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Original Research Article

A Comparative Study to Evaluate the Efficacy of Combined use of Metformin and Methotrexate in Psoriasis Patients with Metabolic Syndrome

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease often linked to metabolic syndrome. This study evaluates the efficacy of combining metformin and methotrexate for treating psoriasis in these patients.

Methods: The present single-blind clinical study was carried out for the duration of 1 year. This involved 50 patients with plaque psoriasis. Participants were assigned to a study group (metformin plus methotrexate) and a control group (methotrexate alone). Treatment outcomes were measured using the Psoriasis Area and Severity Index (PASI) at baseline, 1 month, 2 months, and 3 months.

Results: The study group showed significant PASI score reductions from 21.6 ± 9.2 to 8.8 ± 8.0 at 3 months ($p < 0.001$), while the control group had a higher percentage of moderate responses (56%) compared to the study group (32%, $p < 0.05$).

Conclusion: The combination of metformin and methotrexate is more effective in reducing psoriasis severity in patients with metabolic syndrome, suggesting that targeting metabolic dysfunction may improve treatment outcomes. Further research is warranted to confirm these findings.

Keywords: Metformin, Methotrexate, Metabolic Dysfunction, Psoriasis.

1. Introduction

Psoriasis is a chronic inflammatory disorder characterized by genetic, immunological, and metabolic factors, affecting more than 8 million individuals in the United States [1, 2]. This serious, non-communicable skin disease is marked by epidermal proliferation, abnormal differentiation of the stratum corneum, and increased capillary growth. The clinical presentation includes a variety of forms such as plaques, guttate lesions, widespread erythema, pustules, and nail involvement [3].

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The development of metabolic syndrome in psoriasis patients is thought to be linked to elevated levels of adipocytokines, including tumor necrosis factor-alpha (TNF-α) and adiponectin [4–6]. Recent research indicates that metformin, a well-established medication for managing blood glucose levels in diabetes, may be effective when used in conjunction with methotrexate (MTX) for treating psoriasis [5]. Biochemical analyses suggest that both metformin and methotrexate target the same pathway: AMP-activated protein kinase (AMPK) [7].

Topical treatments are typically the first line of therapy and may be used alone or in combination based on the severity of the disease. Common topical options include corticosteroids, tar derivatives, calcineurin inhibitors, and vitamin D analogues [8, 9]. Another treatment modality is phototherapy, utilizing either PUVA (psoralen and ultraviolet A) or UVB, which can be applied alone or in conjunction with other therapies. Systemic treatments include methotrexate, acitretin, and cyclosporine, as well as various biological agents. Despite the availability of these diverse therapeutic options, psoriasis is not always adequately managed [10, 11].

This study was conducted to evaluate the effectiveness and safety of combination therapy using metformin and MTX in the treatment of psoriasis patients with metabolic syndrome.

2. Methodology

This prospective, randomized placebo-controlled study was conducted from January 2021 to July 2024, involving 50 patients diagnosed with plaque psoriasis receiving treatment. All participants met the full criteria for inclusion in the study. The research received approval from the Ethics Research Committee of the institute. Informed consent was obtained from all participants. The procedures adhered to the ethical standards set by the responsible institutional committee for human experimentation.

Psoriasis patients with metabolic syndrome were divided into two groups:

(i) Treatment group: 35 psoriasis vulgaris patients with metabolic syndrome were treated using metformin + MTX. MTX: started with 7.5 mg/week, divided into 3 doses q12 hr, and sustained for three months (12 weeks). Metformin: 500 mg/day after one meal.

(ii) Control group: 31 psoriasis vulgaris patients with metabolic syndrome were treated using MTX only with the same dosage and usage.

Inclusion Criteria

1. Patients aged 18 to 70 years with both psoriasis vulgaris and metabolic syndrome.
2. Patients must be nonalcoholic, with normal liver and kidney function test results.
3. Patients must provide informed consent to participate in the study.

Exclusion Criteria

1. Patients who are pregnant or breastfeeding.
2. Patients who have used systemic medications for psoriasis—such as cyclosporine, retinoids, or immunomodulatory therapies—for one month or longer.
3. Patients with acute or chronic infections.
4. Patients with contraindications to the use of metformin and methotrexate.

Methodology

Psoriasis diagnosis was based on clinical features: erythematous plaques lesions with scales on the surface, and suggestive characteristics were a circumscribed border, non-infiltration, sites of predilection, mild or severe pruritus, and silvery scales. According to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) and the

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South Asian Modi6ed (SAM)-NCEP, the diagnosis of metabolic syndrome was established when 3 of 5 factors were present [12]

Both groups were assessed using several parameters:

1. **Treatment Outcomes**: The Psoriasis Area and Severity Index (PASI) was used to evaluate treatment results before the intervention and at 1 month, 2 months, and 3 months post-treatment.
2. **Laboratory Tests**: Blood samples were collected prior to treatment and 3 months afterward to analyze a complete blood count, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), cholesterol, triglycerides, and fasting glucose levels. The measurements for AST, ALT, GGT, triglycerides, total cholesterol, and HDL-C were conducted using a HumaStar 600 machine. All tests were performed in the laboratory of the HCMC Hospital of Dermato-Venereology.
3. **Clinical Effects**: The clinical impact was quantified by calculating the percentage reduction in PASI, according to the established formula.

Based on PASI reduction, there are 5 levels:

1. Very good: PASI reduction 90–100%
2. Good: PASI reduction 75%– < 90%
3. Moderate: PASI reduction 50– < 75%
4. Medium: PASI reduction 25– < 50%
5. Bad or no e7ectiveness: PASI reduction <25%.

Data were analyzed using SPSS version 22. The data were analyzed using frequency, percentage, mean, standard deviation, and median.

3. Results

The average age of participants in the study group was 52.3 ± 14.7 years, while the control group had an average age of 53.4 ± 14.4 years, with a p-value of 0.78, suggesting no significant difference.

Variables	Study group	Control Group	p-value
Age	52.3±14.7	53.4±14.4	0.78
Disease duration	37.8±12.4	38.6±13.6	0.80
PASI	22.2±9.4	23.0±10.2	0.81

Table 2: Research group characteristics.

Similarly, the duration of the disease was nearly identical between the groups, with the study group having a duration of 37.8 ± 12.4 months compared to 38.6 ± 13.6 months in the control group, resulting in a p-value of 0.80. Finally, the Psoriasis Area and Severity Index (PASI) scores were also comparable, with the study group averaging 22.2 ± 9.4 and the control group averaging 23.0 ± 10.2, yielding a p-value of 0.81. Overall, these findings indicate that the groups were well-matched at baseline, minimizing potential confounding factors in the study's outcomes.

Group	After (month)	PASI (before treatment) ($X \pm SD$)	PASI (after treatment) ($X \pm SD$)	P-value
Study	1	21.6± 9.2	17.1 ± 8.2	0.01

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Group	2		14.1 ± 7.8	0.0002
	3		8.8 ± 8.0	<0.001
Control Group	1	22.0 ± 8.8	18.8 ± 8.2	0.01
	2		16.4 ± 7.5	0.0002
	3		12.1 ± 9.6	<0.001

Table 3: Treatment results of the study group (*n* =25).

In the study group, the initial PASI score was 21.6 ± 9.2 at one month, decreasing to 17.1 ± 8.2, with a p-value of 0.01, indicating a statistically significant improvement. By the second month, the score further declined to 14.1 ± 7.8 (p-value 0.0002), and by the third month, it dropped to 8.8 ± 8.0, achieving a p-value of <0.001, highlighting a sustained and significant therapeutic effect. Similarly, the control group exhibited improvements in PASI scores, starting from 22.0 ± 8.8 at one month and decreasing to 18.8 ± 8.2 (p-value 0.01), 16.4 ± 7.5 (p-value 0.0002) at two months, and reaching 12.1 ± 9.6 (p-value <0.001) by the third month. Although both groups showed significant PASI reductions, the data suggest that the treatment was effective for both, with the study group's improvements indicating a potentially greater benefit.

	Result				
	Very Good	Good	Moderate	Medium	Bad/ No effect
Study	7 (28%)	1 (4%)	6 (24%)	9 (36%)	2 (8%)
Control	0 (0%)	0 (0%)	14 (56%)	8 (32%)	3 (12%)
p-value	<0.05				

Table 4: Results of treatment in two groups according to the rate of PASI reduction after 3 months (*n* =50).

The results table illustrates a notable difference in treatment outcomes between the study and control groups. In the study group, 28% of participants reported a "very good" response, while 4% had a "good" outcome. Additionally, 24% experienced a "moderate" effect, and 36% reported a "medium" response, with 8% experiencing "bad" or no effect. In contrast, the control group showed no participants achieving a "very good" or "good" response; instead, 56% reported a "moderate" outcome, 32% indicated a "medium" response, and 12% experienced "bad" or no effect. The p-value of <0.05 suggests that these differences in outcomes are statistically significant, indicating that the treatment was more effective in the study group compared to the control group. This finding underscores the potential benefits of the intervention being tested.

4. Discussion

The present study aimed to evaluate the efficacy of combining metformin and methotrexate in treating psoriasis patients with metabolic syndrome. The findings from the trial demonstrate significant improvements in psoriasis severity as measured by the Psoriasis Area and Severity Index (PASI), as well as a favorable treatment response compared to the control group. The baseline characteristics of both groups revealed no significant differences in age, disease duration, or initial PASI scores, indicating that the groups were well-matched at the outset. This is crucial as it minimizes potential confounding variables that could affect treatment outcomes. In terms of PASI scores, both the study and control groups showed significant reductions over the treatment period, with the study group achieving a substantial decrease from 21.6 ± 9.2 at one month to 8.8 ± 8.0 by the third month. This represents a clinically meaningful

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improvement, supported by p-values indicating strong statistical significance (<0.001). The control group also experienced reductions in PASI scores, but the lack of a "very good" or "good" response highlights the relative effectiveness of the combination therapy in the study group.

The categorical treatment outcomes further underscore the advantages of the metformin and methotrexate combination. The study group had a higher percentage of patients reporting "very good" and "good" responses (32%) compared to the control group, which reported no such outcomes. Conversely, a majority in the control group (56%) had "moderate" responses, with a notable percentage also experiencing "bad" or no effect (12%). These results suggest that the combination therapy not only enhances efficacy but also improves overall patient satisfaction with treatment outcomes.

The observed benefits can be attributed to the synergistic effects of metformin and methotrexate. Metformin is known for its ability to improve insulin sensitivity and potentially modulate inflammatory pathways, which may complement methotrexate's established role as an anti-inflammatory agent [12, 13]. This dual action could be particularly beneficial in psoriasis patients who often exhibit metabolic syndrome, thereby addressing both dermatological and metabolic components of their condition.

Moreover, the findings align with existing literature that suggests a link between metabolic syndrome and psoriasis, particularly the role of adipocytokines in exacerbating inflammation [14, 15]. By incorporating metformin, this study not only targets the skin manifestations of psoriasis but also addresses underlying metabolic dysfunction, potentially leading to a more holistic approach to treatment.

Despite these promising results, the study has limitations, including its single-center design and relatively small sample size. Future research with larger, multicenter trials will be essential to validate these findings and explore the long-term safety and efficacy of this combination therapy.

5. Conclusion

The combination of metformin and methotrexate appears to be a promising therapeutic strategy for treating psoriasis patients with metabolic syndrome, offering significant improvements in psoriasis severity and overall treatment response. This approach may pave the way for more effective management of psoriasis, particularly in patients facing comorbid metabolic challenges.

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