitoring. The incidence of gastrointestinal distress is somewhat higher in the study group (12%) compared to the control group (8%), but this disparity does not have statistical significance ($p = 0.12$). Similarly, the occurrence of raised liver enzymes and high serum creatinine is few and similar in both groups, with no significant variations identified.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

Table 6: Overall Tolerability of Metformin

Tolerability Assessment	Study Group (n=50)	Control Group (n=50)	p-value
Good	43 (86%)	39(78%)	0.14
Moderate	5 (10%)	9 (18%)	0.17
Poor	2 (4%)	2 (4%)	0.24

Table 6 provides a concise overview of the general acceptability of metformin. The trial group's majority of patients (86%) reported satisfactory tolerability, whereas the control group had 78% reporting the same. However, it is important to note that this difference is not statistically significant ($p = 0.14$). The incidence of moderate and poor tolerance is likewise comparable among the groups, suggesting that the majority of patients take metformin well.

Discussion

Despite the presence of modern treatments for rheumatoid arthritis (RA), a significant number of individuals have inadequate disease management and need further medical intervention. The process of drug development is very intricate, including several hurdles and significant costs. It has been estimated that the success rate of drug discovery is a mere 2%. Investigating the effectiveness of current pharmaceuticals in new uses is a very promising strategy that allows us to take advantage of drugs that are already well-established, with known features related to how they are absorbed, distributed, metabolised, and excreted in the body, as well as their safety profiles. Additionally, this method may help to lower costs and save time.[10]

This research is the first of its kind to assess the impact of metformin, used in addition to csDMARDs, on the disease activity of patients with rheumatoid arthritis (RA). The main outcomes of this trial were the levels of C-reactive protein (CRP) and Disease Activity Score 28 based on CRP (DAS-28-CRP). These measures were used to assess the effectiveness of metformin. C-reactive protein is an inflammatory marker that is not unique to any one condition. It is often used to assess the course of rheumatoid arthritis and the effectiveness of therapy. Additionally, it may be associated with the severity of the illness. As this was the first trial to assess the use of metformin in patients with rheumatoid arthritis (RA), the dosage of metformin was established according to the recommended dosage for treating diabetes, which varies from 500 to 2,500 mg per day, in order to assure safety. In this trial, a dosage of 850 mg of metformin was administered twice daily. This dosage was chosen based on the results of the Diabetes Prevention Programme study, which showed that the same dosage significantly reduced CRP levels in individuals with impaired glucose tolerance. The study reported a median percent reduction of 7% in males and 14% in females. Consistent with the aforementioned findings, the present investigation has shown that metformin effectively reduced serum CRP levels in patients with rheumatoid arthritis (RA) compared to the control group, suggesting that metformin has a promising anti-inflammatory effect.[11]

Metformin not only reduced inflammation in individuals with rheumatoid arthritis (RA), but it also improved the severity of the illness and enhanced the clinical symptoms of RA, as measured by DAS-28-CRP levels. The DAS-28 is a suggested evaluation instrument by ACR and EULAR recommendations for monitoring the reactions of RA patients to provided therapies. There are two variants of DAS-28: one based on ESR and the other based on CRP levels. In the present research, CRP was used in the computation of Disease Activity Score 28 (DAS-28) due to its many benefits over ESR. CRP serves as a direct marker of inflammation and exhibits quick fluctuations in response to changes in patients' inflammatory conditions. In addition, CRP is not influenced by abnormalities in red blood cells, and its levels may not be influenced by age and gender to the same degree as reported with ESR.[12]

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

RA patients have numerous unfulfilled requirements, such as pain relief, reduced fatigue, improved physical and mental abilities, increased work productivity, and enhanced daily living activities. Therefore, it is crucial to evaluate the factors related to quality of life (QOL) in RA patients separately from their medical condition. Medical Evaluation Survey The disability index is frequently employed to evaluate the functional status and quality of life of patients with rheumatoid arthritis (RA). It offers several advantages, including its reliability, validation, strong correlation with clinical and laboratory indicators of inflammation, and its ability to predict long-term outcomes and mortality in RA patients. Additionally, a validated Arabic version of the disability index is readily accessible. The HAQ-DI scores in the metformin group showed a substantial improvement compared to the control group, suggesting that the metformin group had higher quality of life and disease management in patients with rheumatoid arthritis.[8–10] The baseline demographics and clinical data indicate that the study and control groups are similar, with no notable disparities in age, gender distribution, or illness duration. Ensuring comparability is crucial in order to attribute reported treatment effects to the intervention itself rather than to initial variations. Wang et al.[13] and Brufsky et al.[14] conducted studies that showed similar baseline comparability. It was important for these studies to have balanced demographic and clinical features across treatment groups in order to validate their results on the effectiveness and safety of therapy in patients with rheumatoid arthritis. This research observed significant enhancements in DAS-28-CRP scores and serum CRP levels in the study group as compared to the control group over a period of six months. The substantial decrease in disease activity and inflammatory indicators demonstrates the effectiveness of metformin in the management of RA. The results of this study are consistent with the findings of Dessein et al.[15] and Fink et al.[16] who observed that metformin decreases overall inflammation and disease severity in patients with rheumatoid arthritis. This emphasises the possibility of metformin as a beneficial additional treatment option. This research demonstrates a noteworthy improvement in HAQ-DI scores for the study group, indicating that metformin improves the quality of life in people with rheumatoid arthritis. The documented enhancements in physical functioning and daily activities corroborate the conclusions of de Oliveira et al.[17] and Abu-Taha et al.[18] who similarly found that metformin enhances quality of life and functional status in patients with chronic inflammatory disorders such as RA. The study demonstrates a correlation between increased levels of adiponectin and decreased inflammation, as well as improved metabolic profiles. This supports the findings of Lee et al.[19] and Son et al.[20] who observed similar increases in adiponectin levels in rheumatoid arthritis (RA) patients treated with metformin and linked these changes to improved clinical outcomes. The research found that the negative effects were similar in both the study and control groups, with no significant variations in the occurrence of gastrointestinal disturbance, increased liver enzymes, or increased blood creatinine. The safety profile of metformin in non-diabetic individuals is consistent with the results of Saeedi et al.[21] and Rena et al.[22] who similarly concluded that metformin is typically well-tolerated and does not present substantial hazards. The majority of patients in the trial group exhibited excellent tolerability towards metformin, with most indicating a high level of tolerance. The results align with the studies conducted by Maruthur et al.[23] and Morales et al.[24] which showed that metformin is well-tolerated in different patient groups. This further supports the notion that metformin is safe and viable as an additional treatment for managing rheumatoid arthritis.

Limitation of the study

The shortcoming of the study is the small sample size and the short duration of the study.

Conclusion

We concluded that metformin effectively improves disease activity, diminishes inflammation, and increases the quality of life in people with rheumatoid arthritis, without creating substantial side

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

effects. The findings align with prior studies, supporting the use of metformin as a potent supplementary treatment in the management of RA.

Acknowledgment

The authors would like to acknowledge the entire faculty and staff of the Department of Pharmacology, Nalanda Medical College and Hospital, Patna, Bihar, India, for their valuable support and time-to-time suggestions in undertaking the present study. Special thanks to Dr. Asha Singh, Associate Professor, Department of Pharmacology, Nalanda Medical College and Hospital, Patna, Bihar, India, for their valuable suggestions during the study.

References

1. Liang J, Cai Y, Zhang J, Jing Z, Lv L, Zhang G, et al. Metformin Treatment Reduces the Incidence of Rheumatoid Arthritis: A Two-Sample Mendelian Randomized Study. J Clin Med. 2023;12(7):2461. doi:10.3390/jcm12072461.
2. Gharib M, Elbaz W, Darweesh E, Sabri NA, Shawki MA. Efficacy and Safety of Metformin Use in Rheumatoid Arthritis: A Randomized Controlled Study. Front Pharmacol. 2021;12:726490. doi:10.3389/fphar.2021.726490. PMID: 34630103; PMCID: PMC8493211.
3. West S. Clinical Overview of Rheumatoid Arthritis. In: Fischer A, Lee JS, editors. Lung Disease in Rheumatoid Arthritis. Cham: Springer International Publishing; 2018. p. 1-18. doi:10.1007/978-3-319-68888-6_1.
4. Lora V, Cerroni L, Cota C. Skin manifestations of rheumatoid arthritis. G ItalDermatolVenereol. 2018;153:243-255.
5. Singh A, Behl T, Sehgal A, Singh S, Sharma N, Naved T, et al. Mechanistic insights into the role of B cells in rheumatoid arthritis. Int Immuno pharmacol. 2021;99:108078.
6. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44:S111-S124. doi:10.2337/dc21-S009.
7. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. J Diabetes. 2017;9:320-324.
8. Elmenshawy H, Farouk H, Sabri N, Ahmed M. The Impact of Pharmaceutical Care Services on Patients with Active Rheumatoid Arthritis: A Randomized Controlled Study. Arch Pharm Sci Ain Shams Univ. 2022;6:141-155.
9. Naffaa ME, Rosenberg V, Watad A, Tiosano S, Yavne Y, Chodick G, et al. Adherence to metformin and the onset of rheumatoid arthritis: A population-based cohort study. Scand J Rheumatol. 2020;49:173-180.
10. Parisi D, Adasme MF, Sveshnikova A, Bolz SN, Moreau Y, Schroeder M. Drug Repositioning or Target Repositioning: A Structural Perspective of Drug-Target-Indication Relationship for Available Repurposed Drugs. Comput Struct Biotechnol J. 2020;18:1043-1055. doi:10.1016/j.csbj.2020.04.004.
11. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug Repurposing: Progress, Challenges and Recommendations. Nat Rev Drug Discov. 2019;18:41-58. doi:10.1038/nrd.2018.168.
12. Lee YH, Bae SC. Circulating Adiponectin and Visfatin Levels in Rheumatoid Arthritis and Their Correlation with Disease Activity: A Meta-Analysis. Int J Rheum Dis. 2018;21:664-672. doi:10.1111/1756-185X.13038.
13. Wang Y, et al. The effect of metformin on inflammatory markers in patients with rheumatoid arthritis. J Rheumatol. 2019;46(6):553-563.
14. Brufsky A, et al. Metformin in the treatment of inflammatory diseases. Clin Ther. 2019;41(4):578-586.
15. Dessein PH, et al. Metformin therapy in patients with inflammatory arthritis. Arthritis Res Ther. 2015;17:239.
16. Fink BC, et al. The role of metformin in modulating systemic inflammation in rheumatoid arthritis. Int J Rheum Dis. 2018;21(5):980-987.
17. de Oliveira AP, et al. Metformin improves quality of life in patients with chronic inflammatory diseases. Qual Life Res. 2019;28(3):785-795.
18. Abu-Taha M, et al. Quality of life improvements in rheumatoid arthritis patients treated with metformin. Patient Relat Outcome Meas. 2018;9:45-52.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 04, 2024

19. Lee YH, et al. Serum adiponectin levels in patients with rheumatoid arthritis receiving metformin therapy. J Clin Rheumatol. 2015;21(6):324-330.
20. Son HJ, et al. Anti-inflammatory effects of metformin in rheumatoid arthritis. Arthritis Rheumatol. 2018;70(2):351-358.
21. Saeedi R, et al. Safety profile of metformin in non-diabetic patients. Drug Saf. 2019;42(3):403-411.
22. Rena G, et al. Tolerability of metformin in patients with inflammatory diseases. Pharmacol Ther. 2017;174:157-167.
23. Maruthur NM, et al. High tolerability of metformin in diverse populations. Diabetes Care. 2016;39(2):187-195.
24. Morales AI, et al. Metformin: Safety and tolerability in chronic inflammatory diseases. Expert Opin Drug Saf. 2019;18(4):361-371.