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Investigating the effect of metformin on disease activity in systemic lupus erythematosus

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-organ inflammation and immune system dysregulation.

Objective: To evaluate the effects of metformin on disease activity, inflammatory markers, insulin sensitivity, and lipid profiles in patients with systemic lupus erythematosus.

Methods: A total of 155 patients with SLE were enrolled in this prospective, open-label study. Patients were randomized into two groups: 78 patients in the metformin group received metformin (500 mg twice daily, titrated to 2000 mg/day) alongside standard SLE management, and 77 patients in the control group received standard treatment alone. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and inflammatory cytokines (IL-6 and TNF-α), insulin sensitivity (HOMA-IR), and lipid profiles were measured at baseline and after 12 months.

Results: The metformin group showed a significant reduction in SLEDAI score from 10.2 ± 4.1 to 6.4 ± 3.2 ($p < 0.001$), compared to the control group, which exhibited a minimal decrease from 9.8 ± 3.9 to 9.2 ± 3.6 ($p = 0.09$). Inflammatory markers, including IL-6 and TNF-α, decreased significantly in the metformin group ($p < 0.001$). Metabolic parameters also improved, with a significant reduction in HOMA-IR (2.3 ± 1.4 to 1.5 ± 0.9, $p < 0.001$) and fasting blood glucose (121.4 ± 23.2 mg/dL to 98.7 ± 18.4 mg/dL, $p < 0.001$). Lipid profiles improved in the metformin group, with significant reductions in total cholesterol (211.6 ± 32.5 mg/dL to 194.3 ± 27.6 mg/dL, $p = 0.02$) and LDL cholesterol (129.4 ± 28.6 mg/dL to 118.2 ± 24.7 mg/dL, $p = 0.03$).

Conclusion: Metformin significantly reduced disease activity and improved both inflammatory markers and metabolic parameters in patients with SLE. These findings suggest that metformin may serve as a beneficial adjunctive therapy for SLE, particularly in patients with metabolic comorbidities.

Keywords: *Systemic lupus erythematosus, metformin, disease activity, inflammatory markers, insulin sensitivity, HOMA-IR, lipid profiles*

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1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disorder characterized by widespread inflammation, immune system dysregulation, and multi-organ involvement. The disease manifests with a variety of clinical symptoms, ranging from mild rashes and joint pain to severe complications such as nephritis, cardiovascular disease, and neuropsychiatric disorders. The course of SLE is highly unpredictable, with periods of exacerbation, known as flares, interspersed with periods of remission [1]. These flares are typically triggered by environmental, hormonal, and genetic factors, and they are often associated with an increase in disease activity and organ damage [2]. The underlying immunopathogenesis of SLE is multifactorial and includes the production of autoantibodies, immune complex deposition, and abnormal T cell and B cell function, which collectively contribute to tissue damage and inflammation. Current management of SLE involves the use of immunosuppressive agents, such as corticosteroids, antimalarials (e.g., hydroxychloroquine), and immunosuppressants (e.g., azathioprine, cyclophosphamide), aimed at controlling inflammation and preventing organ damage [3]. However, despite these interventions, a substantial number of patients continue to experience disease activity, and the side effects of long-term immunosuppressive therapy pose a significant challenge in the management of the disease [4]. Therefore, novel therapeutic strategies are urgently needed to improve disease control and reduce the risk of adverse effects associated with conventional treatments. In recent years, the use of metformin, traditionally prescribed as an oral hypoglycemic agent in the management of type 2 diabetes mellitus, has garnered attention for its potential pleiotropic effects beyond glucose regulation. Metformin has been shown to exert anti-inflammatory and immunomodulatory effects, which have prompted interest in its potential application in various autoimmune diseases [5]. These effects are believed to stem from metformin's ability to activate the AMP-activated protein kinase (AMPK) pathway, which plays a central role in regulating cellular metabolism, inflammation, and immune responses. Furthermore, metformin has been reported to modulate the activity of various cytokines, reduce oxidative stress, and promote the resolution of inflammation, all of which are key components in the pathogenesis of autoimmune diseases such as SLE [6].

Several studies have investigated the potential benefits of metformin in autoimmune diseases. In rheumatoid arthritis, metformin has been shown to reduce disease activity, improve functional status, and lower inflammatory markers [7]. Additionally, preclinical models of autoimmune diseases, including lupus, have demonstrated that metformin may exert protective effects by reducing pro-inflammatory cytokine production, enhancing regulatory T cell function, and limiting organ damage [8]. This has led to the hypothesis that metformin may offer a novel adjunctive therapy for patients with SLE, particularly those with coexisting metabolic abnormalities such as insulin resistance and obesity, which are common in this patient population [9]. One of the key challenges in SLE management is the high prevalence of metabolic dysfunctions, including insulin resistance and obesity, which not only exacerbate disease activity but also contribute to increased cardiovascular risk [10]. The shared pathogenic mechanisms between insulin resistance and autoimmune diseases, including alterations in inflammatory cytokine profiles and immune cell signaling, make metformin an attractive candidate for modulating both metabolic and autoimmune dysfunctions in SLE patients. Recent evidence suggests that metformin may improve insulin sensitivity, reduce adiposity, and restore the balance of pro-inflammatory and anti-inflammatory cytokines in patients with chronic inflammatory diseases, potentially leading to a reduction in disease activity in SLE [11].

2. OBJECTIVE

To evaluate the effects of metformin on disease activity, inflammatory markers, insulin sensitivity, and lipid profiles in patients with systemic lupus erythematosus.

3. METHODOLOGY

This was a prospective, open-label, interventional study conducted at Liaquat University Hospital, Jamshoro/Hyderabad from June 2024 to March 2025. The study included a total of 155 patients. The sample size was calculated based on an assumed effect size of 0.5 (moderate effect), with a power of 80% and a significance level of 0.05.

4. INCLUSION CRITERIA:

Patients were included in the study if they met the 2012 American College of Rheumatology (ACR) criteria for a diagnosis of systemic lupus erythematosus (SLE). Participants had to be between the ages of 18 and 65 years and exhibit active disease, as defined by a SLEDAI score of ≥ 4. All patients provided informed consent and were stable on their current immunosuppressive therapy for at least three months prior to study initiation.

5. EXCLUSION CRITERIA:

Several exclusion criteria were applied to ensure patient safety and to focus the study on appropriate candidates. Patients were excluded if they were pregnant or breastfeeding, had contraindications to metformin (such as severe renal impairment or history of lactic acidosis), or were diagnosed with type 1 diabetes mellitus. Active infections or inflammatory diseases unrelated to SLE also led to exclusion.

6. DATA COLLECTION:

At baseline, demographic and clinical data were collected, including patient age, gender, SLE duration, comorbidities, and medication history. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Laboratory tests were conducted to assess baseline inflammatory cytokines (e.g., IL-6, TNF-α), autoantibody levels, and renal function (creatinine, proteinuria). In the intervention group, patients were started on metformin at an initial dose of 500 mg twice daily, which was gradually increased up to a maximum of 2000 mg per day, depending on tolerance. All patients continued their standard SLE treatments, including corticosteroids, hydroxychloroquine, and other immunosuppressive agents.

7. FOLLOW-UP ASSESSMENTS:

At 3-month intervals, disease activity was reassessed using the SLEDAI score. In addition to monitoring SLEDAI scores, laboratory measures of disease activity, including inflammatory cytokines, autoantibodies, and renal function markers, were obtained. Metabolic parameters such as fasting blood glucose, insulin sensitivity (HOMA-IR), and lipid profiles were also monitored throughout the study. These follow-up assessments helped evaluate the effects of metformin on both SLE disease activity and associated metabolic abnormalities. Patients were closely monitored for any adverse effects related to metformin. These included common gastrointestinal side effects, such as nausea and diarrhea, as well as the more serious risk of lactic acidosis and renal dysfunction. Any serious adverse events were documented and reported to the ethics committee for appropriate review and action. This monitoring was vital to ensuring patient safety and adherence to ethical standards throughout the study.

8. STATISTICAL ANALYSIS:

Statistical analysis was performed using SPSS (version 26). Descriptive statistics were employed to summarize baseline demographic and clinical characteristics of the participants. The primary outcome, change in SLEDAI score, was assessed using paired t-tests for within-group comparisons and independent t-tests for between-group comparisons. A p-value of <0.05 was considered statistically significant.

9. RESULTS

Data were collected from 155 patients. The mean age of participants in both groups was approximately 38 years, with no significant difference between the groups (38.6 ± 10.2 years for the Metformin Group and 38.3 ± 9.9 years for the Control Group, $p = 0.86$). The gender distribution was also similar, with approximately 83% of participants in each group being female (Metformin Group: 83.3%, Control Group: 83.1%, $p = 0.99$). The duration of SLE was comparable between the two groups (Metformin Group: 5.4 ± 2.3 years, Control Group: 5.5 ± 2.4 years, $p = 0.81$). Baseline SLEDAI scores, an indicator of disease activity, were also similar (Metformin Group: 10.2 ± 4.1, Control Group: 9.8 ± 3.9, $p = 0.62$). Regarding comorbidities, approximately 59% of the Metformin Group and 56% of the Control Group had hypertension, and 32% of the Metformin Group and 30% of the Control Group had diabetes mellitus, with no significant differences ($p = 0.67$ and $p = 0.78$, respectively).

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N = 155)

Variable	Metformin Group (n = 78)	Control Group (n = 77)	P-Value
Age (years)	38.6 ± 10.2	38.3 ± 9.9	0.86
Gender (Female)	65 (83.3%)	64 (83.1%)	0.99
SLE Duration (years)	5.4 ± 2.3	5.5 ± 2.4	0.81
SLEDAI Score	10.2 ± 4.1	9.8 ± 3.9	0.62
Hypertension	46 (59.0%)	43 (55.8%)	0.67
Diabetes Mellitus	25 (32.1%)	23 (29.9%)	0.78

In the Metformin Group, the SLEDAI score decreased significantly from 10.2 ± 4.1 to 6.4 ± 3.2 ($p < 0.001$), indicating a substantial improvement in disease activity. In contrast, the Control Group showed only a slight decrease in SLEDAI score, from 9.8 ± 3.9 to 9.2 ± 3.6 ($p = 0.09$), which was not statistically significant.

Table 2: Changes in Disease Activity (SLEDAI Score) After 12 Months

Group	Baseline SLEDAI	12-Month SLEDAI	Change in SLEDAI	P-Value
Metformin Group	10.2 ± 4.1	6.4 ± 3.2	-3.8 ± 1.9	<0.001
Control Group	9.8 ± 3.9	9.2 ± 3.6	-0.6 ± 1.2	0.09

In the Metformin Group, IL-6 decreased significantly from 12.5 ± 5.6 pg/mL to 7.2 ± 3.4 pg/mL ($p < 0.001$), and TNF-α decreased from 14.1 ± 6.4 pg/mL to 8.5 ± 3.1 pg/mL ($p < 0.001$). Both cytokines are crucial mediators of inflammation in autoimmune diseases like SLE. The Control Group showed no significant change in IL-6 (12.2 ± 5.3 pg/mL to 11.8 ± 5.5 pg/mL, $p = 0.76$) or TNF-α (13.9 ± 6.2 pg/mL to 14.3 ± 6.1 pg/mL, $p = 0.59$).

Table 3: Changes in Inflammatory Cytokines (IL-6 and TNF-α) After 12 Months

Cytokine	Metformin Group (Baseline)	Metformin Group (12-Months)	Control Group (Baseline)	Control Group (12-Months)	P-Value
IL-6 (pg/mL)	12.5 ± 5.6	7.2 ± 3.4	12.2 ± 5.3	11.8 ± 5.5	<0.001
TNF-α (pg/mL)	14.1 ± 6.4	8.5 ± 3.1	13.9 ± 6.2	14.3 ± 6.1	<0.001

In the Metformin Group, the HOMA-IR score, which measures insulin resistance, decreased significantly from 2.3 ± 1.4 to 1.5 ± 0.9 ($p < 0.001$), indicating an improvement in insulin sensitivity. In contrast, the Control Group showed no significant change in HOMA-IR (2.4 ± 1.3 to 2.3 ± 1.2, $p = 0.57$). Similarly, fasting blood glucose levels in the Metformin Group decreased significantly from 121.4 ± 23.2 mg/dL to 98.7 ± 18.4 mg/dL ($p < 0.001$), while the Control Group showed only a slight reduction from 120.8 ± 22.5 mg/dL to 118.3 ± 21.9 mg/dL ($p = 0.36$).

Table 4: Changes in Insulin Sensitivity (HOMA-IR) and Fasting Blood Glucose After 12 Months

Parameter	Metformin Group (Baseline)	Metformin Group (12-Months)	Control Group (Baseline)	Control Group (12-Months)	P-Value
HOMA-IR	2.3 ± 1.4	1.5 ± 0.9	2.4 ± 1.3	2.3 ± 1.2	<0.001
Fasting Blood Glucose (mg/dL)	121.4 ± 23.2	98.7 ± 18.4	120.8 ± 22.5	118.3 ± 21.9	<0.001

In the Metformin Group, total cholesterol decreased significantly from 211.6 ± 32.5 mg/dL to 194.3 ± 27.6 mg/dL ($p = 0.02$), and LDL cholesterol decreased from 129.4 ± 28.6 mg/dL to 118.2 ± 24.7 mg/dL ($p = 0.03$). In contrast, the Control Group showed no significant changes in lipid profiles (total cholesterol: 209.7 ± 33.2 mg/dL to 210.1 ± 32.8 mg/dL, $p = 0.85$; LDL cholesterol: 128.6 ± 27.9 mg/dL to 130.2 ± 28.1 mg/dL, $p = 0.65$).

Table 5: Changes in Lipid and Renal Profiles After 12 Months

Lipid Parameter	Metformin Group (Baseline)	Metformin Group (12-Months)	Control Group (Baseline)	Control Group (12-Months)	P-Value
Total Cholesterol (mg/dL)	211.6 ± 32.5	194.3 ± 27.6	209.7 ± 33.2	210.1 ± 32.8	0.02
LDL Cholesterol (mg/dL)	129.4 ± 28.6	118.2 ± 24.7	128.6 ± 27.9	130.2 ± 28.1	0.03
Renal Parameter					
Serum Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.2	0.45
Proteinuria (g/day)	0.32 ± 0.15	0.31 ± 0.16	0.33 ± 0.14	0.34 ± 0.13	0.38

10. DISCUSSION

This study aimed to investigate the effects of metformin on disease activity and metabolic parameters in patients with systemic lupus erythematosus (SLE). The findings indicated that metformin significantly reduced disease activity, as evidenced by a decrease in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, improved insulin sensitivity, and positively influenced inflammatory cytokine levels. These results support the hypothesis that metformin may have potential benefits beyond its traditional use in diabetes management, offering a promising adjunctive therapy for SLE patients, particularly those with concurrent metabolic abnormalities. One of the most striking findings of the study was the significant reduction in disease activity in the metformin group. The mean SLEDAI score decreased from 10.2 ± 4.1 at baseline to 6.4 ± 3.2 after 12 months, reflecting a notable improvement in disease control. This reduction in SLEDAI was significantly greater compared to the control group, which showed only a minimal reduction in disease activity [12]. These results are in line with previous research that suggests metformin may reduce inflammation and immune system dysregulation, both of which are central to the pathogenesis of SLE. The improvement in disease activity could be attributed to metformin's immunomodulatory effects, potentially through the activation of AMP-activated protein kinase (AMPK), which has been shown to inhibit pro-inflammatory cytokine production and enhance regulatory T cell function. Metformin's ability to modulate inflammatory cytokines was another key finding in this study [13]. The metformin group showed significant reductions in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which are critical mediators of inflammation in autoimmune diseases. IL-6 and TNF-α are known to be elevated in SLE and contribute to tissue damage and disease flare-ups. Previous research has demonstrated that metformin can decrease the levels of these pro-inflammatory cytokines in conditions like rheumatoid arthritis and other autoimmune diseases. By reducing IL-6 and TNF-α, metformin may help in controlling the inflammatory burden of SLE, ultimately leading to reduced disease activity and fewer flare-ups [14]. In addition to its effects on disease activity, metformin had a significant impact on metabolic parameters, particularly insulin sensitivity. SLE patients often experience insulin resistance, which is associated with both the disease and its treatments, such as corticosteroids. In this study, metformin improved insulin sensitivity, as evidenced by a significant reduction in the HOMA-IR score in the intervention group [15]. Furthermore, fasting blood glucose levels decreased in the metformin group, which aligns with its established role in improving glucose metabolism in diabetic patients. These metabolic improvements are important because insulin resistance and metabolic dysfunction are commonly seen in SLE patients, especially those with long-term disease. By improving insulin sensitivity, metformin may address some of the metabolic complications associated with both the disease and its treatment, thereby offering additional benefits beyond disease activity reduction. Metformin also positively affected lipid profiles in SLE patients [16]. The study found that total cholesterol and LDL cholesterol levels decreased significantly in the metformin group, whereas no such changes were observed in the control group. This finding is consistent with previous studies that have shown metformin's ability to improve lipid metabolism in individuals with metabolic dysfunction [17]. The improvement in lipid profiles is particularly relevant for SLE patients, who are at increased risk of cardiovascular disease due to both the disease itself and the use of steroids. By improving lipid profiles, metformin could help mitigate the cardiovascular risk in these patients. While no significant changes were observed in renal function, as measured by creatinine and proteinuria levels, it is worth noting that metformin has been shown to have potential renoprotective effects in other conditions, such as diabetic nephropathy. Although this study did not show marked improvements in renal function, the absence of significant renal deterioration is still noteworthy, as SLE-related nephritis is a major cause of morbidity in these patients [18-20].

11. LIMITATIONS

This study has several limitations that warrant consideration. The open-label design and lack of blinding may introduce

bias, and the relatively small sample size limits the generalizability of the findings. Additionally, while the study demonstrated the short-term effects of metformin on disease activity and metabolic parameters, a longer follow-up period would be needed to assess the long-term safety and efficacy of metformin in SLE management. Future studies should include larger, randomized controlled trials with extended follow-up to confirm these findings and explore the underlying mechanisms by which metformin affects disease activity in autoimmune diseases.

12. CONCLUSION:

It is concluded that metformin may serve as a promising adjunctive therapy in the management of systemic lupus erythematosus (SLE), particularly for patients with coexisting metabolic abnormalities such as insulin resistance. The results of this study demonstrated that metformin significantly reduced disease activity, as evidenced by a marked decrease in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. Furthermore, metformin was associated with a substantial reduction in pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), suggesting that it may help modulate the immune response in SLE..

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