Efficacy of calcium supplementation in the treatment of severe psoriasis treated with methotrexate

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Abstract

Background: Some patients with various types of severe psoriasis have been found to show disturbances in systemic calcium metabolism, which may affect the severity of the disease and the efficacy of methotrexate therapy.

Objective: This study aimed at evaluating the efficacy of calcium supplementation in the treatment of severe psoriasis treated by methotrexate.

Patients and methods: In this comparative therapeutic study of 80 psoriatic patients, first; they were divided into two groups according to their serum calcium level (40 patients in Group A of low calcium level, and 40 patients in group B of normal calcium level). Half of the patients (20 patients) in each group (A1&B1) were treated with calcium and methotrexate, and the other half (A2&B2) were treated by methotrexate only. The psoriasis area severity index score (PASI) result was analyzed in order to examine the efficacy of calcium supplementation and it was recorded at week 0, 4, 8, 12, 16 and was evaluated by two investigators independently.

Result: The mean of difference in PASI between subgroups (A1&A2) were (34.35%, 25.05% respectively, p=0.003) and between subgroups (B1&B2) were (58.15%, 34.45% respectively, $P < 0.001$) showed statistically significant change in combination therapy in compare to mono-therapy. Also the mean of difference in PASI between subgroups A1 (low Ca2+), & B1 (normal Ca2+) were (34.35%, 58.15% respectively, $P < 0.001$) indicating that calcium supplementation lead to better improvement of psoriasis among patients with normal calcium level .

Conclusion: Calcium supplementation has the synergistic correlation with methotrexate efficacy and reduces methotrexate dosage needed.

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Key words: calcium, psoriasis, combinational therapy, PASI

INTRODUCTION:

Psoriasis is a common, chronic, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role.[1]The clinical presentation varies depending on a number of factors which may cause an individual to present with a few localized psoriatic plaques or with generalized skin involvement and the development of pustules.[2]The pathogenesis of psoriasis can be explained by dysregulation of immunological cell function as well as keratinocyte proliferation/differentiation.[3]

Intracellular calcium plays an important part in the regulation of proliferation and differentiation of keratinocytes.[4] Although hypocalcaemia has been reported to be a triggering factor for generalized pustular psoriasis, it has been demonstrated that decrease of calcium serum leads to intensifying and extending the lesion in most patients.[5,6]

Combinational therapy may afford advance therapeutic option for recalcitrant patients and potentiate treatment outcomes owing to additive or synergistic effect.[7]

Methotrexate, an inexpensive first-line systemic therapy for moderate-to-severe psoriasis, [8] because the effects of methotrexate are most dramatic on rapidly dividing cells, it was originally thought that its beneficial effects in psoriasis were a result of the inhibition of epidermal proliferation, but the effectiveness may be due to an anti-inflammatory effect.[9]

Calcium is also known to influence MTX accumulation in hepatocytes.[10] MTX has been suggested to act through the capacitative calcium entry mechanism and play a metabolic roles in cells.[11] It could inhibit oxygen uptake in mitochondria and tumor cells[12-14] and inhibit transplasma membrane redox activity and ferricyanide-induced proton extrusion.[15]

MTX may act through a calcium–dependent mechanism. The synergistic effects proved between calcium and MTX on keratinocyte growth in vitro and psoriasis-like model mice in vivo.[16]

AIM OF THE STUDY: To evaluate the efficacy of calcium supplementation in the treatment of severe psoriasis treated by methotrexate

Patients and methods:

A hospital based therapeutic comparative study was conducted on cases of severe psoriasis attending consultation department of dermatology and venereology at dermatology teaching center in sulaimaniyah city during the period from April, 2017 to Feb, 2018 .

Eighty patients with severe psoriasis (more than 10 % body surface area (BSA)) from 18 years to 60 years of age, and of both sexes, were allocated by convenient sampling method. Patients in this study were subjected to a detailed history taken and clinical examination including systemic and dermatologic examination. Psoriasis was diagnosed clinically by two consultant dermatologists. Skin biopsy was performed in doubtful and suspicious cases.

Exclusion criteria were: Pregnancy and lactation, childhood and geriatric psoriasis, proven liver and renal disease, any contra –indications to methotrexate therapy, severe anemia, history of tuberculosis and severe pulmonary diseases, patients who had been taking medications affecting calcium-phosphorus, patients diagnosed as parathyroid tumor or other tumor affecting calcium-phosphrus, not use any medications for psoriasis topically or systematically 4 weeks before participation in this study.

A baseline psoriasis area severity index (PASI) score was taken as 100%, and the improvement after MTX in combination with calcium supplementation and MTX alone was expressed as the percentage of this baseline score.

The psoriasis area and severity index (PASI) which evaluates lesions by their characteristic of erythema, induration and scaling as well as by the surface area affected. In Europe, the PASI is a commonly used tool to grade psoriasis severity and is used in the majority of international clinical trials as primary or secondary endpoint .

The patients divided into 2 equal groups:

Group A: forty psoriatic patients with low serum ionizing calcium, then we subdivided them randomly into A1 (20 patients) and A2 (20 patients) (subgroupA1 received calcium supplementation with methotrexate therapy and A2 subgroup treated only by MTX).

Group B: forty psoriatic patients with normal serum ionizing calcium, then also randomly subdivided into B1 (20 patients) and B2 (20 patients) (subgroupB1 received calcium supplementation with methotrexate therapy and B2 subgroup treated only by MTX).

Methotrexate (Ebewe, 2.5mg tablet) was initiated at low weekly dose of 7.5 mg for 2 weeks, followed by 15 mg for 14 weeks. Methotrexate triple-dose schedule, 15mg/weekly in 3 divided oral doses at 12 hours intervals was used with concomitant folic acid 5mg/day.

Calcium carbonate supplementation (caltrate 600mg tablet) was initiated with MTX in both subgroup of low calcium level (subgroup A1) and those with normal calcium level (subgroup B1).

Then all sub-groups followed-up regularly at, 0, 4, 8, 12, 16 weeks by two investigators independently, to assess the efficacy of methotrexate therapy or any side-effects or complications associated with it.

All tests were conducted in central laboratory of sulaimaniyah. Considering available kits, normal total serum calcium (tca^{2+}) was 8.6-10.5mg/dl and for ionized calcium (ica^{2+}) was 1.13-1.31mmol/L .

Laboratory investigations were done for all patients before starting treatment as a base line, like serum calcium level (total and ionizing), complete blood count with platelet, liver function test, blood urea nitrogen level, creatinine level, viral serology tests. Then patients monitored for methotrexate effect by follow-up the patient investigations weekly for first month then every 4 weeks. Investigations were done by Biolis 24i, premium, Tokyo Boeki Medical system equipment and serum calcium level measured by calcium CPC method (BIOLABO SAS, Les Hautes Rives 02160, Maizy, France) reagent.

The data were collected and analyzed using the statistical package for social sciences (SPSS) version 18. Continuous variables were expressed as mean ± SD and analyzed statistically using t-test, while qualitative (categorical) variables were expressed as frequencies and analyzed using chi-square test, and the level of statistical significance was set at p-value less than 0.05. Microsoft office Excel was applied for plotting graphs and charts.

The proposal of this study including the questionnaire was approved by Scientific Committee of Kurdistan board of medical specialties and the confidentiality of information were maintained and informed written consent of study participants was obtained before involving them in the study .

Results:

In this study the range of age for patients in group A1 was (20-60) years and mean of age was 44.87±14.5 and in group A2 range of age was (23- 58) years and mean of age was (43.35±10.2) . The mean duration of disease from onset of the disease in group A1 was (9.85±6.98) years and in group A2 was (7.05±4.286). The mean total serum calcium in A1 was (6.76±1.26) mg/dl and in group A2 was (7.015±0.86). The mean ionizing calcium was (0.8855±0.219) in group A1 and was (0.8965±o.172) mmol/dl in group A2. No significant differences were observed regarding age, duration of disease, total serum calcium and ionized calcium levels ($p > 0.05$). Group A baseline demographics, laboratory calcium levels are presented in Table 1.

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Table1. **Patients (with low calcium level) baseline demographics, laboratory characteristic**.

	Groups	n	Mean ±SD	P-Value
AGE*	A1-combination therapy	20	44.8±14.5	0.361
	A2 - MTX only	20	43.3±10.2	
Disease-duration**	A1- combination therapy	20	9.8±6.98	0.135
	A2- MTX only	20	7.05±4.28	
Calcium*** (tCa^{2+})	A1- combination therapy	20	6.76±1.26	0.461
	A2- MTX only	20	7.01±0.87	
Calcium**** (iCa^{2+})	A1- Combination therapy	20	0.88±0.219	0.861
	A2- MTX only	20	0.89±0.172	

*Mean age is given in years, **Disease duration in years, ***tCa^{2+} in mg/dl, ****iCa^{2+} in mmol/L, and mean ±standard deviation, Combination therapy (calcium supplementation+ MTX).

In group A1 (9 patients 45% were male and 11 patients 55% were female) and in group A2 (7 patients 35% were male and 13 patients 65% were female).

In this study the range of age for patients in group B1 was (19-56) years and mean of age was (45.30±10.7) and in group B2 range of age was (22- 58) years and mean of age was (42.25±8.515). The mean duration of disease from onset of the disease in group B1 was (9.15±5.77) years and in group B2 was (10.20±6.542). The mean total serum calcium in B1 was (9.16±0.45) mg/dl and in group B2 was (9.010±0.374). The mean ionizing calcium was (1.247±0.046) in group B1 and was (1.251±0.047) mmol/dl in group B2. No significant differences were observed regarding age, duration of disease, total serum calcium and ionized calcium levels ($p > 0.05$).

Group B baseline demographics, laboratory calcium levels are presented in Table 2.

Table2. Patients (with normal calcium level) baseline demographics, laboratory characteristic.

	Groups	n	Mean ±SD	P-Value
AGE*	B1-Combination therapy	20	45.3±10.75	0.326
	B2-MTX only	20	42.25±8.51	
Disease-duration**	B1- Combination therapy	20	9.15±5.77	0.594
	B2- MTX only	20	10.20±6.54	

tCa^{2+***}	B1- Combination therapy	20	9.16±0.45	0.264
	B2- MTX only	20	9.01±0.37	
iCa^{2+****}	B1- Combination therapy	20	1.24±0.0468	0.790
	B2- MTX only	20	1.25±0.0474	

Groups	**n**	**Mean of difference(PASI before- PASI after)%**	**SD**	**P**
A1 (Low Ca^{2+}-Rx. Ca^{2+} + MTX)*	**20**	**34.350%**	**14.195**	**0.033**
A2 (Low Ca^{2+}-Rx. MTX)*	**20**	**25.050%**	**12.352**	
B1 (Normal Ca^{2+}-Rx. by Ca^{2+} + MTX)*	**20**	**58.150%**	**20.854**	**< 0.001**
B2 (Normal Ca^{2+}-Rx. by MTX)*	**20**	**34.450%**	**16.220**	

*Mean age is given in years, ** Disease duration in years, ***tCa^{2+} in mg/dl, **** iCa^{2+} in mmol/L, and mean ±standard deviation

In group B1 (7 patients 35% were male and 13 patients 65% were female) and in group B2(7 patients 35% were male and 13 patients 65% were female).

Table3.Effect of calcium administration on the mean of PASI (before and after treatment difference).

*sub-group A1 and B1 treated by calcium supplementation +MTX, A2 and B2 by MTX only.

The mean difference in percentage of PASI (before and after treatment) was (58.150%) in groupB1 which was significantly higher than the mean of difference (34.450%) of group B2 ($p < 0.001$). Same for groups A1 and A2 ($p=0.033$), Also the mean of difference in PASI between subgroups (A1 (low Ca^{2+}), & B1 (normal Ca^{2+}) were (34.35%, 58.15% respectively, $P< 0.001$) indicating that calcium supplementation lead to better improvement of psoriasis among patients with normal calcium level. Table (3) shows that.

At week 16, in the combinational therapy subgroup A1, 10 patients out of 20 (50%) achieved PASI50, 6 patients (30%) achieved PASI75 and 4 out of 20 (20%) reached PASI90 but in the combination therapy subgroup B1, 5 patients out of 20 (25%) achieved PASI50, 9 patients (45%) achieved PASI75 and 6 out of 20 (30%)

reached PASI90. In the mono-therapy subgroup A2, 17 patients out of 20 (85%) showed improvement in the range of 30-40% (PASI< 50) and Only 3 out of 20 (15%) patients achieved PASI50 but in mono-therapy subgroup B2, 14 patients out of 20 (70%) showed improvement in the range of 35-40% and 6 patients (30%) reached PASI50.Table4.

Table4.**Percentage of patients effectively cleared off psoriasis and change in PASI score**.

Groups	PASI*< 50	PASI50	PASI75	PASI90
A1 (Low Ca^{2+}-Rx. Ca^{2+} + MTX)**	0	10 50%	6 30%	4 20%
A2 (Low Ca^{2+}-Rx.MTX)***	17 85%	3 15%	0	0
B1 (Normal Ca^{2+}-Rx. by Ca^{2+} + MTX)**	0	5 25%	9 45%	6 30%
B2 (Normal Ca^{2+}-Rx. by MTX)***	14 70%	6 30%	0	0

*PASI: Psoriasis area severity index, ** combination therapy, *** mono-therapy.

Representative image of psoriatic patients showing recovery following treatment with MTX and calcium supplementation vs. MTX alone is shown in Fig. 1-4.

Figure1. Show recovery in psoriatic erythroderma (normal Ca^{2+} level) following calcium supplementation in combination with MTX, (look to clearance at 4 weeks).

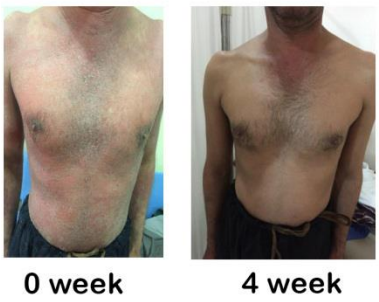


Figure2. Show recovery in plaque psoriasis (normal Ca^{2+}) following treatment by MTX only. Mild scaling and post inflammatory hyperpigmentation remain.

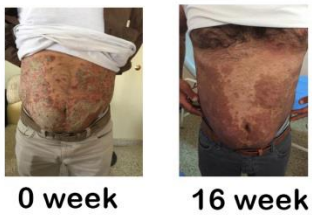


Figure3. Show recovery in pustule psoriasis (low Ca^{2+} level) following calcium supplementation in combination with MTX.(look to erythema and scaling at 4 weeks and clearance at 16weeks).

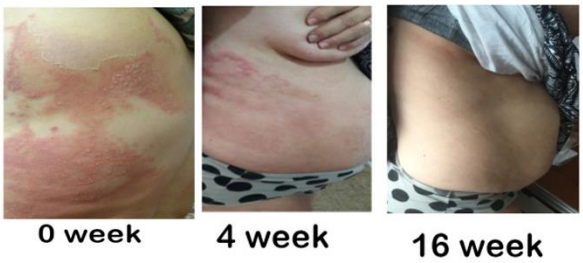
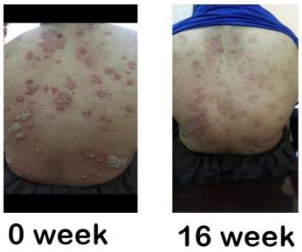


Figure4.Show recovery in severe plaque psoriasis (low Ca^{2+} level) following treatment by MTX only. Erythema and multiple small plaques with scale remain after 16 weeks treatment



DISCUSSION:

Psoriasis is a hyper-proliferative cutaneous disease of multifactorial etiologies, the exact pathogenesis of psoriasis has remained unclear, but some factors are known to trigger, participate or aggravate the disease process. Hypocalcaemia is responsible for triggering and aggravation of psoriasis.[17]

Calcium within the cell plays an important role in the regulation of proliferation and differentiation of keratinocytes. Calcium homeostasis may be involved in the development or exacerbation of psoriasis because hypocalcaemia may damage cell adhesion molecules, such as cadherins which were dependent on calcium.[18]

We used a novel combination treatment modality using MTX and calcium carbonate supplementation through oral route. Our result is in agreement with the results of recent study in Italy[20], which showed a safety and efficacy of calcium folinate in psoriasis, also reduction in the PASI score in the group treated by calcium folinate, but they did not use calcium supplementation in combination with MTX, and they not estimate pre-treatment calcium status .

Our result fully agreed with previous reports in Iran [6] and china[16] provide further evidence that calcium status has to be taken into consideration, when studying severity of psoriasis and giving MTX, but they were use different design, route of administration and sample size of the study, also they did not use calcium supplementation in combination with MTX.

Our findings are consistent with several interesting observations about psoriasis treatment and raise several important observations .

The first is the synergistic action of calcium and MTX in psoriasis treatment. Our study showed that the combination of calcium supplementation orally and MTX resulted in faster reduction in PASI score and a reduction of the MTX dosage needed for a satisfactory response. In our study, greater percentage of patients treated with MTX (15mg/week) and calcium supplementation accomplished study endpoint of PASI 75 at week 16 compared to MTX alone. Clinical data from trials suggest that patients achieved 50-60% improvement in mean PASI at week 16-24 at a dosage of 15-19mg MTX weekly.[19] However, patients may become resistant to MTX over time and increase in dosage can have serious side-effects .

The second observation is that whenever pretreatment serum calcium level is normal the efficacy of MTX will be better and when we used calcium supplementation in combination with MTX, we observed fast response and remarkable reduction in PASI score in compare to mono-therapy with MTX alone .

Our results comparable with the result in the study of Italy, It has been shown that MTX combined with calcium folinate could protect against the side effects of MTX, also enhance the effects of MTX in psoriasis treatment.[16, 20] So that calcium supplementation could enhance efficacy of MTX in directing and accelerating process either through synergistic or additive mechanism.

Conclusion:

In our study, calcium supplementation in combination with MTX improve the PASI score remarkably in severe psoriasis patients, in both groups of normal and low calcium, also decreasing time for clearance and a reduction of the MTX dosage needed for a satisfactory result, but with better response in those with normal level, so it is means calcium increase the efficacy of MTX. Combination treatment of calcium supplementation with MTX was well tolerated by all patients without any serious adverse events.

Limitation: one limitation of our study is the relatively small sample size.

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