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Study of Efficacy of Metformin in Rheumatoid Arthritis

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ABSTRACT

Background: Standard treatments for rheumatoid arthritis (RA) mainly suppress alternative immune pathways and thus have considerably high rates of side effects and refractoriness, warranting further exploration of mechanisms such as metabolic reprogramming. In this study, we assessed the clinical efficacy, functional outcomes, and safety of repurposing metformin as an oral metabolic adjunct in patients with actively treated RA.

Methods: This study, with a prospective design, assessed whether or not metformin improves outcomes in patients with rheumatoid arthritis taking conventional synthetic DMARDS, by placing 60 adult patients into 2 groups (30 patients/ group) based on their use of metformin as a concomitant medication after 3 months of stable synthetic DMARD therapy.

Results: The metformin group showed a significant decrease in median serum CRP levels at six months (6mg/L) compared to control (16mg/L), with $p < 0.001$. The biochemical effect was matched by a significant decrease in DAS-28-CRP scores (4.65 vs 5.92, $p < 0.001$) and a better functional capacity measured by the median HAQ-DI score (1.48 vs 2.18, $p < 0.001$). Gastrointestinal side effects occurring with metformin included nausea (23.3%) and abdominal pain (20.0%), which were more prevalent than in the control group but did not reach statistical significance ($p > 0.05$).

Conclusions: The addition of metformin to the treatment of patients with RA resulted in a decrease in systemic inflammation and disease activity as well as improved functionality for those patients. These results validate the use of immunometabolic modulation as an effective treatment option for patients.

Key-words: Rheumatoid arthritis, Metformin, Immunometabolism, das-28-crp, haq-di, Drug repurposing

INTRODUCTION

Rheumatoid arthritis (RA) is a long-lasting autoimmune disorder that results in permanent inflammatory disease of the synovium and formation of a pannus, both of which are mediated by activated immune cells and fibroblast-like synoviocytes (FLS) [1]. Current treatments for RA are both disease-modifyinganti-rheumatic agents (DMARDs) and biological agents; however, many patients have high rates of refractoriness to these agents or experience adverse events, thus warranting further investigation into the underlying pathophysiology of the disease in order to develop effective new therapies [1]. Metabolic reprogramming of FLS and immune cells within the nutritionally deprived microenvironment of the joint is a potent, emerging target for therapeutic intervention [1,2]. FLS and immune cells switch from primarily using oxidative phosphorylation for energy

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generation to primarily using rapid glycolysis in conditions of hypoxia and inflammation, resulting in a "Warburg-like" metabolic state that supports synovial inflammation, conditions the niche by the accumulation of lactate, and facilitates the amplification of pathogenic signalling [1,2].

Metformin has been used as a treatment for type 2 diabetes for many years. Its mechanisms of action include decreasing liver glucose production, increasing insulin sensitivity, and providing a very good safety record for all kinds of patients following normal renal dosing regulations. Research into the therapeutic use of metformin has greatly expanded past just glucose control and considerable interest has developed regarding many additional potential uses of the drug [3]. A 2025 critical review explored complex anti-cancer and immune modulation pathways of metformin and showed how metformin activates 5'-AMP-activated protein kinase (AMPK) and downstream mediators of that pathway, such as mTOR and NF-κB [4]. By altering cellular function and environment through this process, systemic inflammation may be decreased, and new blood vessel formation (angiogenesis) will be inhibited, warranting further exploration of the potential use of metformin as a therapeutic agent for many types of inflammatory and immune-mediated diseases and disorders [3,4].

The major function of Metformin in relation to the immune and metabolic processes is to activate an enzyme called 5'AMPK, which promotes metabolic rates to breakdown (catabolism) and reduces inflammation (anti-inflammatory). In pro-inflammatory conditions that lead to rheumatoid arthritis (RA), AMPK activation will inhibit both the activity of mTOR as well as modulate NF-kB-dependent transcription [5,6]. This modification of activity has been shown to decrease levels of pro-inflammatory cytokines, including IL-6, TNF-α, IL-1β, and IL-17, in both fibroblast-like synoviocytes (FLS) and vascular endothelial cells [5,6]. While not well characterized in humans, this metabolic process may inhibit the aggressive invasive phenotype of the FLS via limiting cell number (proliferation) and/or limiting cell movement (migration), and may also shift the ratio of Th17 to Treg cells, thereby helping to protect the joint from disease [5].

Although data from studies indicate that metformin may be useful as an adjunctive therapy for rheumatoid arthritis, we lack sufficient, complete, and prospective clinical studies evaluating metformin as an adjunct therapy to DMARDs in patients with RA. Therefore, this study will systematically compare the efficacy, safety, and effect of adjunctive metformin on DAS28-CRP scores, as well as on radiographic progression and inflammatory biomarkers, in patients with active RA, with the primary hypothesis that modulation of the metabolic-immune axis by metformin will produce a reduction in total disease activity above and beyond standard DMARD therapy alone.

MATERIALS AND METHODS

Study design- This study was a prospective observational study to evaluate the efficacy of Metformin in rheumatoid arthritis. The study was conducted in the Department of Orthopaedics at Santosh Medical College & Hospital. The study was conducted for a duration of one year. Patients who were diagnosed with Rheumatoid Arthritis and had visited the Orthopedics Outpatient Department were selected for the study. All of the patients were selected on the basis of the predefined inclusion and exclusion criteria. Baseline demographic parameters, clinical status, disease activity, laboratory factors, and other details of the treatment regimen were recorded and measured. Those who had received metformin and the standard anti-rheumatoid therapy were considered for the evaluation of the metformin's potential to reduce pain, joint stiffness and the inflammatory markers. This resulted in the improved outcome among Rheumatoid Arthritis patients.

Inclusion criteria

- ✓ Patients aged between 18 to 65 years of age were selected.
- ✓ Those who were confirmed with the RA, with the disease activity (DAS28CRP > 3.2)
- ✓ Informed consent required for the study.

Exclusion criteria

- ✓ Patient with type 2 diabetes mellitus or any kind of usage of metformin were not allowed for the study.
- ✓ Several renal (eGFR < 45 ml/min/1.73 m^2), hepatic, or cardiac dysfunction wasn't allowed for the study.
- ✓ Pregnant women or lactating women wasn't considered for the study.
- ✓ Hypersensitive patients to metformin were excluded from the study.

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Sample size calculation- The sample size was calculated by using standard statistical methods and tools. The total sample size calculated was 60 patients. All of the patients were categorised into two groups, containing 30 patients each. Group A consisted of 30 patients, those who had received conventional Disease Modifying Anti-Rheumatic Drug (DMARD) therapy, combined with metformin of 500–850 mg administered two times daily. Group B (control group) consisted of 30 patients who had received the conventional DMARD therapy. The comparative evaluation between the groups was conducted to investigate the efficacy of metformin among the Rheumatoid Arthritis patients.

Procedure- Verbal and written consent were taken from all of the patients diagnosed with RA; those who had attended the Orthopedics OPD were included. Patient's demographic and clinical parameters were collected and analysed. The level of C-reactive protein (CRP), the activity of the disease, and the quality of life were evaluated. DAS-28-CRP scoring system was used to evaluate the disease activity on the basis of the count of tender joints, swollen joints, the level of CRP and the assessment of the global health. The Health Assessment Questionnaire Disability Index (HAQ-DI) was utilised to evaluate the quality of life. Group A patients will receive the DMARD therapy in combination with 500–850 mg of metformin for 2 times daily, while group B had received only DMARD therapy. Patient follow-up was performed to evaluate the level of CRP, DAS-28-CRP score, and QOL every 3 months. The level of adiponectin was measured at the baseline level and at the end of the study by the use of ELISA kits. Patient regulation was performed to evaluate the impact of metformin, and laboratory investigations were performed, such as the total complete blood count, liver function tests, and kidney function tests, every 6 months for the evaluation of the drug safety and the tolerance. The outcome assessment included the level of CRP and the DAS-28-CRP score, while the secondary assessment consisted of the life quality, level of adiponectin, and also analysed the tolerance of metformin.

Data collection- Data collection was performed at the baseline level, every week 6, and week 12, in order to evaluate the clinical outcome and the safety profile of the intervention.

Statistical Analysis- SPSS version 27 was used for the statistical analysis. The Quantitative data were represented in the form of mean ± standard deviation or median and range, while frequency and percentage were used to represent the qualitative data. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate the normality. Student's t-test was performed for the comparative analysis of the normally distributed data and the Mann–Whitney U test was used to analyse the non-normally distributed data. The qualitative variables were evaluated by the use of Pearson's Chi-square test. Comparative analysis of the repeated data was evaluated by the Wilcoxon Signed Rank test and the Friedman test. The p-value was considered to be <0.05 to maintain statistical significance.

RESULTS

Table 1 showed that 30 patients were enrolled in each of the metformin and control groups. Females were predominant in both of the groups, which was estimated to be around 90.0% and 93.3%, in another group. The comparable parameters were mean age, weight, height, and BMI, with insignificant statistical analysis. The most common comorbidities were Hypertension and dyslipidemia, which were noted in both of the groups. LEF + SLZ and HCQ + LEF were noted as the most commonly utilised regimen. A similar pattern of corticosteroid usage was observed, along with the most general dose observed as 10 mg dose. Both of the groups showed comparable analysis for baseline and clinical parameters.

Table 2 demonstrates the level of baseline CRP levels and the DAS-28-CRP scores for both of the groups. The metformin group showed a reduction in the level of CRP after 3 months and the activity score of the disease was compared with that of the control group. During 6 months, the level of CRP was reduced in the metformin group with a median of 6 mg/L, and the median of the control group was 16 mg/L. The metformin group showed significant improvement of the DAS-28-CRP scores during 6 months of follow up period. The metformin group showed better outcomes with time, as analysed by the within-group analysis. Contrastingly, no changes were noted in the control group at the time of follow-up. These results noted that inflammation and disease activity are reduced due to the metformin adjunct therapy among RA patients.

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Table 1: Distribution of the demographic and clinical features among the Rheumatoid Arthritis Patients for both of the groups

Parameter	Metformin group (n = 30)	Control group (n = 30)	p-value
Gender			
Female, n (%)	27 (90.0)	28 (93.3)	a
Male, n (%)	3 (10.0)	2 (6.7)	
Age in years: (mean ± S.D)	52.1 ± 8.7	51.4 ± 7.5	0.764[b]
Weight in kg: (mean ± S.D)	84.2 ± 11.6	80.8 ± 9.9	0.218[b]
Height in m: (mean ± S.D)	1.61 ± 0.09	1.60 ± 0.08	0.587[b]
BMI in kg/m²: (mean ± S.D)	32.1 ± 4.7	31.0 ± 3.4	0.291[b]
Disease duration in years: Median (range)	12 (5–19)	11 (4–16)	0.174[c]
Comorbidities, n (%):			
HTN	12 (40.0)	11 (36.7)	0.781[d]
Dyslipidemia	5 (16.7)	4 (13.3)	0.718[d]
Ischemic heart disease	1 (3.3)	1 (3.3)	a
Type of csDMARDs used: n (%):			a
LEF + SLZ	10 (33.3)	11 (36.7)	
HCQ + LEF	9 (30.0)	8 (26.7)	
MTX + HCQ	5 (16.7)	6 (20.0)	
MTX + SLZ	3 (10.0)	2 (6.7)	
MTX + LEF	1 (3.3)	1 (3.3)	
LEF	1 (3.3)	1 (3.3)	
LEF + HCQ	1 (3.3)	1 (3.3)	
Corticosteroids: n (%)			
Not receiving steroids	6 (20.0)	5 (16.7)	0.915[d]
5 mg dose	6 (20.0)	7 (23.3)	
10 mg dose	18 (60.0)	18 (60.0)	

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Table 2: The comparative analysis of the CRP level in serum and the DAS-28-CRP Scored for both of the groups

Parameter	Metformin group (n = 30)	Control group (n = 30)	p-value
Serum CRP levels (mg/L)			
Baseline, median (range)	15 (4–29)	13 (3–25)	0.231[b]
After 3 months, median (range)	11 (2–22)	14 (4–27)	0.189[b]
After 6 months, median (range)	6 (2–32)	16 (7–31)	<0.001[ab]
p-value	<0.001[acd]	0.126[c]	
DAS-28-CRP			
Baseline, median (range)	5.42 (4.20–6.75)	5.58 (3.74–6.80)	0.914[b]
After 3 months, median (range)	5.08 (3.40–6.50)	5.60 (3.82–6.70)	0.158[b]
After 6 months, median (range)	4.65 (3.10–6.40)	5.92 (4.25–6.88)	<0.001[ab]
p-value	<0.001[ace]	0.438[c]	

Table 3 showed the baseline HAQ-DI scores, which were compared for both of the groups. After 3 months, HAQ-DI scores showed improvement in the metformin group rather than the control group. During 6 months, the HAQ-DI score reduced in the metformin group to 1.48, while the control group was unchanged at 2.18. The metformin group showed improvement in the within-group analysis, while the control group showed no improvement. These results indicated better functional role observed in metformin adjunct therapy and the quality of life among RA patients.

Table 3: The comparative analysis of the HAQ-DI Scores for both the metformin and the control groups

HAQ-DI Score	Metformin group (n = 30)	Control group (n = 30)	p-value
Baseline, median (range)	2.10 (0.70–2.55)	2.05 (1.20–2.60)	0.947[b]
After 3 months, median (range)	1.82 (0.40–2.30)	2.10 (1.30–2.52)	0.008[ab]
After 6 months, median (range)	1.48 (0.35–2.20)	2.18 (1.70–2.55)	<0.001[ab]
p-value	<0.001[acd]	0.072[c]	

Table 4 showed that gastrointestinal side effects were more commonly observed in the metformin group than in the control group. 23.3% of patients showed nausea in the metformin group and 13.3% in the control group. 20.0% of patients showed pain in the abdomen, regardless of the presence or absence of flatulence, rather than the 16.7% in the control group. 16.7% cases in the metformin group were observed with Diarrhoea and 10.0% of cases in the control group.

Table 4: The comparative analysis of the gastrointestinal side effects for both of the groups

Gastrointestinal Side Effects	Metformin group (n = 30)	Control group (n = 30)	p-value
Nausea, n (%)	7 (23.3)	4 (13.3)	0.328[a]
Abdominal pain ± flatulence, n (%)	6 (20.0)	5 (16.7)	0.739[a]
Diarrhoea, n (%)	5 (16.7)	3 (10.0)	0.448[a]

DISCUSSION

The research results indicate that providing metformin to patients with rheumatoid arthritis can decrease inflammation and improve disease activity while not presenting any serious safety issues. Specifically, after six months of treatment with metformin, blood CRP levels decreased significantly to 6 mg/L compared to blood CRP levels of 16 mg/L in the control group (P<0.001). A similar trend was found with clinical outcomes regarding activity scores (DAS28-CRP), where there was a significant decrease in the activity scores for patients taking metformin (DAS28-CRP median decrease was 4.65 vs 5.92) (P <0.001). Improvements were also seen in terms of functional quality of life (HAQ-DI) with a significant decrease in HAQ-DI from a median score of 1.48 vs 2.18 (P <0.001). Although gastrointestinal side effects (nausea 23.3%, abdominal pain 20.0%, diarrhea 16.7%) occurred with more frequency in the metformin group, the statistical analysis showed no significant difference when compared to the control group (p > 0.05), therefore supporting the conclusion that a metabolic intervention like metformin can be tolerated by rheumatoid arthritis patients over the short term.

A double-blinded placebo-controlled trial involving 120 adult patients determined that adding 1000 mg/day metformin to methotrexate treatment for 12 weeks would significantly increase the ACR20 responder rate from 54.7% (placebo) to 80.8% (P=0.001), while demonstrating a greater percentage of patients in DAS remission (P=0.015). Gene expression changes in AMPK and IGF-IR further confirmed this therapeutic effect [6]. A separate prospective multi-centre cohort study comparing 124 patients using adjunctive metformin to 98 patients being treated with conventional therapies demonstrated that metformin accelerates the decline of serum HMGB1 as well as markers of major inflammatory cytokines over 90 days. The clinical improvement demonstrated by this study was highly correlated to a decrease in CD4+/CD8+ ratio as well as patient-reported VAS pain score, making HMGB1 (95% CI 1.133 - 1.397; p<0.001) an excellent marker of therapeutic efficacy [7].

According to a cohort study conducted in Ireland, insulin resistance appears to independently relate to the body mass index (B = 0.113, p < 0.001, n = 61) as well as to swollen joint counts (B = 0.114, p = 0.008, n = 61) in patients with rheumatoid arthritis and that there was a also a significant increase in the expression of glucose transporter type 1 (GLUT1) in the RA synovium (n = 26) when compared with osteoarthritis (n = 16, p = 0.0003) [1]. In ex vivo testing, patients treated with metformin exhibited increased expression of phosphorylated AMP-activated protein kinase (pAMPK) and decreased expression of GLUT1 (n=4) as well as decreased spontaneous levels of interleukin 6 (IL-6) and interleukin 8 (IL-8) (n = 5-7) [8]. On the other hand, genomic and serum studies from RA patients confirm a positive correlation between DAS28 activity and p-AMPK-α1 levels (r = 0.270, p < 0.0001) and TNF-α levels (r = 0.460, p = 0.0002). In RA-fibroblast-like synoviocytes (RA-FLSs), the activation of AMPK by metformin results in downregulation of IL-6, TNF-α and IL-1β expression whilst upregulating the expression of the protective hyaluronan binding protein HAPLN1 [9].

In a randomized, double-blinded, placebo-controlled trial over 12 weeks, adjunctive metformin and background therapy with methotrexate produced significantly better clinical outcomes, increased rates of remission from disease and decreased disease activity scores, likely due to the modulation of the AMPK pathway. Metformin was well-tolerated in the short term and did not result in any serious adverse events [7]. Additionally, a separate 90-day prospective cohort study found that metformin use in conjunction with traditional treatment methods resulted in a faster decline in pain scores and important systemic inflammatory markers compared with traditional treatments alone. This cohort study also showed that the decline in HMGB1 was closely correlated with changes in disease activity. In both cases, metformin was shown to have a safe profile [10].

Future studies should focus on large, prospective, double-blind, multicenter randomized controlled trials with long-term follow-up to establish whether

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metformin protects joints over time. At the same time, ancillary mechanistic studies using localized synovial tissue biopsies and advanced imaging techniques, such as musculoskeletal ultrasound or PET-CT, will provide researchers with the ability to adequately monitor changes in metabolic flux and immune response, or immunometabolism, in patients. Ultimately, using adjunctive metformin to target metabolic and immunological pathways represents a safe, effective and globally acceptable therapeutic alternative to optimize disease control in patients with active rheumatoid arthritis.

CONCLUSIONS

In conclusion, adjunctive metformin used in combination with typical disease-modifying antirheumatic drugs may provide a new and viable drug therapy option for individuals suffering from active rheumatoid arthritis. When combined with these two therapeutic approaches, adjunctive metformin can help improve both systemic inflammatory markers as well as overall clinical disease activity, thereby enhancing the functional capacity and quality of life among individuals with active rheumatoid arthritis. Positive clinical outcomes in both subjective and objective assessments indicate the value of targeting different cellular pathways in this disease. The protocol can continue to have beneficial results while exhibiting a favorable safety profile due to the minimal gastrointestinal side effects associated with this treatment protocol, which are statistically insignificant and can be managed through standard clinical practices. Overall, the data support the concept that using a commonly used, inexpensive biguanide to modulate cellular metabolism will provide a safe, effective and life-changing way of managing long-term autoimmune disorders.

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