Does Short-Term Low-Dose Methotrexate Treatment Affect Homocysteine Blood Level in Patients with Psoriasis?

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Received: May 24, 2009
Accepted: July 24, 2009

Abstract

Background: An elevated homocysteine level is an independent risk factor for cardiovascular disorders. Psoriatic patients have an increased risk of cardiovascular diseases; In addition, hyperhomocysteinemia is a complication of methotrexate treatment. We undertook a study to evaluate the plasma levels of homocysteine, vitamin B12 and folate in patients with psoriasis before and after short-term low-dose methotrexate treatment.

Methods: Twenty six patients with psoriasis were recruited. The plasma levels of homocysteine, vitamin B12 and folate were evaluated before and 8 weeks after methotrexate therapy (in the peak of methotrexate effect).

Results: No significant difference was found between the plasma profile of homocysteine, vitamin B12 and folate before and after methotrexate treatment.

Conclusion: In the short-term treatment of psoriasis, methotrexate does not increase homocysteine level. *(Iran J Dermatol 2009;12: 9-12)*

Keywords: homocysteine, methotrexate, psoriasis

Introduction

Previous studies have provided strong evidence that homocysteine is an independent risk factor for atherosclerotic disorders including cardiovascular diseases.[1] Homocysteine is thought to promote atherosclerosis by damaging endothelial cells, stimulating smooth muscle cell proliferation in the lamina of vessel walls, increasing low-density lipoprotein (LDL) oxidation, decreasing flexibility of blood vessels, reducing blood flow, and also formation of blood clots.[1, 2, 3, 4]

Different genetic and acquired factors may lead to an elevated homocysteine level. Acquired factors are more common than genetic disorders, and include vitamin B12, B6 and folate deficiency, smoking, coffee and alcohol consumption and some drugs (methotrexate, phenytoin, carbamazepine and many more).[1]

Psoriasis is an inflammatory chronic disease with a higher prevalence of cardiovascular disorders. This disease is also associated with obesity, hypertension, diabetes and dyslipidemia which lead to increased cardiovascular morbidity and mortality in these patients.[1, 5, 6]

Low dose methotrexate (MTX) therapy is used in the management of severe psoriasis. MTX is a folic acid antagonist which influences the homocysteine-methionine pathway by inhibiting the dihydrofolate reductase and decreasing the availability of the reduced folate level.[7]

In this study, we evaluated the effect of low-dose short-term methotrexate treatment on plasma homocysteine, vitamin B_{12} and folate levels in patients with psoriasis, as previous data are inconclusive

Patients and Methods

This before and after clinical trial was conducted according to the principles of the declaration of Helsinki and was approved by the Medical Ethics Review Board of the Skin Research Center of Shahid Beheshti University of Medical Sciences. A written consent was obtained from each participant.

Subject

The study group included 26 patients with psoriasis (19 males and 7 females), with a mean age of 37±17.2 years. All patients had been diagnosed clinically and histologically by a dermatologist. Severity of psoriasis was assessed according to Psoriasis Area and Severity Index (PASI). The median PASI score of the patients was 27±17.3.

Exclusion criteria

Exclusion criteria were as follows: pregnancy; breast feeding; more than 20 consumptions of alcohol per week; elevated liver transaminases (above the upper limit of normal); cytopenia; smoking more than 1 pack per week; renal failure, diabetes (FBS was checked before entering the study), other endocrine disorders and taking daily supplements containing folic acid. We also excluded patients with a history of anesthesia or consumption of drugs such as anticonvulsants, penicillin, clofibrate, penicillamine, levodopa, cyclosporine and isoniazide in the past two months. We asked all patients not to change their patterns of smoking, drinking alcohol or coffee during the study. None of the patients had taken systemic drugs for psoriasis in the past two months.

Laboratory evaluations

Blood samples were collected from patients from March 2007 to May 2008 in order to obtain whole blood, plasma and serum. None of the collected samples was icteric or haemolysed.

Two blood samples were taken in a fasting state before and 8 weeks after MTX treatment (5-7 days after the last dose of MTX).Blood samples were collected in vacutainers containing EDTA. For evaluating total homocysteine level, one sample was centrifuged immediately and plasma was stored at -200^{0}C. Total homocysteine level was measured by high performance liquid chromatography. Plasma levels of folic acid and vitamin B_{12} were measured by Electrochemiluminescence. Complete blood cell count, liver and kidney function tests and urine analysis were performed before therapy and weekly for up to 4 weeks and then monthly during the MTX therapy.

Methotrexate treatment

At the beginning of the study, all patients received an oral dose of 5-10 mg MTX per week; then, the dose was adjusted according to the patients' responses. No folate supplementation was administered. If any major complication of MTX (clinical or laboratory) was observed, the drug was discontinued.

Statistical analysis

Results are expressed as mean ±standard deviation (SD). Statistical analysis was performed using SPSS version 16. To evaluate the statistical differences between groups (before and after therapy), we used paired T-test. For assessing the correlation between PASI score and homocysteine, vitamin B12 and folate levels, we used Pearson's correlation coefficient. P-value <0.05 was considered significant.

Results

The results were analyzed in two ways to investigate the differences between blood levels of homocysteine, folate, MCV and vitamin B12 before and after therapy and on the other hand, to investigate the relationship between blood levels of these parameters and PASI score.

A total of 26 psoriatic patients including 19 males and 7 females (mean age: 37±17.2 years, age range: 17-78), were investigated in this study. Patients had moderate to severe psoriasis with a PASI ranging from 8 to 60 (median: 27±17.3).

The results are summarized in table 1. No statistically significant difference was noted in the mentioned parameters before and after therapy.

We also analyzed the values according to disease severity. No correlation was found between studied parameters and disease severity.

Discussion

Present evidence indicates that psoriasis is a chronic inflammatory and multisystemic disease which may affect other organs more than skin. Psoriasis is also associated with diabetes mellitus and rheumatoid arthritis. These associated diseases

***Table 1**: Homocysteine, folate, vitamin B12 and MCV level in patients before and after methotrexate therapy*

	Before treatment	After treatment	P-value *
Homocysteine** µmol/L	15.8±6.2	14.7±5.1	0.34
Folate** ng/mL	8.5±4.3	15.1±31.8	0.27
Vitamin B12** pmol/L	241.5±107.6	230.3±115.9	0.35
MCV** FL	84.7±5.2	85.9±5.4	0.096

*P-value <0.05 was considered significant

**Reference value: homocysteine: 5-12 µmol/L, folate: 3.1-17.5 ng/mL, vitamin B12:145-637 pmol/L, MCV: female 81-99/male 80-94 FL

are known as "oxidative stress conditions" and psoriasis as an inflammatory disorder may cause an oxidative stress condition which may lead to increased cardiovascular disorders.[8, 9]

An elevated homocysteine level is an independent risk factor for atherothrombotic vascular diseases [5]. Hyperhomocysteinemia has been reported in patients with psoriasis [1, 2, 5, 10, 11], which may be due to folate deficiency. The mechanism of the possible folate deficiency in psoriasis is still unclear. Reduced folate levels in patients with psoriasis have been reported in previous studies.[1, 5, 10, 12, 13, 14] This decreased folate level may be due to increased utilization in the hyperproliferative epidermis and/or because of the reduced absorption from the intestine [1]. Whatever the cause is, folate deficiency leads to hyperhomocysteinemia. Furthermore, Refsum et al. suggested that additional factors (other than folate deficiency) were involved in the elevation of the homocysteine level in psoriatic patients; hyperhocysteinemia in these patients may be caused by homocysteine export from the proliferating germinative cell layer.[10]

Other than folate, vitamin B_{12} deficiency has also been reported in patients with psoriasis;[5] although vitamin B_{12} influences the level of blood homocysteine, its role is less important than folate.[15]

MTX is an effective therapy in severe psoriasis. As an antineoplastic agent, this drug reduces the proliferating germinative cell layer; but on the other hand, MTX leads to hyperhomocysteinemia by influencing the homocyteine-methionine pathway.[6] As there is no previous report on the effects of MTX on folate and homocysteine levels, we performed this study to investigate the effect of methotrexate on folate and homocysteine blood levels in patients with psoriasis.

Baseline homocysteine level in our patients was more than 15μmol/L which indicated hyperhomocysteinemia in these patients. This finding was consistent with other studies;[1, 2, 5, 10] ,but vitamin B_{12} and folate baseline levels and MCV were in a normal range.

Our data showed that methotrexate therapy did not increase homocysteine level. This was in contrast to the findings of Hanrahan et al. who found a statistically significant positive association between long-term, low dose methotrexate therapy and an elevated serum homocystein level. Although in their cross-sectional study homocysteine level in patients with psoriasis on long-term MTX therapy was evaluated and compared with patients on topical or phototherapy, no comparison was performed before and after MTX therapy. Moreover, the timing of blood sampling regarding the last dose of MTX was not mentioned.[16]

The only study that mentioned the time of blood sampling accurately was performed by Refsum et al.[10] This study showed that methotrexate in patients with psoriasis induced a transient increase in the plasma level of homocysteine which returned to baseline within six days, and remained approximately constant during 8 weeks in the 2 patients who were followed in this period. No difference was observed in the homocysteine level before and eight weeks after methotrexate therapy in our study which is consistent with the findings of Refsum et al., because the second blood sample (after 8 weeks of MTX therapy) was taken 5 to 7 days after the last dose of MTX which was simultaneous with returning homocysteine to its baseline level.

There are some reports evaluating the effect of MTX on homocysteine level in other disorders. One cross-sectional case-control study performed on patients with ankylosing spondilitis (AS),[17] showed increased homocysteine levels in AS patients receiving sulfasalazine or MTX for treatment, but this study was cross-sectional and did not mentioned the time of blood sampling. In another study performed on patients with cancers, Refsum et al. reported that high dose methotrexate had acute and chronic effects on the plasma level of homocysteine; increasing the homocysteine level in the acute phase and decreasing its level, even lower than the baseline level, in the chronic phase. This decreased level may be due to leucovorin administration with each MTX dose or rapid loss of proliferative cells after high cytotoxic doses of MTX.[18] Similar to our study, Huemer et al. reported that the plasma level of homocysteine is high in juvenile idiopathic arthritis, but not influenced by methotrexate therapy.[19] Van Ede et al. reported that low-dose MTX treatment in rheumatoid arthritis patients leads to hyperhomocysteinemia[7] which may be due to the measurement of the homocysteine level 16 hours after MTX administration which is the time of maximum effect of MTX. According to Refsum et al.[18], this elevated level may return to normal after 48 hours.

There was no significant relationship between PASI score and serum levels of homocysteine, vitamin B_{12} and folate in our study which is consistent with the findings of Kural et al.[5] but in contrast to Cakmak et al.[20] The correlation between PASI score and studied parameters should be investigated in a larger study with more patients

because of two reasons: first, our cases were not sufficient for investigating this correlation and second, all our patients had severe or resistant psoriasis which made them eligible for MTX treatment.

In conclusion, this study showed that low dose/short-term MTX therapy had no effects on homocysteine, folic acid and vitamin B_{12} levels. Moreover, MTX, through reducing chronic inflammation, may reduce the risk of cardiovascular diseases. However, the relationship between methotrexate and hyperhomocysteinemia and the benefits of this drug in controlling the hyperproliferative and inflammatory state in psoriasis should be investigated in a larger study with more patients with a control group.

Acknowledgments

We would like to express our gratitude to those who helped us with this project: Dr. R.M Robati, Dr. L. Gachkar and Dr. Ahmadi as well as the staff of Day Hospital Laboratory. This study was supported by Skin Research center, Shohada-e-Tajrish hospital, Tehran, Iran.

References

1. Malebra M, Gisondi P, Radaeli A, et al. Plasma homocysteine and folate levels in patients with chronic plaque psoriasis. Br J Dermatol 2006; 155:1165-69.
2. Tobin AM, Hughes R, Leong T,et al. Homocysteine status and cardiovascular risk factors in patients with psoriasis: a case control study. Br J Dermatol 2006; 155(suppl. 1): 1-9.
3. Hoekstra M, Haagsma CJ, Doelman CJ, van de Laar MA.Intermittent rises in plasma homocysteine in patients with rheumatoid arthritis treated with higher doses methotrexate. Ann Rheum Dis 2005;64:141-3.
4. Karabudak O, Ulusoy RE, Erikci AA, Solmazgul E, Dogan B, Harmanyeri Y. Inflammation and hypercoagulable state in adult psoriatic men. Acta Derm Venereol 2008; 88:337-40.
5. Vanizor Kural B, Orem A, Cimsit G, et al. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. Clinica Chimica Acta 2003; 332:23-30.
6. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavorable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007; 190:1-9.
7. van Ede AE, Laan RF, Blom HJ, Boers GH, et al. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis.Rheumatology(oxford) 2002; 41:658-65.
8. Rocha-Pereira P, Santos-Silva A, Rebelo I, et al. Dislipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease. Clinica Chimica Acta 2001; 303:33-9.
9. Singh RB, Niaz MA. Antioxidants, oxidants and free radical stress in cardiovascular disease. J Assoc Physicians India 1996; 44:43-8.
10. Refsum H, Helland S, Ueland PM. Fasting plasma homocysteine as a sensitive parameter of antifolate effect: a study of psoriasis patients receiving low-dose methotrexate treatment. Clin Pharmacol Ther 1989; 46:510-20.
11. Gisondi P, Fantuzzi F, Malerba M, Girolomoni G. Folic acid in general medicine and dermatology. J Dermatolog Treat 2007; 18:138-46.
12. Hild DH. Folate losses from the skin in exfoliative dermatitis. Arch Intern Med 1969; 123:51-7.
13. Fry L, Macdonald A, Almeyda J, Griffin CJ, Hoffbrand AV.The mechanism of folate deficiency in psoriasis. Br J Dermatol 1971;84:539-44.
14. Touraine R, Revuz J, Zittoun J, Jarret J, Tulliez M. Study of folate in psoriasis: blood levels, intestinal absorption and cutaneous loss. Br J Dermatol 1973; 89:335-4.
15. Bunout D, Garrido A,Suazo M,et al. Effects of supplementation with folic acid and antioxidant vitamins on homocysteine levels and LDL oxidation in coronary patients. Nutrition 2000; 16:107-10.
16. Hanrahan E, Barnes L. Elevated serum homocysteine levels in patients with psoriasis receiving long-term, low-dose methotrexate therapy. Br J Dermatol 2001;145:43-6.
17. Wei JC,Jan MS,Yu CT,et al. Plasma homocysteine status in patients with ankylosing spondylitis. Clin Rheumatol 2006;26:739-42.
18. Refsum H, Ueland PM, Kvinnsland S. Acute and long-term effects of high-dose methotrexate treatment on homocysteine in plasma and urine. Cancer Res 1986; 46:5385-91.
19. Huemer M, Fodinger M, Huemer C, et al. Hyperhomocysteinemia in children with juvenile idiopathic arthritis is not influenced by methotrexate treatment and folic acid supplementation: a pilot study. Clin Exp Rheumatol 2003;21:249-55.
20. Cakmak SK, Gül U, Kılıç C, Gönül M, Soylu S, Kılıç A . Homocysteine, vitamin B (12) and folic acid levels in psoriasis patients. J Eur Acad Dermatol Venereol 2009;23:300-3.