

Evaluation of the glycemic effect of methotrexate in psoriatic arthritis patients with metabolic syndrome: A pilot study

Tannaz Dehpouri,¹
 Ghasem Rahmatpour Rokni,²
 Nematollah Ahangar Narenjbon,³
 Mohamad Goldust,²
 Paul S. Yamauchi,^{4,5} Uwe Wollina,⁶
 Torello Lotti,⁷ Leon Kircik,⁸
 Vito Giuseppe Di Lernia,⁹
 Sidharth Sonthalia,^{10,11}
 Aleksandra Vojvodic,¹²
 Jacek Szepietowski,¹³
 Philippe Bahadoran,¹⁴
 Enzo Errichetti,¹⁵ Carmen Cantisani,¹⁶
 Laura Atzori,¹⁷ Elham Rezaee,¹⁸
 Zekayi Kutlubay,¹⁹ Burhan Engin,¹⁹
 Steven Nisticò,²⁰
 Giovanni Damiani,^{21,22}
 Rosalynn R.Z. Conic,²³ Andy Goren,⁷
 Leo Čabrijan,²⁴ Georgi Tchernev²⁵

¹Student Research Committee, Mazandaran University of Medical Sciences, Ramsar International Branch, Ramsar, Iran; ²Department of Dermatology, Mazandaran University of Medical Sciences, Sari, Iran; ³Department of Pharmacology, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran; ⁴Dermatology Institute and Skin Care Center, Santa Monica, California, USA; ⁵Division of Dermatology, David Geffen School of Medicine at University of California, Los Angeles, California, USA; ⁶Department of Dermatology and Allergy, Städtisches Klinikum Dresden, Academic Teaching Hospital of the Technical University of Dresden, Dresden, Germany; ⁷Department of Dermatology, “Guglielmo Marconi” University, Rome, Italy; ⁸Icahn School of Medicine at Mount Sinai, New York, NY, USA; ⁹Dermatology Unit, Santa Maria Nuova-IRCCS Hospital, Reggio Emilia, Italy; ¹⁰SkinNocence: The Skin Clinic & Research Center, Gurugram, Haryana, India; ¹¹DermaSource India, Gurugram, Haryana, India; ¹²Department of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia; ¹³Department of Dermatology, Venereology and Allergy, Wrocław Medical University, Wrocław, Poland; ¹⁴Department of Dermatology,

University Hospital of Nice, Nice, France; ¹⁵Department of Experimental and Clinical Medicine, Institute of Dermatology, University of Udine, Udine, Italy; ¹⁶Department of Dermatology, “Umberto I” Hospital, “Sapienza” University of Rome, Rome, Italy; ¹⁷Dermatology Clinic, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; ¹⁸Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran; ¹⁹Department of Dermatology, Cerrahpasa Faculty of Medicine, University of Istanbul, Istanbul, Turkey; ²⁰Department of Health Sciences, “Magna Graecia” University of Catanzaro, Catanzaro, Italy; ²¹Department of Medical and Surgical Pathophysiology and Transplantation, University of Milan, Dermatology Unit, IRCCS Ca’ Granda Foundation, Ospedale Maggiore Policlinico, Milan, Italy; ²²Young Dermatologists Italian Network (YDIN), Centro Studi GISED, Bergamo, Italy; ²³Department of Dermatology, Case Western Reserve University, Cleveland, OH, USA; ²⁴Department of Dermatovenereology, Rijeka Clinical Hospital Center, Rijeka, Croatia; ²⁵Medical Institute of Ministry of Interior (MVR), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria

Correspondence: Ghasem Rahmatpour Rokni, Department of Dermatology, Mazandaran University of Medical Sciences, Sari, Iran. Tel.: +989125443956 - Fax: +981133261248. E-mail: Dr.rokni@yahoo.com

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in both genders (men: P=0.131, women: P=0.803). In addition, HbA1c levels in PsA patients with metabolic syndrome were not different before and after treatment (P=0.250). Finally, HbA1c levels did not change in PsA patients without metabolic syndrome before and after therapy (P=0.506). MTX in PsA patients does not appear to have hyperglycaemic effects in the short-term and can be safely used in patients with metabolic syndrome and diabetes.

Abstract

Methotrexate (MTX) is a systemic immunosuppressant drug used for the treatment of psoriasis and psoriatic arthritis. Previous studies demonstrated a potential association between psoriasis and diabetes mellitus, obesity, atherosclerosis, hypertension, eventuating into metabolic syndrome. This study aimed at exploring the glycemic effects of MTX in psoriatic arthritis (PsA) patients. In this prospective cross-sectional study, 27 patients with PsA were evaluated. The status of PsA and presence of accompanying metabolic syndrome was determined by standard criteria and indices. Blood indicators including HbA1c, erythrocyte sedimentation rate, fasting blood sugar, total cholesterol, high-density lipoprotein, triglycerides, and C-reactive protein were examined before and 12 weeks after MTX therapy. There were no significant changes between HbA1c levels before and after MTX therapy

Introduction

Psoriasis (PsO) is defined as a systemic, inflammatory dermatologic disease which affects approximately 2-3% of the global population.^{1,2} Furthermore, psoriatic arthritis (PsA) can develop in 7-48% of all PsO subjects.^{3,4} Patients with PsO and/or PsA are at a higher risk for development of other chronic pathologic diseases, which can complicate the management of these patients.⁵⁻⁷ Previous studies have proved that metabolic syndrome is related to a state of chronic low-grade inflammation.^{8,9} The underlying mechanism is partially unknown, but a group of cytokines, including tumor necrosis factor- α (TNF- α), have been evidenced to reduce the activity of insulin, contributing to insulin resistance.⁹⁻¹¹ Unfortunately, there is limited data on association between metabolic syndrome and rheumatological disorders, even though a

few studies have reported an increased incidence of metabolic syndrome in patients with rheumatologic disease.¹²⁻¹⁴ Besides, a few previous studies have indicated that there is an association between the metabolic syndrome and PsO.^{15,16} Additionally, epidemiological evidence has proposed that systemic anti-inflammatory therapy might be helpful to decrease the risk of cardiovascular disease (CVD) in patients suffering from psoriasis.^{17,18} Methotrexate (MTX) is an anti-rheumatic drug with its cytotoxic, anti-inflammatory and immune modulatory activities often used in psoriasis treatment. However, despite its use for the last 60 years, a close evaluation of its adverse effects and related risk factors has not been performed.¹⁹ In spite of growing concerns about cumulative toxicity, there are no detailed data for complications associated with an increased cumulative dose of MTX.²⁰ Studies have demonstrated significant reductions in CVD-related mortality in patients treated with methotrexate.²¹ This finding has been attributed to the potent anti-inflammatory properties of methotrexate.^{21,22} The aim of this study was to explore the effects of short-term methotrexate therapy on the blood levels of glucose and HbA1c in patients having psoriasis.

Materials and Methods

Subjects

In this multicenter cross-sectional study, 27 patients (aged 30-60 years) with PsA from February 2016 to February 2018 were enrolled. The evaluation subjects included the evidence of lifestyle factors including smoking behavior, medical history, taking medications, presence of diabetes

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Blood analysis

Following serum sampling, they were kept at -80°C until further processing. The HbA1c and erythrocyte sedimentation rate were primarily measured. Also, the serum concentrations of fasting blood sugar (FBS), total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides and C-reactive protein were measured using an automated analyzer (Model 912, Hitachi, Japan). All these parameters were examined before and after 12 weeks of treatment with methotrexate.

Statistical analysis

Data was expressed as mean \pm standard deviation (SD). Statistical analysis was conducted using SPSS version 18 (SPSS, Inc, Chicago, IL, USA). Differences were evaluated with the paired t test and chi-square test. The normality of data was checked using the one-sample Kolmogorov-Smirnov Test. The significant level of differences was set at 0.05.

Results

Inclusion criteria were met by 35 patients. Among these, 27 patients continued the study with the mean age of 43.22 \pm 8.9. Nine (33.33%) patients were female and 18 (66.66%) were male. Demographic data and clinical features of patients before and after treatment are shown in Table 1. Hyperlipidemia was present in 7 (25.93%) patients at baseline for

Inclusion and exclusion criteria

In this study, PsA was diagnosed and confirmed by expert rheumatologists based on the CASPAR.²⁸ Subjects with other inflammatory rheumatic diseases, myocardial infarction (MI), stroke, hyperglycaemic status different from diabetes mellitus type 2 *e.g.* hyperthyroidism and hyperglycaemic, renal insufficiency, lung or liver

Table 1. Demographic and clinical features of the study patients.

Variation	Patients with PsA before treatment n=27	Patients with PsA after treatment n=27	P value
Age (years)	43.22 \pm 8.9	-	-
Gender			
Men N (%)	18 (66.7)	-	-
Women N (%)	9 (33.3)	-	-
History of diabetes N (%)	2 (10.0)	-	-
History of stroke N (%)	10 (35.0)	-	-
History of Hyperlipidemia N (%)	7 (20.0)	-	-
FBS (mg/dL)	103.2 \pm 30.2	101.3 \pm 22.8	0.624
Total cholesterol (mg/dL)	165.7 \pm 26.9	166.5 \pm 33.2	0.881
HDL (mg/dL)	39.6 \pm 7.7	42.8 \pm 6.2	0.005
LDL (mg/dL)	98.7 \pm 22.7	104.6 \pm 22.7	0.059
CRP	100% negative	100% negative	0.21
ESR (mm/hour)	24.2 \pm 17.9	23.5 \pm 17.6	0.722

PsA, psoriatic arthritis patients; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

which 5 (18.52%) patients were using medications. Family history of stroke was present in 10 (37%) patients. In this study, 7 (25.93%) patients had a normal weight, 10 (37%) patients were overweight, and the other 10 patients were obese. HbA1c test was taken before and after using methotrexate. At baseline, 2 (7.41%) patients had diabetes while the rest were negative. There were no significant differences between HbA1c levels among genders before and after treatment with methotrexate (men: $P=0.131$, women: $P=0.803$) (Figure 1). According to the NCEP, 20 (74.04%) patients had the signs of metabolic syndrome while the other 7 (25.93%) did not. However, according to IDF, 19 (70.37%) patients showed the signs of metabolic syndrome and 8 (29.63%) patients didn't. Furthermore, based on the NCEP index, HbA1c levels in PsA patients with metabolic syndrome were $5.7\pm 0.9\%$ before and $5.9\pm 0.9\%$ after methotrexate therapy ($P=0.250$). However, HbA1c levels in PsA patients without metabolic syndrome were $5.6\pm 0.4\%$ and $5.7\pm 0.5\%$ before and after methotrexate therapy respectively ($P=0.506$) (Figure 2).

Discussion

Several studies have proposed that

patients with PsA are at increased risk of CVD, obesity, diabetes and fatty liver disease.²⁹⁻³¹ Additionally, previous reports have indicated that HbA1c as the primary screening tool for glucose intolerance and the major predictive factor for cardiovascular events.^{32,33} In the present study, we prospectively examined the influence of short-term anti-psoriatic therapy with methotrexate on HbA1c. The findings showed that there was no significant alteration in the HbA1c levels after 12 weeks of continuous treatment. Previously, deRotte and Perdan-Pirkmajer *et al.* demonstrated that MTX reduced HbA1c concentrations in patients with RA or PsA.^{33,34} However, in a retrospective cohort study, Wu *et al.* showed that PsO, PsA, and RA patients under treatment with TNF inhibitors associated with MTX displayed no significant differences in terms of the HbA1c level.³⁵ Solomon *et al.* reported that there is a non-significantly lower risk of incident diabetes mellitus within patients suffering from PsA, PsO, or RA who were treated with methotrexate without tumor necrosis factor inhibitors or hydroxychloroquine. Nonetheless, in contrast to our study, Solomon *et al.* did not determine levels of HbA1c and FBS in their research.³⁶ Furthermore, Gisondi *et al.* conducted a survey of two groups of psoriasis patients who were newly treated with methotrexate and demonstrated that there was no detected changes in the FBS level.³⁷ In a 24-week

retrospective study comparing TNF inhibitor, efalizumab, and methotrexate there was no significant alterations in FBS in any of the groups.³⁸ Cuchacovich *et al.* examined 37 patients with RA treated with methotrexate (mean 34.7 months), and found no significant changes have been in FBS.³⁹ All these reports are consistent with the results of our study. It appears that the administration of methotrexate for treatment of PsA does not have hyperglycaemic effects and thus it can be used in PsA patients with metabolic syndrome and diabetes. Moreover, the most important part of controlling the chronic disorders is following a healthy lifestyle along with proper medication. In addition, regular screening of diabetes by monitoring BMI, FBS levels, blood pressure and cholesterol levels may help early detection and management of new-onset diabetes in PsA patients being treated with methotrexate.

Conclusions

To conclude, the use of methotrexate was not related to a significant alteration in HbA1c or FBS levels in patients with PsA. According to the data obtained in this study, methotrexate can be used in the treatment of PsA patients without the risk of developing diabetes.

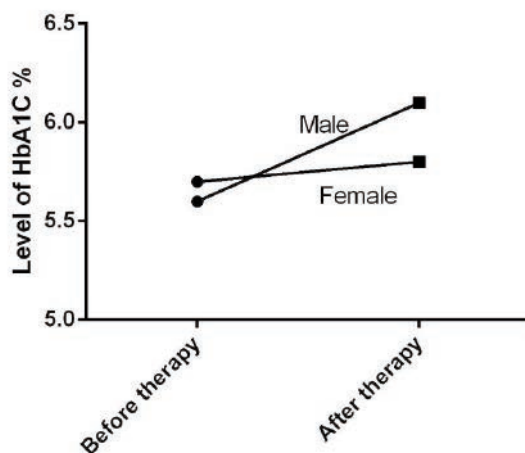


Figure 1. The level of HbA1c based on the gender of psoriatic arthritis patients. The results are presented as mean \pm SEM. Statistically significant differences between control and patients ($P<0.05$).

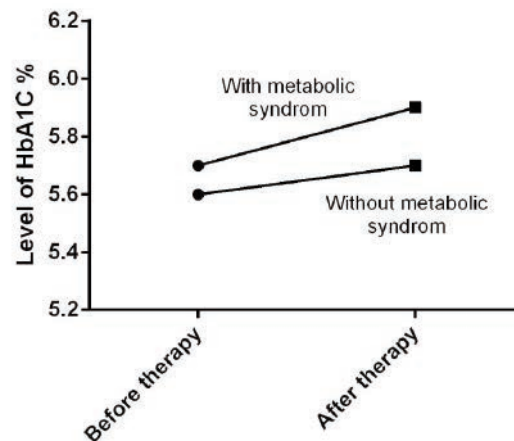


Figure 2. The level of HbA1c based on the National Cholesterol Education Program Adult Panel index in psoriatic arthritis patients with and without metabolic syndrome. Results are presented as mean \pm SEM. Statistically significant differences between control and patients ($P<0.05$).

References

1. Puig L, Strohal R, Husni ME, et al. Cardiometabolic profile, clinical features, quality of life and treatment outcomes in patients with moderate-to-severe psoriasis and psoriatic arthritis. *J Dermatol Treat* 2015;26:7-15.
2. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol* 2012;26:3-11.
3. Sommer DM, Jenisch S, Suchan M, et al. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Archiv Dermatol Res* 2007;298:321.
4. Channul J, Wu JJ, Dann FJ. Effects of tumor necrosis factor- α blockade on metabolic syndrome components in psoriasis and psoriatic arthritis and additional lessons learned from rheumatoid arthritis. *Dermatol Ther* 2009;22:61-73.
5. Gladman DD. Psoriatic arthritis from Wright's era until today. *J Rheumatol Suppl* 2009;83:4-8.
6. Ahlehoff O, Gislason GH, Charlot M, et al. Psoriasis is associated with clinically significant cardiovascular risk: A Danish nationwide cohort study. *J Intern Med* 2011;270:147-57.
7. Kwon O, Kang SJ, Kang SH, et al. Relationship between serum inflammatory marker levels and the dynamic changes in coronary plaque characteristics after statin therapy. *Circ Cardiovasc Imaging* 2017;10:e005934.
8. Boscarino JA. PTSD is a risk factor for cardiovascular disease: Time for increased screening and clinical intervention. *Prevent Med* 2013;166:806-14.
9. Jialal I. The role of the laboratory in the diagnosis of the metabolic syndrome. *Am J Clin Pathol* 2009;132:161-2.
10. Ruan H, Lodish HF. Insulin resistance in adipose tissue: direct and indirect effects of tumor necrosis factor- α . *Cytokine Growth Factor Rev* 2003;14:447-55.
11. Chandalia M, Cabo-Chan Jr AV, Devaraj S, et al. Elevated plasma high-sensitivity C-reactive protein concentrations in Asian Indians living in the United States. *J Clin Endocrinol Metabol* 2003;88:377.
12. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. *Circulation* 2005;112:2735-52.
13. Johnson LW, Weinstock RS. The metabolic syndrome: concepts and controversy. *Mayo Clinic Proceed* 2006;81:1615-20.
14. Pereira RMR, de Carvalho JF, Bonfá E. Metabolic syndrome in rheumatological diseases. *Autoimmun Revi* 2009;8:415-9.
15. Love TJ, Qureshi AA, Karlson EW, et al. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003-2006. *Archiv Dermatol* 2011;147:419-24.
16. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. *J Am Acad Dermatol* 2013;68:654-62.
17. Ahlehoff O, Skov L, Gislason G, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. *J Intern Med* 2013;273:197-204.
18. Prodanowich S, Ma F, Taylor JR, et al. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005;52:262-7.
19. Nicola PJ, Maradit-Kremers H, Roger VL, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. *Arthritis Rheum* 2005;52:412-2.
20. Borja F, Jury EC, Mauri C, Ehrenstein MR. Defects in CTLA-4 are associated with abnormal regulatory T cell function in rheumatoid arthritis. *Proceed Nation Acad Sci* 2008;105:19396-401.
21. Choi HK, Hernán MA, Seegar JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173-7.
22. Dessein PH, Joffe BI, Stanwix AE. Effects of disease modifying agents and dietary intervention on insulin resistance and dyslipidemia in inflammatory arthritis – a pilot study. *Arthritis Res* 2002;4:12-8.
23. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286-91.
24. Prevoo M, Van't Hof M, Kuper H, et al. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheumatol* 1995;38:44-8.
25. Marra CA, Woolcott JC, Kopec JA, et al. A Comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. *Soc Sci Med* 2005;60:1571-82.
26. Targher G, Bertolini L, Tessari R, et al. The International Diabetes Federation definition of the metabolic syndrome independently predicts future cardiovascular events in Type 2 diabetic patients. The Valpolicella Heart Diabetes Study. *Diabetic Med* 2006;23:1270-1.
27. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
28. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheumat* 2006;54:2665-73.
29. Cohen AD, Gilutz H, Henkin Y, et al. Psoriasis and the metabolic syndrome. *Acta Dermato-venereol* 2007;87:506-9.
30. Johansson H, McInnes Lb, Sattar N, Cardiovascular and metabolic risks in psoriasis and psoriatic arthritis: pragmatic clinical management based on available evidence. *Ann Rheum Dis* 2012;71:480-3.
31. Chin YY, Yu HS, Li WC, et al. Arthritis as an important determinant for psoriatic patients to develop severe vascular events in Taiwan: a nation-wide study. *J Eur Acad Dermatol Venereol* 2013;27:1262-8.
32. Khaw K-T, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk Cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 2001;322:15.
33. de Rotte MC, de Jong PH, den Boer E, et al. Effect of methotrexate use and erythrocyte methotrexate polyglutamate on glycosylated hemoglobin in rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:2026-36.
34. Perdan-Pirkmajer K, Pirkmajer S, Thevis M, et al. Methotrexate reduces HbA1c concentration but does not produce chronic accumulation of ZMP in patients with rheumatoid or psoriatic arthritis. *Scand J Rheumatol* 2016;45:347-55.
35. Wu JJ, Rowan CG, Bebcuk JD, Anthony MS. No Association between TNF inhibitor and methotrexate therapy

- versus methotrexate in changes in hemoglobin A1C and fasting glucose among psoriasis, psoriatic arthritis, and rheumatoid arthritis patients. *J Drugs Dermatol* 2015;14:159-66.
36. Solomon DH, Massarotti E, Garg R, et al. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* 2011;305:2525-31.
37. Gisondi P, Cotena C, Tessari G, Girolomoni G. Anti-tumour necrosis factor- α therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2008;22:341-4.
38. Saraceno R, Schipani C, Mazzotta A, et al. Effect of anti-tumor necrosis factor- α therapies on body mass index in patients with psoriasis. *Pharmacol Res* 2008;57:290-5.
39. Cuchacovich R, Espinoza LR. Does TNF-alpha blockade play any role in cardiovascular risk among rheumatoid arthritis (RA) patients? *Clin Rheumatol* 2009;28:1217-20.