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Original Article

# Clinical efficacy and quality of life under micronutrients in combination with methotrexate therapy in chronic plaque of psoriatic patients

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ABSTRACT

*Background/objectives:* Psoriasis is a common dermatologic disorder, with fluctuating response to treatments. We aimed to investigate the efficacy of methotrexate (MTX) plus micronutrient supplement (MM) compare to MTX only on Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) in psoriasis patients in a double-blinded clinical trial study.

*Materials and methods:* A total number of 30 psoriasis patients who had lesions up to 20 percent of body skin involvement were divided randomly into two groups. Group A were treated by oral methotrexate and group B were received the MTX plus one tablet of micronutrient supplement daily for 12 weeks. Clinical response (scaling, erythema, involvement and thickness of patient's lesion), PASI score and DLQI index were recorded baseline and after 12 weeks. PASI-50, PASI-75, and PASI-90 evaluated as indicators of clinical improvements.

*Results:* PASI 50/75/90 response rates were 100%, 73.3%, 40% in group B and they were 66.6%, 40%, 20% in group A respectively. Both treatments were effective and caused significant improvements in PASI score and DLQI ($P < 0.05$). Group B showed a noticeable and more rapid reduction of PASI score, scaling and involvement of lesions compared to group A ($P = 0.04$; $P = 0.01$; $P = 0.03$, respectively). The decline of DLQI in group B ($6.80 \pm 2.33$) was higher than that in group A ($5.40 \pm 2.84$).

*Conclusion:* Daily usage of supplements along with methotrexate is safe and concomitant with the significant reduction of PASI score and improvement of DLQI compared to the usage of MTX alone.



## Introduction

Psoriasis is a common chronic inflammatory skin disease that has a significant impact on affected person's health-related quality of life (HRQoL).[1] Among widespread dissatisfaction of existing anti-psoriasis therapy,[2] Methotrexate (MTX) as a derivative of aminopterin, an analog, and antimetabolite of folic acid, was first used in the treatment of psoriasis in 1951.[3] Today, MTX shows promises for the treatment of practically all forms of moderate or severe psoriasis.[4] Due to the excellent efficacy of MTX for psoriasis treatment, MTX-based therapy of psoriasis patients could be conducted, as long as all recommendations concerning dosage and safety of treatment are considered.[5,6] After all, MTX is a relatively inexpensive drug and thereby it is available easily to low-income patients.

For decades, the effects of dietary and vitamin supplements in the management of psoriasis have been neglected. The oral 1,25 dihydroxy vitamin D3 [1,25(OH)2-D3] in the treatment of psoriasis is known to have some beneficial effects.[7] Moreover, the combined use of calcipotriol (1,25-(OH)2-D3) with MTX treatment increased the relapse time of psoriasis patients following discontinuation of MTX.[8] Various topical and systemic vitamin A derivatives were highly effective in the treatment of psoriasis and had potential benefits related to decreasing psoriasis area and severity index (PASI).[9] The potential efficacies of intramuscular and systemic

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vitamin B12 in the treatment of psoriasis have been demonstrated previously.[10] A recent randomized, controlled trial study revealed the role of supplementation containing selenium, coenzyme Q10, and vitamin E in hastening the clinical improvement in psoriasis patients compared the patients who were received placebo.[11] Furthermore, statistically significant decrease in the mean PSAI score of chronic plaque psoriatic patients was recorded under high-pressure shower regimen and selenium-rich spa water daily for three weeks.[12] Furthermore, improvement of PASI score by receiving inositol[13] and zinc supplementation[14] were demonstrated previously. Today, due to the increase in the number of recent studies on psoriasis, interests in the field of examining nutrition and functional ailments on milder flare-ups and reduction of scales and erythema have been increased accordingly.[15]

In psoriasis, physical measures of disease severity such as the affected body surface area or PASI score do not always correspond with the impact of psoriasis on the patient's HRQoL.[16] Therefore, both physical and HRQoL measurements are necessary to assess disease severity when decisions are made over psoriasis treatment and when assessing the outcome of such decisions.[17,18] In the majority of trials the Dermatology Life Quality Index (DLQI) has been used as the dermatology-specific HRQoL outcome.[19,20] In present study for the first time, we aimed to investigate the impact of consumption of micronutrient supplementation (MM) along with MTX compared to MTX only on the clinical efficacy and DLQI in psoriasis patients.

## Methods

### *Study participants*

This randomized double-blind trial was conducted on patients with psoriasis vulgaris who were referred to our Dermatology Department with the approval of the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. This trial was registered on Iranian Registry of Clinical Trials (IRCT) under the registry number: IRCT 2014012016275N1. The considered cases of psoriasis patients had ages between 20 and 50 years old and lesions with up to 20% of body skin involvement. Exclusions were patients under 20 years old, patients who wanted to leave the study for any reason, patients who had type one diabetes mellitus, patients with cardiovascular disease, pregnant or lactating women, patients with familial hyperlipidemia, history of liver disease, consumption of alcohol or alcoholic beverages during study, and variations in hepatic enzymes (more than 2.5 times of normal level). Furthermore, patients who previously were taking Methotrexate, phototherapy and any systemic therapy during last two months for psoriasis treatment were also excluded. Diagnosis of plaque-type psoriasis was made by punch biopsy after taking the separate written informed consent.

### *Sample size*

According to previous investigations on psoriasis treatment protocols, PASI-75 is considered as a benchmark for severity of disease evaluation.[21–23] Therefore, we considered PASI-75 score as defined reduction in PASI by 75% from baseline, during 12 weeks therapy. Thus, with 75% cure rate, 85% power and a 5% two-sided type I error, 11 subjects were required in each group. Moreover, considering a loss to follow-up of 20%, this number raised to 15 patients for each group. Initially, fifty psoriasis patients were enrolled according to the inclusion criteria. Then, 16 cases were excluded due to lack of eligible criteria or consent withdrawn (Fig. 1). Therefore, 34 psoriasis patients have entered the study. However, four patients were excluded due to their absence in follow-up periods. Hence, we completed our treatment protocol on 30 psoriasis patients.

### *Study protocol*

Demographic profile including gender, age and age onset of disease and weight of patients were collected. Moreover, past medical history of all patients was also noted. First, patients were divided randomly into two different modalities of treatment (group A and group B) based on random table numbers and referral date of patients. The patients who were referred in odd days were considered as group A and those who were referred in even days were considered as group B. Patients were blind about treatment groups due to receiving their therapies with masked trademarks and as mentioned above their referring into different days. Moreover, they did not have any contact with each other.

Two studied groups (group A and group B) received 7.5–15 mg per week oral methotrexate (0.2–0.3 mg/kg/week) for 12 weeks according to the standard protocol of MTX consumption.[24] Folic acid was given to the patients at 5 mg once daily except on the day of MTX consumption.[24] In addition, patients of group B were received one tablet daily of micronutrient (Immunace, Vitabiotics Ltd, London, UK). The composition of this micronutrient supplement (see supplementary file), was higher than the recommended daily allowances (RDA) for healthy individuals due to the greater need of psoriasis patients to micronutrients.[25] Patients were advised to report to the dermatologist any occurrence of unwilling adverse effects including redness, burning, itching and erosion during 12 weeks of therapy. Baseline and weekly complete blood count (CBC) and liver function test (LFT) including measuring of alanine aminotransferase (SGOT), aspartate aminotransferase (SGPT), and alkaline phosphatase (ALP) enzymes were carried out to monitor the side effects of methotrexate.

Furthermore, the factors including the site of involvement, the size of plaques, and skin examination (erythema, thickness, and scaling of lesions), at baseline and after 12 weeks' therapy, were evaluated by three independent investigators. These investigators were not aware of treatment groups and types of patient's therapies. Moreover, they calculated independently the efficacy of treatment under Psoriasis Area and Severity Index (PASI) system (Table 1).[26] The index combines the area of affected skin (head (10%); upper extremities (20%); lower extremities (40%); trunk (30%) of whole body surface) and the grade of erythema, thickness and scaling of lesion (scored for each criterion from 0 to 4). We calculated the score of erythema, thickness, and scaling of the lesion based on the sum of their related rating score for each patient's (0–4, Table 1) head, upper limbs, trunk and lower limbs. Besides, the degree of involvement was considered as the sum of related rating score for each patient's (0–6, Table 1) head, upper limbs, trunk and lower limbs.

Then effectiveness indicator targets of our study process were evaluated with three cut points as a reduction in PASI by 50%, 75% and 90% (remission point) from baseline (PASI -50, PASI-75 and PASI-90).

### *The Dermatology Life Quality Index*

DLQI questionnaire was selected as a widely used dermatology-specific questionnaire[27] to evaluate health-related quality of life. This questionnaire included 10 questions concerning HRQoL related to the last week, before patient admission, which ranged from 0 (no impairment of HRQoL) to 30 (maximum impairment of HRQoL). DLQI is subdivided into six areas related to different features of a person's HRQoL consisting of symptoms and feelings (questions 1, 2), daily activities (3, 4), leisure (5, 6), work/school (7),

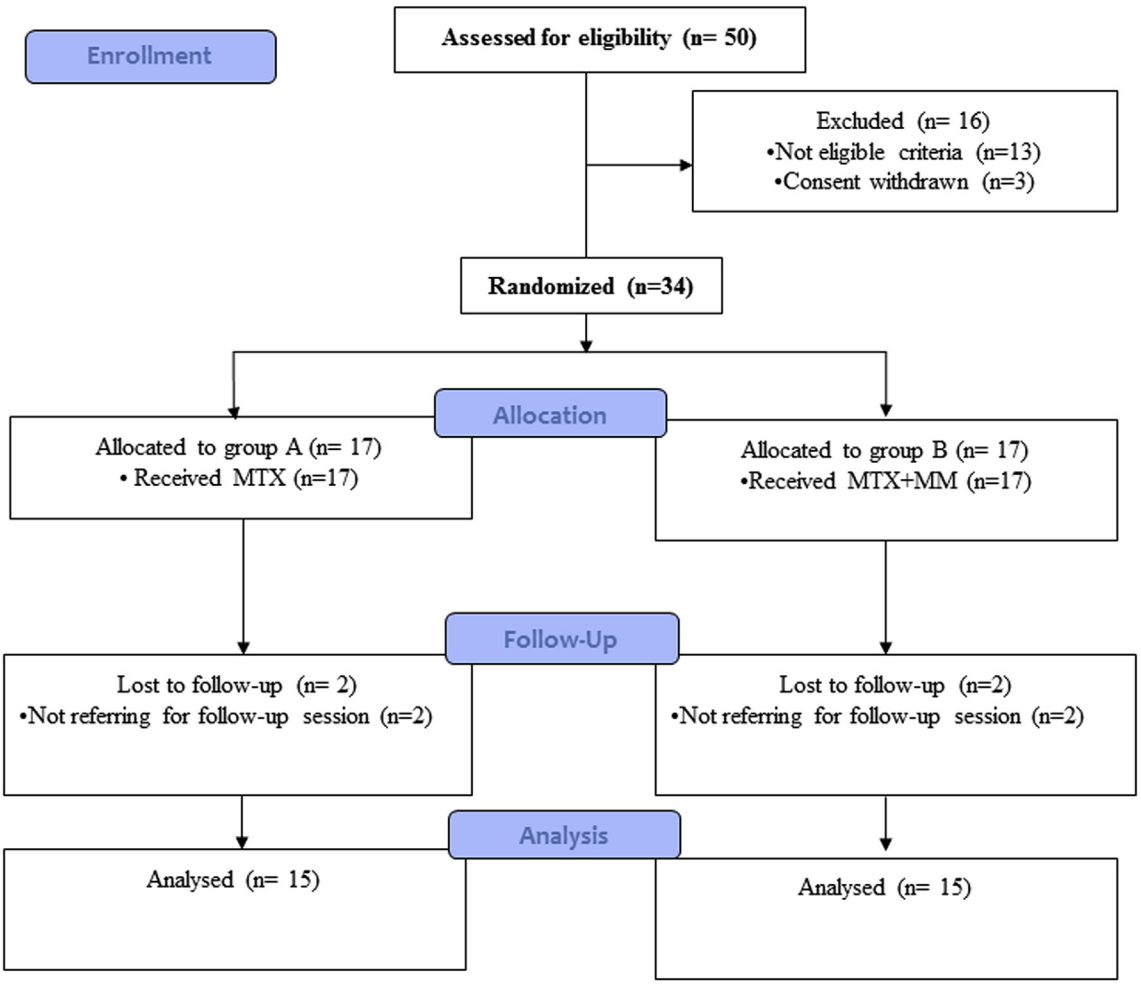


**Fig. 1** Flow diagram of studied patients in randomized trial according to CONSORT 2010 Flow Diagram. MM: Micronutrients, MTX: Methotrexate.

**Table 1** Assessment of psoriasis severity based on PASI score sheet = 0.1(Eh + Th + Sh) Ah+0.2(Eu + Tu + Su) Au+0.3(Et + Tt + At) At+0.4(El + Tl + Sl) Al.

| Area scoring | Degree of involvement | Rating score erythema, thickness, scaling |
|---|---|---|
| 1 | 1–9% | 0 = Non |
| 2 | 10–29% | 1 = Slight |
| 3 | 30–49% | 2 = Moderate |
| 4 | 50–69% | 3 = Severe |
| 5 | 70–89% | 4 = Very severe |
| 6 | 90–100% | |

E = Erythema, T = Thickness, S = Scaling, A = Area (Degree of involvement), h: Head, u: Upper limbs, t: Trunk, l: Lower limbs.

personal relationships (8, 9) and treatment (10). All the patients were asked to complete DLQI before and after 12 weeks' treatment.

### *Statistical analysis*

Data was analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). The qualitative data including gender, site of involvement and efficacy were shown by frequency and percentage. Normality of data was checked by Kolmogorov–Smirnov test. Paired T-test was used to check the differences in PASI scores, DLQI scores, skin examination and variations in liver enzymes between data obtained before and after the trial. Furthermore, independent sample T-test was performed to check the differences in demographic variables, PASI and DLQI scores in two groups. Moreover, repeated measurements were performed to determine differences in skin examination (erythema, involvement, and thickness), PASI and DLQI changes during the study between two groups. The Spearman correlation test was used for checking the correlation of clinical response (PASI) with age, age onset of disease and DLQI between group A and group B. P value of less than 0.05 was considered as significant value.

## Results

### *Participant's basic information*

Basic demographic information of studied patients is presented in Table 2. In total, 30 patients (18 males and 12 females) were enrolled. The age range of studied patients was 38.53 ± 11.05 years old. There was not any significant difference between the age of group A and group B (P = 0.97). The age onset of the disease of study patients was 29.83 ± 12.8 years. However, there were not any significant difference between age onset of disease between group A and group B (P = 0.40). The weights of studied participants in both groups were almost similar. It was (67.53 ± 5.37, kg) for group A and (61.90 ± 12.87, kg) for group B (P = 0.13). In addition, the studied participants in group A (13.5 ± 1.07, mg/week) and group B (12.38 ± 2.57, mg/week) were received a similar dosage of MTX during the study (P = 0.13).

**Table 2** Patient baseline demographic information respect to treatment regime and change in PASI score during study.

| Group | Age/Sex | Age onset, year | Weight, Kg | Psoriasis area and severity index | | PASI-50 | PASI-75 | PASI-90 |
|---|---|---|---|---|---|---|---|---|
| | | | | Week 0 | Week 12 | | | |
| A | 23/M | 20 | 67 | 23.2 ± 0.63 | 12.5 ± 0.41 | × | × | × |
| A | 59/F | 55 | 72 | 24.7 ± 0.25 | 3 ± 0.07 | √ | √ | × |
| A | 45/F | 43 | 72 | 19.5 ± 1.22 | 1.3 ± 0.01 | √ | √ | √ |
| A | 47 F | 43 | 70 | 26 ± 0.81 | 3.4 ± 0.02 | √ | √ | × |
| A | 45/F | 44 | 75 | 17.1 ± 0.04 | 1.3 ± 0.021 | √ | √ | √ |
| A | 45/M | 30 | 70 | 41.2 ± 0.14 | 12.3 ± 0.01 | √ | × | × |
| A | 27/M | 25 | 67 | 56.4 ± 0.33 | 29.9 ± 0.02 | × | × | × |
| A | 48/M | 28 | 75 | 47.4 ± 1.07 | 10.8 ± 0.01 | √ | √ | × |
| A | 32/M | 25 | 57 | 26.2 ± 0.24 | 7 ± 0.001 | √ | × | × |
| A | 37/F | 32 | 72 | 29.1 ± 1.17 | 2 ± 0.01 | √ | √ | √ |
| A | 23/M | 20 | 38 | 26.1 ± 0.52 | 7.5 ± 0.02 | √ | × | × |
| A | 47/F | 29 | 68 | 22 ± 0.08 | 11 ± 0.001 | × | × | × |
| A | 43/M | 40 | 70 | 30.1 ± 1.73 | 7.9 ± 0.03 | √ | × | × |
| A | 20/M | 9 | 75 | 37.7 ± 0.16 | 34.3 ± 0.03 | × | × | × |
| A | 40/M | 33 | 70 | 26.8 ± 0.02 | 16 ± 0.01 | × | × | × |
| B | 44/M | 32 | 52 | 22.4 ± 0.12 | 1.9 ± 0.03 | √ | √ | √ |
| B | 35/M | 33 | 62 | 30.2 ± 0.04 | 2.7 ± 0.07 | √ | √ | √ |
| B | 32/M | 28 | 68 | 51.7 ± 0.38 | 10 ± 0.02 | √ | √ | × |
| B | 45/M | 35 | 58 | 35.6 ± 0.06 | 3 ± 0.01 | √ | √ | √ |
| B | 58/F | 52 | 72 | 34.5 ± 0.02 | 2.1 ± 0.03 | √ | √ | √ |
| B | 48/F | 32 | 70 | 21.6 ± 1.06 | 3.6 ± 0.03 | √ | √ | × |
| B | 47/M | 38 | 37.5 | 36.4 ± 0.15 | 6.7 ± 0.87 | √ | √ | × |
| B | 53/M | 48 | 53 | 21.6 ± 0.19 | 6.6 ± 0.01 | √ | × | × |
| B | 32/M | 28 | 52 | 24.9 ± 0.01 | 3 ± 0.001 | √ | √ | × |
| B | 30/F | 20 | 69 | 45.8 ± 0.31 | 3.4 ± 0.02 | √ | √ | √ |
| B | 26/F | 9 | 68 | 24.4 ± 0.12 | 2 ± 0.03 | √ | √ | √ |
| B | 39/F | 11 | 67 | 35.5 ± 0.02 | 10.8 ± 0.001 | √ | × | × |
| B | 26/M | 14 | 65 | 18.8 ± 0.06 | 6.9 ± 0.08 | √ | × | × |
| B | 42/M | 27 | 75 | 49 ± 0.40 | 14.9 ± 0.05 | √ | × | × |
| B | 20/F | 12 | 55 | 24.6 ± 0.24 | 5 ± 0.07 | √ | √ | × |

Group A and Group B definitions mentioned within the text, F; Female, M; Male, PASI; Psoriasis Area and Severity Index, √; Positive, ×: Negative.

### *Analysis of study protocol*

*Laboratory assay*

Changes in liver function tests (LFT) before and after the study are presented in Table 3. LFT change was meaningful after the study in both studied groups (Table 3, $P < 0.05$). There was not any significant difference respect to SGPT ($P = 0.49$; $P = 0.69$), SGOT ($P = 0.06$, $P = 0.19$) and ALP ($P = 0.28$, $P = 0.28$) levels between group A and group B respectively.

*Clinical assay*

Erythema, thickness, scaling and involvement of psoriasis lesions were evaluated in each group before and after the study (Table 3). Both treatments of studied groups (group A and group B) were experienced a significant decrease of erythema, thickness, scaling and involvement of psoriasis lesions ($P < 0.05$). There was not any significant difference in erythema ($P = 0.58$), thickness ($P = 0.93$), scaling ($P = 0.23$) and percentage of body involvement ($P = 0.35$) of psoriatic plaques before the study ($P > 0.05$). By the end of the trial, we found that erythema, scaling, thickness and percentage of body involvement decreased in both groups (Fig. 2). The decrease of scaling was more prominent for group B (8.06 ± 2.96) compared to group A (5.26 ± 2.62) ($P = 0.01$). The decrease of erythema and thickness during the study in both groups were not different significantly ($P > 0.05$). Moreover, variations in lesion involvement showed that more decrease of lesion involvement was observed in group B (8.8 ± 1.97) compared with group A (6.66 ± 3.24) ($P = 0.03$).

**Table 3** Evaluation the laboratory data clinical and during the study between two group.

| Variables | | | Before | After | P-value |
|---|---|---|---|---|---|
| LFT | SGPT | Group A | 27.46 ± 3.58 | 37.06 ± 4.73 | 0.001 |
| | | Group B | 24 ± 3.46 | 34.43 ± 4.65 | 0.002 |
| | SGOT | Group A | 30.46 ± 4.49 | 33.66 ± 3.93 | 0.021 |
| | | Group B | 20.66 ± 2.03 | 27.53 ± 2.45 | 0.002 |
| | ALP | Group A | 210.80 ± 12.77 | 226.47 ± 12.50 | 0.005 |
| | | Group B | 190.20 ± 13.87 | 204.07 ± 16.38 | 0.088 |
| Psoriasis Evaluation | Erythema | Group A | 10.13 ± 2.35 | 5.13 ± 2.26 | 0.001 |
| | | Group B | 9.73 ± 1.53 | 4.26 ± 1.48 | 0.001 |
| | Thickness | Group A | 10.13 ± 2.50 | 5.40 ± 2.29 | 0.001 |
| | | Group B | 10.06 ± 2.08 | 3.80 ± 1.85 | 0.001 |
| | Scaling | Group A | 9.40 ± 3.26 | 4.13 ± 2.99 | 0.001 |
| | | Group B | 10.60 ± 2.20 | 2.53 ± 2.13 | 0.001 |
| | Involvement | Group A | 15.53 ± 2.85 | 6.86 ± 4.06 | 0.001 |
| | | Group B | 14.53 ± 2.94 | 5.73 ± 2.63 | 0.001 |

Liver function test (LFT); Group A and Group B definitions mentioned within the text. SGPT, SGOT and ALP refer to alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase respectively, P value less than 0.05 consider as significant level.

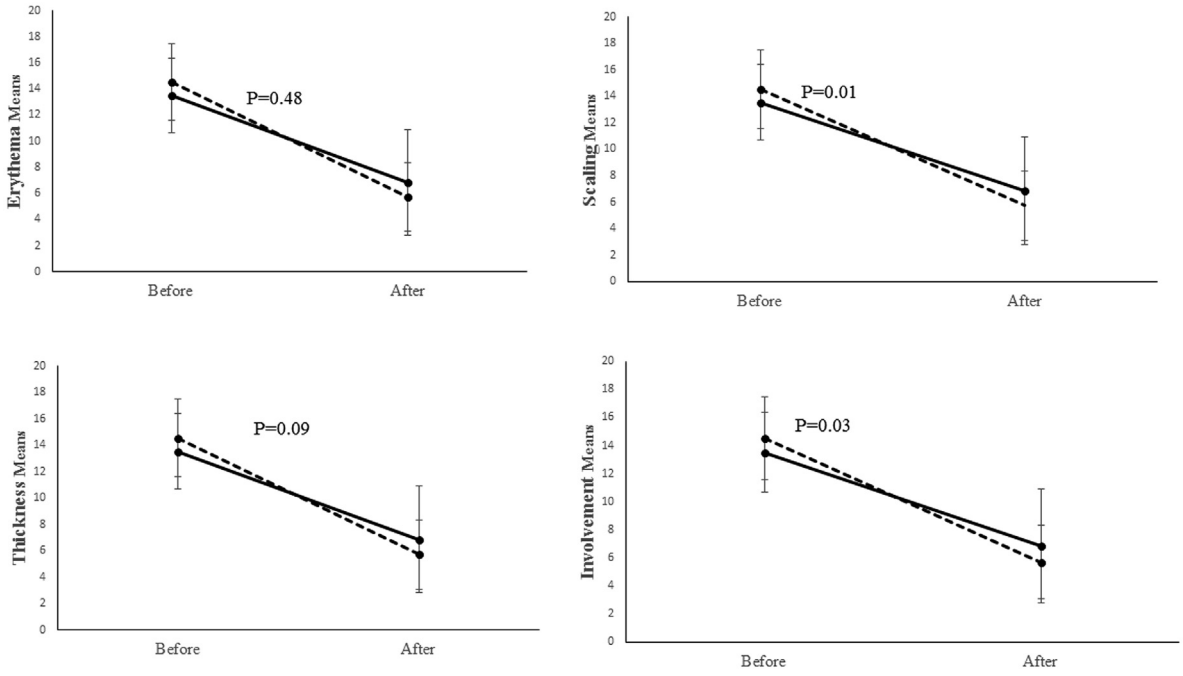


**Fig. 2** Changes of lesion erythema, involvement, thickness and scaling during the study period. Black and hachure lines show group A and group B respectively. P value compares changes of mentioned factors between two groups.

*Variations of PASI and DLQI during study*

At week 12, all patients in the combinational therapy group achieved PASI-50, 11 out of 15 (73.33%) achieved PASI-75 and 6 out of 16 (40%) reached PASI-90 (Table 2). While 10 (66.66%), 6 (40%) and 3 (20%) of patients in group A reached to PASI-50, PASI-75 and PASI-90 respectively at week 12 (Table 2). Analysis related to PASI targets (PASI-50, PASI-75 and PASI-90) demonstrates that there were significantly higher numbers of patients of group B compared to group A who achieved to PASI-50 and PASI-75 after the treatment course ($P < 0.05$, Fig. 3), although, there was not any significant difference regarding PASI-90 between two study groups ($P = 0.21$, Fig. 3). Changes of PASI was statistically significant in both groups after the trial ($P = 0.01$, Fig. 4). However, the decrease of PASI was more significant for group B compared to group A after the study ($P = 0.04$, Fig. 4).

DLQI of both studied groups were similar before the study (Fig. 4, $P > 0.05$). Although the decline of DLQI in patients of group B ($6.80 \pm 2.33$) was higher than that in patients in group A ($5.40 \pm 2.84$) by the end of the study, however, this was not meaningful (Fig. 4, $P = 0.20$).

Analysis of correlation between PASI score and DLQI index shows that there was not any significant correlation between these mentioned factors before and after the trial (Table 4). In addition, any significant correlation between disease severity and age and age onset of disease were not found (Table 4, $P > 0.05$).

## Discussion

Psoriasis is a common papulosquamous disorder that responds to therapy with various reported results and it still causes

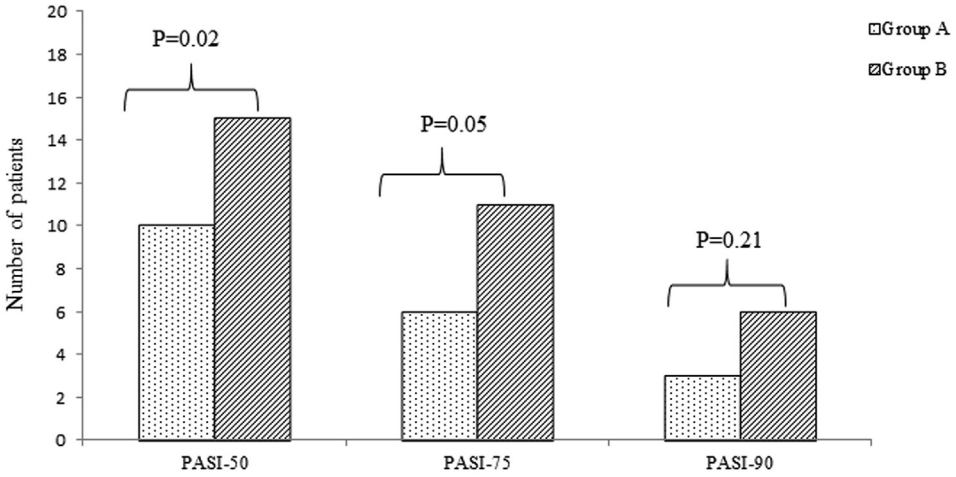


**Fig. 3** Treatment outcome under evaluation by psoriasis area and severity index (PASI)-50, PASI-75 and PASI-90 score during the study period between group A and group B. P value compares changes of mentioned factors between two groups.

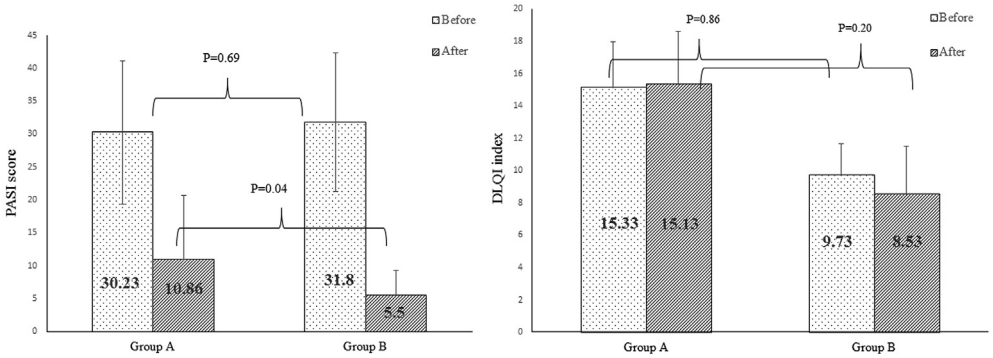


**Fig. 4** Changes in psoriasis area and severity index (PASI) and dermatology life index (DLQI) during the study period. Numbers in each bar shows mean value of PASI score and DLQI index. P value compares changes of mentioned factors before and after study between two groups.

**Table 4** Correlation of psoriasis area and severity index (PASI) and other investigated data.

| Variables | | Group A | | Group B | |
|---|---|---|---|---|---|
| | | Sig P-value | Correlation coefficient | Sig P-value | Correlation coefficient |
| Age, year | Before | 0.39 | 0.23 | 0.96 | 0.01 |
| | After | 0.09 | 0.44 | 0.80 | 0.07 |
| Age onset, year | Before | 0.11 | 0.42 | 0.91 | 0.03 |
| | After | 0.06 | 0.67 | 0.38 | 0.24 |
| DLQI | Before | 0.79 | 0.07 | 0.43 | 0.21 |
| | After | 0.68 | 0.11 | 0.60 | 0.14 |

Dermatology life index (DLQI); Group A and Group B definitions mentioned within the text. P value less than 0.05 consider as significant level.

controversies among dermatologist who are treating patients with different approaches. We have devised a novel risk-free combinational treatment modality using MTX and micronutrients which caused impressive decreasing of the clinical symptoms including severity of erythema, scaling, the involvement of lesions and PASI score, compared to the patients treated with MTX alone. Although after the trial, improvement of DLQI index was more noticeable in the combined treatment group, however, these differences were not significant.

Methotrexate is a relatively safe and effective option for psoriasis treatment which administered either as monotherapy or in combination with the other schemes.[6] Methotrexate exerts its effects by acting as both immunomodulatory and antimetabolite agent due to the down-regulating of T cell-mediated pro-inflammatory markers and inhibition growth of keratinocytes and decreasing the endothelial expression of ICAM-1 and E-selectin.[28,29] Clinical data from trials suggest that 24%–100% of psoriasis patients achieved PASI-75 at week 12 at MTX dosage of 7.5–15 mg weekly.[24] However, we found that 73% and 40% of patients reached PASI-75 at week 12 in group B and A respectively.

On combined therapies, first Katz in 1997 revealed that combined use of MTX and vitamin D analog caused an estimated 75% or greater lesion improvement in 75%–100% of the patients.[30] It was also supported that the view that a combination of vitamin D analog with MTX achieved better results than monotherapy alone.[31] However, there are only a few reports on using the supplement along with MTX in psoriasis.[32,33] Recently use of dietary supplementations, have been increasing due to the decrease in disease severity and its impact on health HQoRL and consequently on DLQI index of psoriasis patients.[33,34] The nutritional supplementations include vitamin D and vitamin A analogous, vitamin E, selenium, vitamin B12, zinc and various combined therapies provide an alternative treatment for psoriasis vulgaris patients.[15,35,36]

In the present study, we employed a higher dose of micronutrients considering its low levels in psoriasis patients.[15,35] However, there were not enough relevant literature on linking multiple micronutrient consumption or dietary supplements and their related mechanisms in improving psoriasis lesions. It is possible that micronutrients have improved the immune response by improving the T-lymphocyte function or one or more components of the innate immune system or blockage of the activity of inflammatory cytokines in psoriasis patients.[37] Similarly, vitamin A supplements may regulate several elements of the immune response,[38] or suppress the pro-inflammatory cytokines of psoriasis such as IL- 1, IL-17 and TNF-α.[39] On the other hand, clinical efficacy of vitamin D3 was established previously due to suppressing of IL-1 family, IL-12/23 p40, and TNF-α and development of TGF-β-dependent Foxp3(+) T-reg cells or IL-10-dependent IL-10(+) T-reg cells which down-regulate in psoriatic lesions.[39–41] Moreover, the role of vitamin E supplementation in improving indices of cell-mediated immunity or in the association of selenium supplementation with an improvement of T-cell function and the control of the immune response in psoriasis lesions were documented.[42] Besides the role of vitamin B12 in maintaining of immune function and decreasing pro-inflammatory cytokine[43] and dietary zinc in activating the NF-κB, expression of IL-1b and TNF-α, and neutrophil infiltration during the early stages of cutaneous wound healing were confirmed in previous studies.[44]

Therefore, in present study improving results in combined therapy group could be assumed due to the synergy between micronutrients and MTX, which allowed enhancing the efficacy of MTX along with no adverse effect. The significant response in PASI-75 or better results in PASI-90 as remission cut pint in combined therapy compared with MTX only can also be considered as a result of this combined therapy. However, the exact mechanism of vitamins or minerals is not fully understood and need to future controlled trial research.

Most of the previous studies focused on complementary micronutrients therapies are in non-controlled designed format. These studies did not gain the general acceptance in the

management of psoriasis either as combined with first-line therapies or as diet therapy alone. However, due to better psoriasis control, most of them recommended dietary approaches along with consumption of one of first line therapies. On the other hand, recently the controlled clinical trial studies on psoriasis according to their strict inclusion and exclusion criteria as well as the treatment protocol have reflected the situation of day-to-day treatment for the patient and the physician only to a limited extent. Therefore, aspects including the handling of therapy due to safety, acceptable result, cost effectiveness and availability of medicine, the acceptance and satisfaction of patients and improving in dermatology quality of life index are noticeably important consideration factors.

This is the first study that investigated combined use of MTX, as a safe, cost-effective, available and gold standard therapy for moderate to severe psoriasis, plus micronutrients in contrast with MTX alone. In conclusion, our findings revealed that decrease in PASI score was significantly higher in patients who were received both supplement and MTX compared with the patients received MTX alone. In the group treated by combined therapy, no side effects were reported and the patient's satisfaction was prominent along with a decline in DLQI. Considering these impressive results, the authors suggest the usage of micronutrients along with methotrexate in psoriasis patients. However, the low number of study sample size undoubtedly limits this evidence, which needs to be confirmed by larger numbers of patients. Moreover, for understanding the mechanism of this combined therapy, more sensitive in-vitro studies or immune-pathological analysis on inflammatory markers are essential and could constitute future steps of this study. Studies are underway in our laboratory to identify the specific immunological pathway of micronutrients targets and ascertain whether MTX and micronutrients act on same or different immunological pathways.

## Conflict of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dsi.2017.06.005.