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Original Research Article

The Study of the Efficacy of Metformin in Rheumatoid Arthritis and its Effect on Serum C-Reactive Protein at a Tertiary Centre

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Conflict of interest: Nil

Abstract:

Background: The prevalence rate of Rheumatoid arthritis (RA) is around 0.4 percent to 1.1 percent globally. There is no reliable statistical data available in India. More research is required in this area. Metformin has been shown in preclinical studies to have anti-arthritis and anti-inflammatory effects through a number of mechanisms, including the inhibition of osteoclast gene expression, the suppression of IL-17-producing Th17 cells, the up-regulation of Treg cells, and the reduction of pro-inflammatory cytokine production.

Aims and Objectives: To determine the Efficacy of Metformin in Rheumatoid Arthritis and its impact on serum C-Reactive Protein.

Materials and Methods: This was a prospective, randomised, single-blinded, controlled study carried out on 70 Eastern Indian RA patients.

Results: The mean age of the participants was 49.78±8.64 years, where 43 (71.6%) of them were obese (body mass index (BMI) ≥ 30 kg/m2) and 15 (25%) were overweight (25 ≤BMI≤ 29.9). The identified comorbidities in the study groups were hypertension, dyslipidemia, and ischemic heart disease, where 16 (45.71%) of participants had hypertension, 5 (14.28%) had dyslipidemia, and 2 (5.71%) had ischemic heart disease.

Conclusion: Use of metformin in Rheumatoid Arthritis as an adjuvant is highly advisable because metformin enhances quality of life after one year of treatment.

Keywords: Metformin, C - reactive protein (CRP), Rheumatoid Arthritis, Adjuvant, Quality of Life (QOL).

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disease with an estimated prevalence ranging from 0.4 to 1.1% globally and 0.3% in the Egyptian population [1, 2]. Genetic predisposition, which accounts for 60% of cases, and female gender are the main risk factors for RA. Women are two to three times more likely to develop RA than men [2]. The clinical presentation of RA includes articular manifestations of pain and reduced mobility as well as extra-articular manifestations and several comorbidities related to systemic inflammation [2, 3]. Poor quality of life (QOL), decreased productivity, diminished work ability, and increasing socioeconomic difficulties are all caused by these problems [4, 5].

Metformin is an oral anti-diabetic agent that is widely used as a first-line treatment for type II diabetes [6]. It has been reported to have many pleiotropic effects that are independent of its anti-hyperglycemic role, including cardio-protective, anti-neoplastic, anti-aging, and anti-inflammatory effects [7, 8]. Metformin has been shown in preclinical studies to have anti-arthritis and anti-inflammatory effects through a number of mechanisms, including the inhibition of osteoclast gene expression, the suppression of IL-17-producing Th17 cells, the up-regulation of Treg cells, and the reduction of pro-inflammatory cytokine production [9, 10]. The first-line management strategy for RA is based on using conventional synthetic disease-modifying anti-rheumatic drugs (cs DMARDs) [11, 12].

Using biologic DMARDs has been shown to enhance RA outcomes [13]. However, many

patients and healthcare systems cannot afford them due to their expensive costs [14]. Hence, alternative, low-cost strategies are needed to control RA disease activity and improve patients' QOL.

Aims and Objectives

This study was designed to evaluate the potential benefits and efficacy of metformin use as an adjuvant therapy in RA arthritis patients with moderate and high disease activity and its effect on serum C-reactive protein.

Materials and Methods

This was a prospective, randomized, single-blinded, controlled study carried out on 70 Eastern Indian RA patients. The study was conducted at the Pharmacology Department in collaboration with the Medicine Department at Nalanda Medical College and Hospital, Patna, Bihar, India. The study protocol has been revised and approved by the institute's Research Ethics Committee. The study was done from January 2022 to December 2022.

Adult patients (older than 18 years) were included in the study with an established diagnosis of RA based on C-reactive protein (CRP) levels, receiving a consistent dose of one or more csDMARDs for at least the previous three months.

Exclusion Criteria

There were a known hypersensitivity to metformin; a prior diagnosis with diabetes mellitus; receiving metformin for any other indications; receiving biologic DMARD therapy; impaired kidney functions (estimated glomerular filtration rate (eGFR) <30 ml/min), impaired liver functions (liver transaminase level ≥ three times upper normal limits), pregnancy, and nursing, as well as the presence of any of the following comorbidities: congestive heart failure; history of myocardial infarction; severe anaemia; active infections; other inflammatory diseases; and malignancies.

Inclusion Criteria

Mild to moderate cases between 20 and 60 years old were taken up for the study.

Methodology

The subjects were thoroughly examined, and their detailed histories were taken. Taking all necessary aseptic precautions, blood was drawn and sent to the Biochemistry lab for the baseline evaluation of CRP levels. The patients were started on metformin. The other treatment was continued, and metformin was added. The dose depended on the weight of the patient and other compliance factors. It was in the range of 500mg to 1500mg in divided doses. The patients were followed up after 1 month, 3 months, and 6 months. Serum CRP levels were checked, and the levels have been reported in this study.

All patients' baseline demographics and clinical characteristics were examined. Serum CRP levels, disease activity, and the patient's QOL were assessed at baseline and every 3 months thereafter. Disease activity was assessed using serum CRP levels. Patients were informed of the potential risks and/or side effects of metformin and were instructed to report any occurrences. A complete blood count (CBC), liver function tests, and kidney function tests were also routinely performed every 6 weeks to assess the toxicity of csDMARDs. The study's primary outcomes were CRP levels, while secondary outcomes were quality of life and metformin tolerability.

Statistical analysis was done using SPSS version 22 and Microsoft Excel 15 to calculate Numerical data was expressed as mean and standard. Frequency and percentage were used to represent qualitative data. For normally distributed quantitative data, comparisons between two groups were done using the student t-test, and a p-value < 0.05 was considered significant.

Sample Size Calculation

The sample size calculation was done by the Statulator online calculator available at http://statulator.com/SampleSize/ss2M.html. The study included 70 subjects: 35 experimental study subjects and 35 control subjects.

Patients were simply randomized to receive either metformin 850 mg twice daily (Metformin group, n = 35) or placebo twice daily (Control group, n = 35) in addition to their stable anti-rheumatic regimen and followed up for 6 months. Serum C-reactive protein (CRP) and quality of life (QOL) were evaluated at baseline and then every 3 months.

Results

90 patients with RA were assessed for eligibility. Only 70 patients fulfilled the inclusion criteria and were included in the present study. The mean age (Mean±S.D) of the participants was 49.78±8.64 years,where 43(71.6%) of them were obese (body mass index (BMI) ≥ 30 kg/m2) and 15 (25%) were overweight (25 ≤BMI≤29.9).

The identified comorbidities in the study groups were hypertension, dyslipidemia, and ischemic heart disease, where 16(45.71%) of participants had hypertension, 5(14.28%) had dyslipidemia, and 2(5.71%) had ischemic heart disease. The number of participants who received prednisolone as DMARDS was 57 (81.4%). P value > 0.05, there were no significant differences between groups regarding baseline demographics and clinical characteristics, as shown in Table 1 and Figure 1.

Table 1: Comparision of baseline characteristics between study and control groups

Parameters	Study/ Metformin group (n=35)	Control group (n=35)	P value
Gender			
Male	03(8.57%)	00	
Female	32(94.28%)	35(100%)	
Age in Years (Mean±SD)	49.78±8.64	48.97±7.21	0.641
Height in Metres (Mean±SD)	1.52±0.19	1.52±0.19	0.358
Weight in Kg (Mean±SD)	84.75±10.67	80.21±67	0.291
BMI in Kg/m^2 (Mean±SD)	32.50±5.86	31.69±3.82	0.247
Comorbidities			
HTN	16(45.71%)	14(40%)	
Ischaemic Heart disease	2(5.71%)	0(0%)	
Dyslipidemia	5(14.28%)	5(14.28%)	

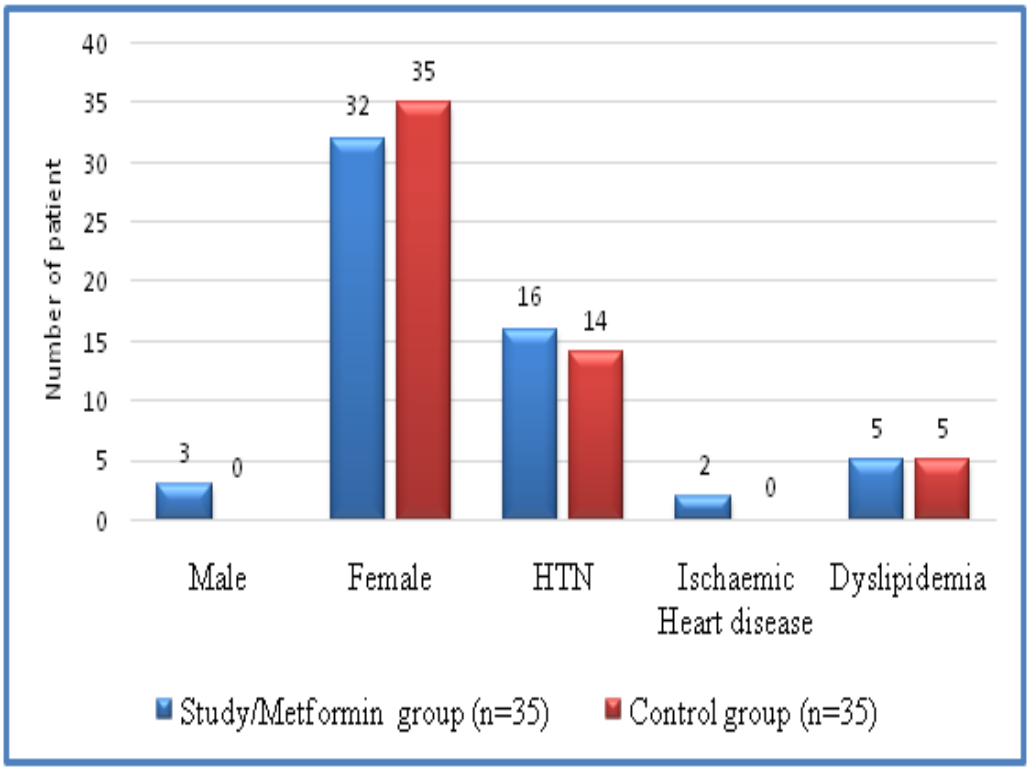

Figure 1: Comparison of baseline characteristics between study and control groups

Table 2: Effect of Metformin on CRP Level

Parameters	Metformin Group (n=35)	Control group (n=35)	P value	Remarks
	CRP Level in Mg/L (Mean±SD)			
Baseline(At the start)	15.37±4.62	11.43±1.91	0.381	Non-Significant
After one month	13.69±2.85	12.97±2.31	0.231	Non-Significant
After three months	11.50±1.98	13.75±2.89	0.267	Non-Significant
After six months	7.89±0.61	14.68±3.65	0.001	Significant

There was no significant difference between the two groups regarding serum CRP levels at baseline or after 3 months. However, after 6 months, the metformin group showed significantly lower serum levels of CRP compared to the control group. These data are summarised in Table 2 and Figure 2.

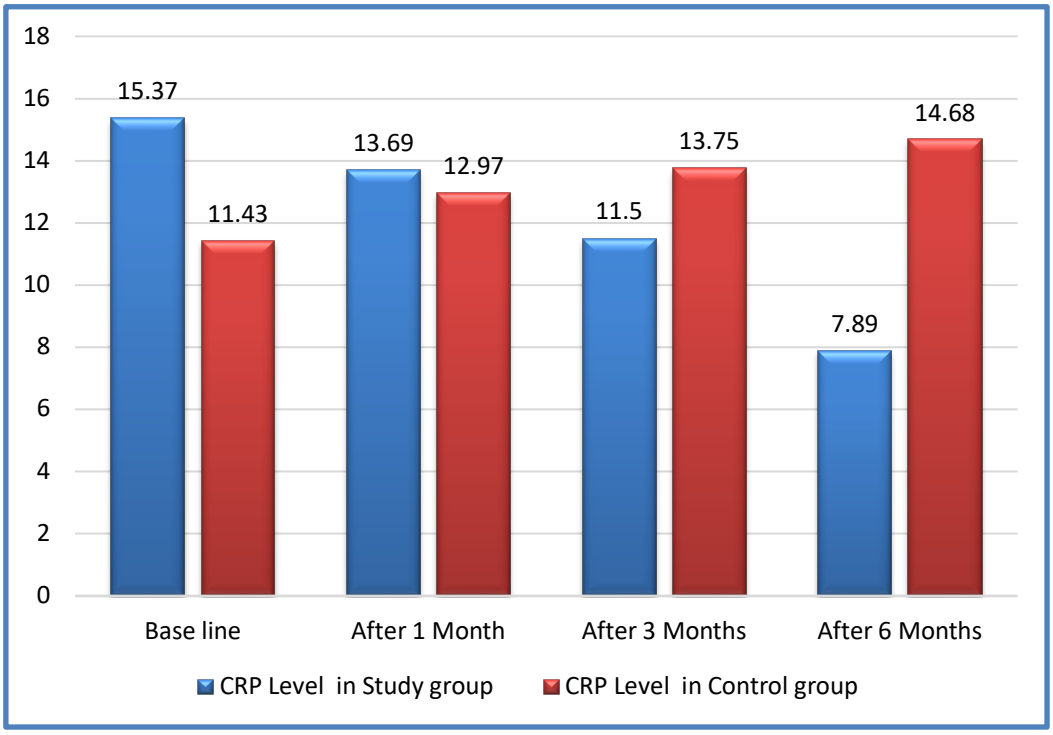

Figure 2: Effect of Metformin on CRP Level (in Mg/L)

The quality of life in these patients has drastically improved when compared to the initial quality of life after 6 Months. The pain and restriction in the joints also markedly decreased.

Evaluation of the Tolerability of Metformin in RA Patients

Three patients in the metformin group withdrew from the study because of intolerance to metformin GIT side effects: three patients reported abdominal pain and severe diarrhoea; two patients reported nausea, abdominal pain, and severe diarrhoea; and another patient reported nausea and abdominal pain with severe flatulence. Other GIT side effects reported by the patients in both groups were mild to moderate and tolerable, requiring no specific intervention and dissipating with time. Routine CBC analysis and kidney, liver, and other function testing in both groups did not show any negative effects associated with the administration of either metformin or csDMARD.

Discussion

Despite the availability of updated therapies for RA, many patients are poorly controlled and need intervention (Smolenet et al., in 2018) [13]. Exploring the efficacy of already existing drugs in new indications is a very promising approach, offering the opportunity to benefit from already established drugs with known pharmacokinetic characteristics and safety profiles, as well as reduce costs and save time (Pushpakom et al., 2019) [15].

This is the first randomized controlled clinical study to evaluate the effect of metformin as an adjunctive therapy to csDMARDs on the disease activity of RA patients. This study used CRP levels as the primary outcome to evaluate the efficacy of metformin. C-reactive protein is a nonspecific inflammatory marker that has been used as a tool to evaluate RA progression and treatment response and can be correlated with disease severity (Wells et al., 2009) [16].

The dosage of metformin was chosen based on its recommended range for treating diabetes, which ranges from 500 to 2,500 mg/day (Nathan et al., 2009) [17], to ensure safety as this was the first study to look into its usage in RA patients. Based on the results of the Diabetes Prevention Programme study, a dose of 850 mg of metformin twice daily was used in this trial. This dose was found to significantly lower CRP levels in people with impaired glucose tolerance, with median percent reductions of 7 and 14% in males and females, respectively (Haffner et al., 2005) [18].

In accordance with the previously mentioned results, the current study has shown that metformin significantly decreased serum CRP levels in RA patients compared to controls, indicating that metformin has a potential anti-inflammatory effect. Metformin not only reduced inflammation in RA patients, but it also lessened the severity of the disease and enhanced the clinical symptoms of RA as measured by DAS-28-CRP scores. The DAS-28 is one of the recommended assessment tools by ACR and EULAR guidelines to follow up on RA patients'

responses to offered treatments (Singh et al., 2016; Smolen et al., 2016) [11,12].

In the current study, CRP was used in the calculation of DAS-28 because CRP has many advantages over ESR, as it is a direct indicator of inflammation and its levels change rapidly according to the changes in patients' inflammatory status. Additionally, abnormalities in erythrocytes have no effect on CRP levels, and it's possible that age and gender have less of an effect on CRP levels than they do on ESR (Siemons et al., 2014) [19].

Health Assessment Questionnaire The disability index is commonly used for assessment of functional status and QOL in RA patients, having the advantages of being reliable, validated, strongly correlated with clinical and laboratory markers of inflammation, and a good predictor of long-term outcomes and mortality in RA patients (Maska et al., 2011), [20], as well as being available in a validated Arabic form. As compared to the control group, the metformin group's HAQ-DI scores considerably increased in the current study, showing better quality of life and disease control in RA patients.

Assuming that no changes in dietary habits were reported in the current study, changes in serum adiponectin levels after metformin administration could reflect the change in inflammatory state in these patients. According to this study, serum adiponectin levels significantly increased in the control group, while they significantly decreased in the metformin group. Adiponectin has pro-inflammatory roles in RA, and there is evidence that metformin has a potential anti-inflammatory effect. The decrease in blood adiponectin levels in the metformin group was in line with the improvement in CRP levels. Evaluation of the safety of metformin in RA patients revealed no major safety concerns in the two groups during the entire study duration. However, GIT disturbances were the most commonly reported side effects by the patients in both groups, including nausea, abdominal pain, flatulence, and diarrhoea. These side effects were severe in three patients who withdrew from the study because of intolerance to metformin use.

It has been reported that GIT effects associated with metformin use affect up to 25% of the users, and only 5% can tolerate these side effects at all (Mc Creight et al., 2016) [21], It is worthy to mention that metformin might have additional benefits in RA patients due to its positive effects on cardiac outcomes, including reduced cardiac ischemia, myocardial infarction, cardiovascular death, and all-cause mortality in patients with type II diabetes (Griffin et al., 2017) [22]. As a consequence, it might reduce cardiovascular problems in RA patients, which could be examined in future studies as an additional outcome in RA patients.

Limitation of Study

This study was limited by its small sample size, being a single-centre study, and its short duration. In addition, a low male-to-female ratio was observed in the current study.

Conclusion

In this study, metformin was shown to improve quality of life after one year of treatment. The use of metformin in Rheumatoid Arthritis as an adjuvant is highly advisable. The action is not immediately visible, but the effect was very clear after six months of continuous treatment. The addition of metformin to csDMARDs in RA patients significantly decreased serum CRP levels, reflecting its potential anti-inflammatory effects. Moreover, metformin decreased disease activity and improved patients' QOL. Metformin has many benefits, including low cost and high tolerability in most patients. As a result, people with RA may benefit from metformin as a potential csDMARD add-on therapy. Even though it was used only as an adjuvant in this study, the potential of this drug seems massive. The drug is easily available, is very cheap compared to other drugs used in the treatment, and thus opens the door for a low-cost, effective treatment of this dreaded condition.

Author Contributions

Mrityunjay Kumar gave concept and idea, study design, and manuscript drafting data collection and analysis; Asha Singh, Navin Kumar, and S.M. Inamul Haque gave data collection and analysis, manuscript revision, and data interpretation.

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