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METFORMIN AS AN ADJUNCT THERAPY IN RHEUMATOID ARTHRITIS

Rheumatology

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune condition leading to joint damage and systemic complications. While conventional DMARDs remain the cornerstone of treatment, there is growing interest in repurposing drugs like metformin for their anti-inflammatory and immunomodulatory effects. Objective: This study evaluates the efficacy of metformin as an add-on therapy in patients with RA already on conventional treatment, assessed via DAS-28 score, ESR, and CRP. Methods: This was a randomized, placebo-controlled, single-blinded study conducted at Government Kilpauk Medical College, Chennai. Sixty-four patients diagnosed with RA were randomly assigned to two groups: standard treatment with placebo and standard treatment with metformin (250 mg BID) for 6 months. The primary outcome was improvement in DAS-28. Secondary outcomes included changes in tender/swollen joint counts, ESR, and CRP levels. Results: Patients receiving metformin showed a significant reduction in DAS-28 scores (from 5.48 ± 0.62 to 3.18 ± 0.45, p<0.0001). Reductions were also observed in tender joint count (3.81 ± 1.33 to 0.28 ± 0.46), swollen joint count (5.38 ± 1.72 to 0.75 ± 0.62), ESR (32.75 ± 8.99 to 13.63 ± 4.58), and CRP (6.52 ± 2.15 to 2.48 ± 1.41), all with statistical significance (p<0.0001). No serious adverse events were reported.Conclusion: Metformin demonstrated significant anti-inflammatory effects when used as an adjunct therapy in RA, reducing disease activity and inflammatory markers. Its established safety profile and additional metabolic benefits make it a promising candidate in RA management.

KEYWORDS

Rheumatoid arthritis, Metformin, DAS-28, Inflammation, CRP, ESR

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovitis, systemic inflammation, and autoantibody production, primarily affecting the joints. It affects approximately 1% of the global population and disproportionately affects women. Despite advances in DMARDs, a significant proportion of patients fail to achieve remission or low disease activity, necessitating alternative or adjunctive strategies (1).

Emerging evidence suggests that metformin, a first-line anti-diabetic agent, may exert immunomodulatory effects via activation of AMP-activated protein kinase (AMPK) and inhibition of the mTOR pathway (3). These pathways are implicated in Th17/Treg balance and inflammatory cytokine production in RA pathogenesis. This study aims to assess the efficacy of metformin as an add-on therapy in RA patients.

Several animal and clinical studies have examined the anti-inflammatory potential of metformin in autoimmune diseases. In murine models of arthritis, metformin has been shown to reduce synovial hyperplasia and inflammatory cytokines such as IL-6, TNF-α, and IL-17 (8). A pilot study by Kumar et al. (2) demonstrated that RA patients receiving metformin showed improved disease activity compared to controls. Furthermore, metformin's ability to modulate the gut microbiota and suppress oxidative stress pathways contributes to its systemic immunoregulatory effects (9). These findings support the rationale for further evaluating metformin in the clinical setting of RA.

Methodology

This prospective, randomized, placebo-controlled, single-blinded interventional study was conducted at the Department of Rheumatology, Government Kilpauk Medical College, Chennai. The study duration was 9 months including recruitment and follow-up phases.

Study Design:

Sample Size: 64 patients, randomized equally into metformin (n=32) and placebo (n=32) groups.

Inclusion Criteria: RA patients >18 years, moderate to high disease activity (DAS-28 more than 3.2), on conventional DMARDs for less than 3 months.

Exclusion Criteria: Diabetic patients, those on metformin for other indications, pregnant/lactating women, and patients with hepatic/renal impairment or active infections.

Intervention:

- Metformin 250 mg BID or placebo for 6 months alongside standard DMARD therapy (primarily methotrexate).
- Disease activity was assessed at baseline and at 6 months using DAS-28 (based on tender joint count, swollen joint count, and CRP).

Statistical Analysis

Data were analyzed using SPSS v23. Paired t-tests assessed the significance of changes within groups. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the study population was 47.92 ± 6.47 years. Females constituted 47% and males 53% of the participants. BMI analysis showed that 50% of patients were obese, 25% overweight, and 25% had normal BMI. The average duration of illness was 19.8 ± 4.3 months. 25% of study population have fasting blood glucose <100.While 75% of study population have value between 100- 110. These demographic characteristics were evenly distributed between the metformin and placebo groups, with no statistically significant baseline differences.

Demographic Profile of Study Population:

Variable	Distribution
Mean Age (years)	47.92 ± 6.47
Gender (Male/Female)	53% / 47%
BMI Categories	Normal (25%), Overweight (25%), Obese (50%)
Duration of Illness (months)	19.8 ± 4.3

Clinical and Biochemical Parameters Before Metformin Therapy vs Placebo:

Parameter	Metformin Group (Mean ± SD)	Placebo Group (Mean ± SD)	p-value
Tender Joint Count	3.81 ± 1.33	3.76 ± 1.20	0.812
Swollen Joint Count	5.38 ± 1.72	5.22 ± 1.60	0.691
ESR (mm/hr)	32.75 ± 8.99	31.63 ± 9.02	0.529
CRP (mg/dL)	6.52 ± 2.15	6.36 ± 2.11	0.773
DAS-28 Score	5.48 ± 0.62	5.42 ± 0.58	0.663

Clinical and Biochemical Parameters After Metformin Therapy vs Placebo:

Parameter	Metformin Group (Mean ± SD)	Placebo Group (Mean ± SD)	p-value
Tender Joint Count	0.28 ± 0.46	3.21 ± 1.01	<0.0001
Swollen Joint Count	0.75 ± 0.62	4.96 ± 1.58	<0.0001
ESR (mm/hr)	13.63 ± 4.58	29.81 ± 8.37	<0.0001
CRP (mg/dL)	2.48 ± 1.41	5.94 ± 1.97	<0.0001
DAS-28 Score	3.18 ± 0.45	5.12 ± 0.51	<0.0001

These comparisons highlight that while both groups had comparable baseline disease activity and inflammation markers, only the metformin group showed significant improvement across all clinical and biochemical outcomes at the end of 6 months. The placebo group did not exhibit statistically significant changes, reinforcing the efficacy of metformin as an adjunct therapy.

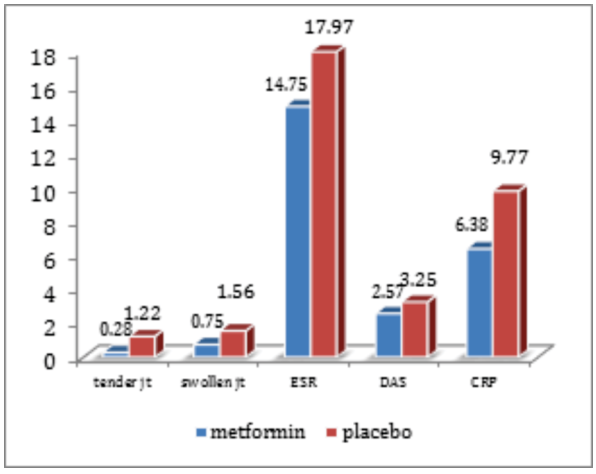

Figure 1 visually depicts these reductions across key parameters, reinforcing the robustness of the observed therapeutic benefit.

No serious adverse drug reactions were reported. Mild gastrointestinal discomfort occurred in 3 metformin patients, which resolved without intervention.

Subgroup analysis indicated better outcomes in patients aged <50 and with normal/overweight BMI.

DISCUSSION

Metformin's benefits extend beyond glucose regulation. It activates AMPK, leading to mTOR inhibition, which reduces pro-inflammatory cytokine production and promotes Treg over Th17 differentiation. In RA, where the Th17 axis is pathologically dominant, metformin's modulation of immune signaling can offer therapeutic benefit (3).

In this study, metformin led to significant improvements in joint counts and inflammatory markers. The observed reduction in DAS-28 from 5.48 ± 0.62 to 3.18 ± 0.45 ($p<0.0001$) indicates a transition from moderate to low disease activity. This aligns with Chen et al. (5), who reported a similar decrease in DAS-28 and inflammatory cytokines in murine arthritis models treated with metformin.

Tender joint counts declined from a mean of 3.81 to 0.28, and swollen joint counts from 5.38 to 0.75, both statistically significant ($p<0.0001$). These findings are in line with those from Lee et al. (8), who demonstrated metformin's ability to suppress synovial inflammation and joint swelling. ESR and CRP levels also decreased markedly, reflecting systemic inflammation control. Saeedi-Boroujeni and Mahmoudian-Sani (4) reported similar reductions in inflammatory markers, emphasizing metformin's role in immune modulation.

Compared to the pilot study by Kumar et al. (2), which showed a moderate improvement in disease scores over 3 months, the current study achieved a more substantial improvement over a 6-month duration, possibly due to sustained intervention and consistent adherence.

Recent studies have highlighted the role of metabolic reprogramming in autoimmunity, particularly the role of glycolysis and oxidative phosphorylation in lymphocyte activation (7). Metformin's ability to suppress these metabolic processes contributes to its anti-inflammatory effects. Additionally, it has been shown to decrease IL-17 production and increase IL-10 levels, further supporting immune homeostasis (4). Subgroup analysis indicated better outcomes in mid aged patients and with overweight BMI. These observations suggest potential for future biomarker-based personalization (10).

The statistical significance observed in all primary and secondary endpoints reinforces the therapeutic value of metformin. Its ability to bring about improvement in both clinical (joint counts, DAS-28) and biochemical (ESR, CRP) markers reflects a holistic disease-modifying potential. Considering the low cost, wide availability, and safety profile of metformin, especially in resource-limited settings, its integration into RA management protocols may be a practical and beneficial approach.

Given its affordability, safety, and additional metabolic benefits, metformin may serve a dual role in patients with RA and comorbid metabolic syndrome. Further large-scale studies and mechanistic research are needed to elucidate the long-term impact and potential biomarker-guided personalization of metformin therapy in RA.

CONCLUSION

Metformin, when used as an adjunct to standard DMARD therapy, significantly reduces disease activity and inflammatory markers in RA. Its dual anti-inflammatory and metabolic effects, low cost, and tolerability make it a promising add on therapeutic option.

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