Randomized Placebo Control Study of Metformin in Psoriasis Patients with Metabolic Syndrome (Systemic Treatment Cohort)

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Abstract

Background: Psoriasis has been found to be associated with obesity, metabolic syndrome (MS), diabetes, and cardiovascular risk factors. Metformin treatment showed improvement in cardiovascular risk factors and hyperinsulinemia. Objective: To evaluate the efficacy and safety of metformin in psoriasis patients with MS. Materials and Methods: This was a single-center, parallel-group, randomized, open-label study with blinded end point assessment of metformin (1000 mg once daily for 12 weeks; n = 20) and placebo (n = 18) in psoriasis patients with MS. Total sample size was 38 participants. Results: Statistically significant improvement was observed in mean percentage change in erythema, scaling, and induration (ESI) (P = 0.048) in metformin as compared to placebo while mean percentage change in psoriasis area and severity index (PASI) and physician global assessment (PGA) scores was not significant (PASI - P = 0.215, PGA - P = 0.070). There was a statistically significant difference in percentage of parameters of MS improved following 12 weeks of treatment in metformin (19%) as compared to placebo (8.9%) group (P = 0.046). Statistically significant difference in percentage of patients achieving 75% reduction in ESI scores (P = 0.024). Significant improvement was observed in mean weight, body mass index (BMI), total cholesterol, and low-density lipoprotein (LDL) cholesterol in metformin group as compared to placebo. Improvement in BMI, fasting plasma glucose, serum triglycerides, high-density lipoprotein, LDL, systolic blood pressure, diastolic blood pressure, and total cholesterol was statistically significant in metformin group over the period of 12 weeks. There was no significant difference in adverse events in two groups except weight gain. Conclusion: Metformin has shown improvement in psoriasis and parameters of MS, hence can be used for the benefit of psoriasis patients having MS. Large, controlled studies are needed to confirm.

Keywords: Insulin sensitizers, metabolic syndrome, metformin, psoriasis

Trial registration number: Registered in Clinical Trial Registry of India (CTRI) Registration Number: CTRI/2011/12/002252.

INTRODUCTION

Psoriasis has been found to be associated with systemic disorders namely obesity, metabolic syndrome (MS), diabetes mellitus, and cardiovascular morbidity. MS is a cluster of risk factors including central obesity, high triglyceride level, low high-density lipoprotein cholesterol (HDL-C) level, hypertension, and glucose intolerance and is a strong predictor of coronary heart disease, diabetes, and stroke. The pathophysiological features of psoriasis involve inappropriate production of interferon-γ, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-8, IL-12, IL-17, IL-19, and IL-23, which are the mediators for MS. Metformin has been shown to improve cardiovascular risk factors. Metformin has shown additional beneficial effects in adults with Type 2 diabetes, including weight reduction, decreased hyperinsulinemia, improved lipid profiles, augmented fibrinolysis, and enhanced endothelial function. Metformin acts as an anti-inflammatory agent by activating adenosine monophosphate-activated protein kinase (AMPK). Activated AMPK induces inhibition of dendritic cell and T-cell activation as well as cell proliferation, which is the hallmark of psoriasis. As metformin has shown to prevent the progression of MS into overt diabetes and can induce weight loss, we planned to evaluate the efficacy and

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safety of metformin in psoriasis patients with MS. This study is a part of larger study in which we evaluated the prevalence of MS in psoriasis. Psoriasis patients having MS were divided into systemic (moderate-to-severe psoriasis, randomized into metformin and placebo arms) and topical treatment cohort[13] (mild psoriasis, randomized into metformin, pioglitazone, and placebo arms) and were evaluated for the effect of insulin sensitizers on disease parameters and MS. In this paper, we have discussed the results of systemic cohort.

**MATERIALS AND METHODS**

**Clinical trial design**

This was a single-center, parallel-group, randomized, open-label study with blinded end point assessment of metformin and placebo in psoriasis patients with MS satisfying inclusion and exclusion criteria. Study was approved by the Institute Ethics Committee of Postgraduate Institute of Medical Education and Research, Chandigarh, India (PGIMER letter number - MS/1145/DM/8229, dated April 1, 2010), and this study was registered on the Clinical Trial Registry of India (CTRI) website (the registration number of the trial is CTRI/2011/12/002252).

All patients visiting psoriasis clinic at our institute were screened for MS and other eligibility criteria. Both men and women, >18 years with plaque psoriasis (moderate [3%-10% body surface area] to severe disease [>10% body surface area][19] disease on treatment [had taken even a single dose of systemic therapy in the past] or treatment naïve [no past history of treatment for their disease]) and having MS and willing to provide written informed consent, were included in the study. MS is defined as the presence of three or more criteria of the modified National Cholesterol Education Program’s Adult Treatment Panel III (NCEP ATP III):[20] waist circumference >90 cm in men and >80 cm in women, hypertriglyceridemia ≥150 mg/dl, HDL-C <40 mg/dl in males and <50 mg/dl in females, blood pressure ≥130/85 mmHg, and fasting plasma glucose (FPG) ≥110 mg/dl. Patients with mild disease and systemic therapy other than methotrexate, pregnant or nursing women, significant hepatic impairment (serum bilirubin, aspartate transaminase, alanine transaminase, and alkaline phosphate >1.5 times the upper limit of normal), renal insufficiency-serum creatinine ≥1.5 mg/dl (men) or ≥1.4 mg/dl (women), and contraindication to metformin were excluded from the study.

Clinical examination including the psoriasis area and severity index (PASI) scores and erythema, scaling, and induration (ESI) scores was done. Clinical photographs of patients were taken at baseline and at the end of treatment. Baseline investigations were done and eligible patients were randomized by simple randomization, in an open-label manner to either placebo or metformin 1000 mg once daily, for a period of 12 weeks after taking written informed consent. All patients were given standard systemic methotrexate and folic acid in addition to study drugs. Methotrexate was started at a dose of 10–30 mg once/week, decreased or increased at the rate of 5 mg fortnightly, depending on the decrease or increase in disease severity, respectively. Although most studies have reported starting methotrexate at low dose and then gradually escalating the dose based on response,[21] However, at some centers, it is started at higher dose as mentioned in the US Food and Drug Administration approved label.[22] This regimen has shown excellent clinical efficacy and good safety profile with overall short duration of therapy with low cumulative dose.[23] Folic acid was administered at the dose of 5 mg twice every week. The randomization codes were computer generated. Randomization codes were concealed in an opaque envelope. The drug dispensation was done by a person who was not involved with the assessment of the study end points. Evaluation for efficacy parameters was done at 0 and 12 weeks. Safety evaluation was also done throughout the study. Hemoglobin and blood counts were done every 2 weeks and liver function tests were done every 4 weeks.

**Efficacy evaluation**

Blinded end points assessment of the efficacy parameters was done at 12 weeks. Psoriasis lesions were evaluated using PASI (0–72) score[24] and ESI[25] severity (0–3) score. Each component of ESI was graded from 0 to 3; 0 - clear, 1 - mild, 2 - moderate, and 3 - severe. The most severe condition was given 9 points whereas the absence of disease been given 0 points.

All the parameters of MS as defined by modified NCEP ATP III criteria[20] were assessed at baseline and 12 weeks. Serum IL-6 and TNF-α levels was done at 0 and 12 weeks in subgroup (8 patients each in placebo and metformin groups) of patients by Human ELISA Kit (RayBiotech, Inc., Georgia, USA).

The primary efficacy end point was mean percentage change in PASI or ESI scores from baseline after 12 weeks of therapy given along with standard treatment for psoriasis. The secondary efficacy end point was number of parameters of MS improved, change in individual parameters of MS, IL-6, and TNF-α from baseline after 12 weeks of treatment with metformin or placebo. The mean percentage change in physician global assessment (PGA) from baseline and percentage of patients achieving 75% reduction in PASI score in the two treatment groups were other end points.

**Sample size calculation**

Assuming a standard deviation of 10 in PASI scores and a difference of 10 in PASI score between drug and placebo arm at 12 weeks to be clinically significant at α = 0.05 and with 80% power, a sample size of 16 patients per group has been calculated. Keeping in mind a dropout rate of about 20%, 19 patients will be required to be included in each group.

**Statistical analysis**

Mean percentage change in PASI, ESI, and PGA scores at 12 weeks from baseline between two groups was carried out using Student’s t-test. Chi square test or Fischer’s Exact test was used
to compare categorical variables. Intragroup comparison of mean changes in individual parameters of MS and lipid profile was carried out by paired $t$-test and intergroup comparison by Student’s $t$-test. Independent $t$-test was used for comparison of numerical variables between two treatment groups. Results were analyzed as intention-to-treat (ITT) analysis with last observation carried forward (LOCF). A two-sided $P < 0.05$ was considered as statistically significant.

**Results**

A total of 51 psoriasis patients with MS were screened for enrollment in the study from June 2010 to April 2011 [Figure 1]. Out of 51, 13 were excluded from the study. Eighteen and twenty patients were randomized to placebo and metformin treatment groups, respectively. Disposition of patients and reasons for withdrawal were summarized in Figure 1. A total of 17 patients in placebo arm and 18 patients in metformin arm completed the study. All participants as randomized were included in the final analysis as it is ITT analysis with LOCF.

No significant difference was observed in baseline demographics and metabolic characteristics among two treatment groups except joint involvement [Table 1].

**Psoriasis area and severity index, erythema, scaling, and induration, and physician global assessment scores and parameters of metabolic syndrome**

Statistically significant improvement was observed in mean percentage change in ESI ($P = 0.048$) scores in metformin group as compared to placebo group [Figure 2] while no significant difference was observed in mean percentage change in PASI ($P = 0.215$) and PGA scores ($P = 0.070$). There was statistically significant difference in percentage of parameters of MS improved following 12 weeks of treatment in metformin (19%) as compared to placebo (8.9%) group ($P = 0.046$) [Figure 3]. Statistically significant difference in percentage of patients achieving 75% reduction in ESI scores in metformin (75%) versus placebo (38.9%) ($P = 0.024$) [Figure 4]. Significant improvement was observed in mean weight, body mass index (BMI), waist circumference (WC), FPG, serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) [Table 2] in metformin group as compared to placebo. Improvement in BMI, WC, FPG, serum triglycerides, HDL, LDL, systolic blood pressure (SBP), diastolic blood pressure (DBP), and total cholesterol was statistically significant in metformin group over the period of 12 weeks. There was no significant difference in mean change in serum levels of IL-6 (placebo = $-65.4 \pm 100.1$, metformin = $-33.6 \pm 57.4$; $P = 0.449$) and TNF-$\alpha$ (placebo = $13.9 \pm 290.0$, metformin = $-12.1 \pm 82.3$; $P = 0.810$). There was no significant difference in the mean number of adverse events in two groups except weight gain [Table 3].

**Discussion**

Metformin group had greater percentage reduction in mean PASI, ESI, and PGA scores as compared to placebo (% reduction in mean PASI scores – 86.3% vs. 72.0%, % reduction in mean ESI scores – 82.0% vs. 60.4%, and % reduction in mean PGA scores – 79.6% vs. 60.0% in metformin and placebo groups, respectively). Reduction in mean percentage change in PASI score was more in metformin group although not statistically significant. Significance was not achieved probably because of the rapid and almost 100% of patients responded to methotrexate in placebo group as well as an anti-inflammatory response.\[17\] Methotrexate inhibits AICAR transformylase thereby increasing AICAR concentration which causes activation of AMPK.\[17\] Second, remitting-relapsing nature of the psoriasis disease might be responsible for the nonsignificant difference between two groups. Metformin acts...
AMPK activation not only inhibits inducible nitric oxide synthase, dendritic T cell, and monocyte/macrophage activation but also activates IL-10 and TGF-β, thereby exerting its anti-inflammatory action. [17]

Percentage of PASI change in placebo group taking methotrexate was 72% in our study, as compared to the study by Flytström who observed 58% improvement in PASI in methotrexate group. [27] Champion trial [21] and study done by Heydendael et al. [28] reported 75% reduction in PASI in 35.5% and 60% of the patients, respectively. The higher response in our study may be due to the difference in characteristics of psoriasis patients as our patient population had MS. After 12 weeks of treatment with metformin or placebo, group with improvement of MS had greater percentage reduction in mean through activation of AMPK in extracellular signal-related kinase 1/2 signaling pathway leading to cell cycle arrest and therefore inhibition of cell proliferation, hallmark of psoriasis. [26] AMPK activation not only inhibits inducible nitric oxide synthase, dendritic T cell, and monocyte/macrophage activation but also activates IL-10 and TGF-β, thereby exerting its anti-inflammatory action. [17]

Table 1: Baseline characteristics of two treatment groups

| Baseline characteristics                          | Placebo (n=18) | Metformin (n=20) | P (two-sided) |
|--------------------------------------------------|----------------|-----------------|--------------|
| Age (years), mean±SD                             | 45.8±12.7      | 50.7±10.4       | 0.197        |
| Male/females, n (%)                              | 13/5           | 12/8 (60/40)    | 0.506        |
| Total duration of disease (years), mean±SD       | 10.3±8.9       | 13.6±12.6       | 0.354        |
| Seasonal exacerbation, n (%)                     | 16 (88.9)      | 16 (80)         | 0.663        |
| Seasonal improvement, n (%)                      | 15 (83.3)      | 16 (80)         | >0.99        |
| Remission, n (%)                                 | 17 (94.4)      | 15 (75)         | 0.184        |
| Nail involvement, n (%)                          | 14 (77.8)      | 14 (70)         | 0.719        |
| Joint involvement, n (%)                         | 1 (5.6)        | 7 (35)          | 0.045        |
| DM, n (%)                                        | 2 (11.1)       | 3 (15)          | >0.99        |
| HTN, n (%)                                       | 3 (16.7)       | 7 (35)          | 0.278        |
| Family history of psoriasis, n (%)               | 1 (5.6)        | 2 (10)          | >0.99        |
| Alcohol, n (%)                                   | 3 (16.7)       | 4 (20)          | >0.99        |
| Smoking, n (%)                                   | 3 (16.7)       | 3 (15)          | >0.99        |
| Vegetarian, n (%)                                | 11 (61.1)      | 12 (60)         | >0.99        |
| BMI (kg/m²), mean±SD                             | 26.9±4.0       | 27±6.4          | 0.952        |
| Waist circumference (cm), mean±SD                | 101.8±9.5      | 100.6±14.4      | 0.827        |
| PASI, mean±SD                                    | 16.9±5.5       | 16.9±7.9        | 0.964        |
| ESI, mean±SD                                     | 7.9±1.0        | 8.1±0.9         | 0.453        |
| PGA, mean±SD                                     | 5.4±0.7        | 5.4±0.8         | 0.963        |
| FPG (mg/dl), mean±SD                             | 95.9±35.8      | 104.2±28.7      | 0.434        |
| Total cholesterol (mg/dl), mean±SD               | 190.8±45.9     | 191.3±52.0      | 0.977        |
| Triglycerides (mg/dl), mean±SD                   | 181.3±83.4     | 186.5±71.5      | 0.837        |
| HDL (mg/dl), mean±SD                             | 46.3±10.9      | 42.1±12.0       | 0.267        |
| LDL (mg/dl), mean±SD                             | 113.8±34.2     | 118.9±34.8      | 0.652        |
| SBP (mmHg), mean±SD                              | 138.6±19.5     | 138.1±14.4      | 0.935        |
| DBP (mmHg), mean±SD                              | 89.4±12.6      | 86.1±6.9        | 0.310        |
| Calcium channel blockers, n (%)                  | 1 (5.6)        | 0               | 0.474        |
| Thyroxine, n (%)                                 | 0              | 1 (5)           | >0.99        |
| Angiotensin receptor blockers, n (%)             | 0              | 1 (5)           | >0.99        |
| Oral hypoglycemics, n (%)                        | 2 (11.1)       | 0               | 0.218        |
| Antidepressants, n (%)                           | 1 (5.6)        | 0               | 0.474        |

Values are presented as mean±SD or n (%). DM: Diabetes mellitus, HTN: Hypertension, BMI: Body mass index, ESI: Erythema, scaling, and induration, PGA: Physician global assessment, FPG: Fasting plasma glucose, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ACE inhibitors: Angiotensin-converting enzyme inhibitors, SD: Standard deviation, PASI: Psoriasis area severity index

Figure 2: Mean percentage change in PASI, ESI, and PGA scores in two treatment groups from baseline (intention to treat analysis). Intergroup comparisons for mean percentage change in PASI, ESI, and PGA scores at 12 weeks from baseline carried out by Student’s t test. *Metformin versus placebo, PASI: Psoriasis area severity index, ESI: Erythema, scaling, and induration, PGA: Physician global assessment

Figure 2: Mean percentage change in PASI, ESI, and PGA scores in two treatment groups from baseline (intention to treat analysis). Intergroup comparisons for mean percentage change in PASI, ESI, and PGA scores at 12 weeks from baseline carried out by Student’s t test. *Metformin versus placebo, PASI: Psoriasis area severity index, ESI: Erythema, scaling, and induration, PGA: Physician global assessment
In our study, 45% of the patients had complete improvement in MS in metformin group as compared to 33.3% patients in placebo group (\( P = 0.52 \)). Greater percentage reduction in mean percentage change in PASI, ESI, and PGA scores with metformin might be because of the effect of metformin on MS parameters. Statistically insignificant difference may be attributed to methotrexate use in both the groups. The use of methotrexate has been shown to reduce cardiovascular mortality and the incidence of myocardial infarction in rheumatoid disease.\(^{[29]}\) Mitigation of apoptosis in ischemic myocardium by metformin accounts for improved cardiovascular protection.\(^{[30]}\)

In addition, metformin group had significantly more improvement in percentage of MS parameters as compared to placebo group. Furthermore, patients taking metformin had statistically significant decrease in weight, BMI, waist circumference, FPG, serum triglycerides, total cholesterol, and LDL-C as compared to patients taking placebo. Mean increase in HDL-C observed in metformin group was 3.0 ± 22.0 (\( P = 0.571 \)) and 4.3 ± 4.8 (\( P = 0.001 \)) \( \text{mg/dl} \), respectively. However, difference in mean change in

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**Table 2: Mean change in weight, body mass index, individual parameters of lipid profile, and metabolic syndrome after 12 weeks of treatment in two treatment groups from baseline (intention to treat analysis)**

| Parameters       | Placebo (\( n=18 \)) | Treatment (\( n=20 \)) | Student’s \( t \)-test† |
|------------------|-----------------------|-------------------------|-------------------------|
|                  | Mean change (mean±SD) (\( P \)) | Mean difference (mean±SD) (\( P \)) | Mean difference (\( P \)) (two-sided) |
| Weight (kg)      | 74.2±12.7 75.3±13.3 | Weight change -1.1±1.9 (0.026)* | 2.07 (0.72-3.34) 0.004* |
| BMI (kg/m²)      | 26.9±3.9 27.3±4.1 | Change -0.4±0.8 (0.030) | 0.77 (0.27-1.27) 0.003* |
| Waist circumference (cm) | 101.8±9.6 103.1±10.2 | Change -1.2±2.6 (0.058) | 3.22 (-1.14-5.31) 0.003* |
| FPG (mg/dl)      | 95.9±35.9 92.9±19.0 | Change 3.0±22.0 (0.571) | 0.024* |
| Triglycerides (mg/dl) | 181.3±83.4 175.9±89.3 | Change 5.3±26.3 (0.406) | 0.030* |
| HDL (mg/dl)      | 46.3±10.9 46.9±8.6 | Change -0.6±6.8 (0.730) | 0.025* |
| SBP (mmHg)       | 139.1±19.0 136.2±12.6 | Change 2.9±8.8 (0.180) | 0.014* |
| DBP (mmHg)       | 90±12.3 87±6.7 | Change 3.0±7.8 (0.122) | 0.004* |
| Total cholesterol (mg/dl) | 190.8±45.9 189.1±47.6 | Change -1.8±15.5 (0.638) | 0.003* |
| LDL (mg/dl)      | 113.8±34.2 114.3±34.0 | Change -0.5±16.4 (0.897) | 0.003* |

Values are expressed as mean±SD. *Statistically significant difference compared to baseline, †Intragroup comparisons for individual parameters carried out by paired \( t \)-test, ‡Inter‑group comparisons for individual parameters carried out by Student’s \( t \)-test. FPG: Fasting plasma glucose, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, LDL: Low-density lipoprotein, SD: Standard deviation.
Table 3: Adverse events observed in placebo and metformin treatment groups in systemic treatment arm

| Adverse event                  | Placebo (n=18) | Metformin (n=20) | P (Fisher’s exact test) |
|-------------------------------|----------------|------------------|-------------------------|
| Redness                       | 0              | 0                | -                       |
| Pain                          | 0              | 0                | -                       |
| Hyperpigmentation             | 5              | 4                | 0.709                   |
| Hypopigmentation              | 0              | 0                | -                       |
| Exacerbation                  | 0              | 0                | -                       |
| Hypothyroidism                | 0              | 0                | -                       |
| Edema                         | 0              | 0                | -                       |
| Complaint of weight gain      | 0              | 0                | -                       |
| Anemia                        | 2              | 1                | 0.595                   |
| Corticosteroid-induced cataract| 0              | 1                | >0.99                   |
| Hepatitis'                    | 1              | 0                | 0.474                   |
| Gallstone                     | 1              | 0                | 0.474                   |
| Abdominal pain                | 0              | 1                | >0.99                   |
| Headache                      | 0              | 1                | >0.99                   |
| Gastritis                     | 1              | 0                | 0.474                   |
| Nausea                        | 1              | 1                | >0.99                   |
| Vomiting                      | 1              | 1                | >0.99                   |
| Dizziness                     | 1              | 0                | 0.474                   |
| >3 times SGOT/SGPT            | 0              | 0                | -                       |
| Slight increase in SGOT/SGPT  | 1              | 0                | 0.474                   |
| Increased TLC                 | 1              | 0                | 0.474                   |
| Weight gain ≥1 kg             | 10             | 4                | 0.042*                  |
| Recurrence after 3 months     | 3              | 3                | >0.99                   |

Intergroup comparison was done by Fisher’s exact test; P<0.05 was considered statistically significant. *Statistically significant difference between two groups. Hepatitis because of HCV, TLC: Total leukocyte count, SGOT: Glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, HCV: Hepatitis C virus

HDL-C, SBP, and DBP was not significantly different from placebo. The baseline characteristics between two groups were similar. Thus, the difference in efficacy between metformin and placebo group observed in our study can be ascribed to the additive effect of methotrexate and metformin as both exert anti-inflammatory effect by activation of AMPK.[17]

BMI is a major risk factor for Type II diabetes.[31] For every 1 kg weight gain, there is nearly a 5% increase in the risk of diabetes.[32] Our study results revealed a mean reduction of 0.9 ± 2.2 kg and 0.4 ± 0.8 kg/m² in weight and BMI in metformin group, significantly more as compared to placebo group. In the substudy of the UK Prospective Diabetes Study (UKPDS), metformin therapy was associated with a 32% risk reduction for any diabetes-related end point (P = 0.0023), a 42% reduction in diabetes-related death (P = 0.017), 39% fewer myocardial infarctions (P = 0.01), and a 36% reduction in all-cause mortality (P = 0.011) compared with conventional treatment group.[33] Despite the similar levels of HbA1C achieved in metformin and other intensively treated groups (sulfonylureas and insulin), an additional benefit of metformin was observed in reduced risk for any diabetes-related end point, all mortality, and stroke.[34] Similar to our study results, many studies had shown that metformin mildly decreases total and LDL C,[35 37] decreases triglyceride levels,[36,38,39] and may even slightly increase HDL C.[36,38,39] This modest beneficial effect of metformin on lipid profile might partially contribute to benefit on macrovascular disease in the UKPDS study. Metformin prevents the development of MS.[40] It may be concluded that psoriasis patients with MS can benefit from the long-term use of metformin as shown by the improvement in parameters of MS, lipid profile, and weight loss in our study participants and the results of the UKPDS study.

In subgroup analysis, both metformin and placebo group had shown decline in the mean IL-6 and TNF-α levels, but no statistically significant difference was observed. It might be because of the effect of methotrexate on the serum IL-6 and TNF-α level which is given to all the patients. Twenty-five percent (2/8) of patients in both placebo and metformin groups had shown no decline or rather increase in the IL-6 and TNF-α levels, consistent with the relapse in psoriasis within next 6 months. Although number of patients had relapse in the next 6 months were 3 out of 18 in placebo group and 3 out of 20 in metformin group.

The study also has some limitations. Intermediate dose of metformin (1000 mg/day) was used in the study. Second, it was an open-label study although blinded end point assessment was done. The use of metformin had shown improvement in weight reduction, lipid profiles,[41] and hyperinsulinemia.[15,16] The treatment results of our study have demonstrated the overall superiority of metformin over placebo.

**Conclusion**

Metformin methotrexate combination might improve the clinical outcome in psoriasis patients by improving MS parameters as a result of antiproliferative[26] and anti-inflammatory action of both drugs.[17] However, large, controlled studies are needed to confirm this preliminary finding.

**Declarations**

**Ethical approval**

We also declare that the study was assessed and approved by the Institutional Ethics Committee, PGIMER, Chandigarh, and that letter of approval is available with us for examination. Ethics Committee letter number for the approval of study is MS/1145/DM/8229, dated April 1, 2010. From all patients, written informed consent was taken before randomization.

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Conflicts of interest
There are no conflicts of interest.

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