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

Tannaz Dehpouri,1 Ghasehm Rahmatpour Rokni,2 Nematollah Ahangar Narenjbon,3 Mohamad Goldust,1 Paul S. Yamauchi,4,5 Uwe Wollina,6 Torell 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 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

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; 5Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 6Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 7Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 8Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 9Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 10Skinnocence: The Skin Clinic & Research Center, Gurugram, Haryana, India; 11Dermasource India, Gurugram, Haryana, India; 12Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital of the Technical University of Dresden, Dresden, Germany; 13Department of Dermatology, “Guglielmo Marconi” University, Rome, Italy; 14Ichak School of Medicine at Mount Sinaï, New York, NY, USA; 15Dermatology Unit, Santa Maria Nuova-IRCCS Hospital, Reggio Emilia, Italy; 16Skinonecence: The Skin Clinic & Research Center, Gurugram, Haryana, India; 17Dermasource India, Gurugram, Haryana, India; 18Department of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia; 19Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; 20Department of Dermatology, University Hospital of Nice, Nice, France; 21Department of Experimental and Clinical Medicine, Institute of Dermatology, University of Udine, Udine, Italy; 22Department of Dermatology, “Umberto I” Hospital, “Sapienza” University of Rome, Rome, Italy; 23Dermatology Clinic, Department Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy; 24Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran; 25Department of Dermatology, Cerrahpasa Faculty of Medicine, University of Istanbul, Istanbul, Turkey; 26Department of Health Sciences, “Magn Graecia” University of Catanzaro, Catanzaro, Italy; 27Department of Medical and Surgical Pathophysiology and Transplantation, University of Milan, Dermatology Unit, IRCCS Ca’ Granda Foundation, Ospedale Maggiore Policlinico, Milan, Italy; 28Young Dermatologists Italian Network (YDIN), Centro Studi GISED, Bergamo, Italy; 29Department of Dermatology, Case Western Reserve University, Cleveland, OH, USA; 30Department of Dermatovenerology, Rijeka Clinical Hospital Center, Rijeka, Croatia; 31Medical Institute of Ministry of Interior (MVR), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria

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 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.

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.10-11 Unfortunately, there is limited data on association between metabolic syndrome and rheumatological disorders, even though a
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 mellitus, hypertension, duration of disease, comorbidities, and clinical examinations which were obtained to discover the presence of PsA. Also, physical examination included recording the number of tender and swollen joints. To confirm the suspect of PsA we also performed joints radiogram and enthesis sonography. The diagnosis of PsA was established by standard criteria for psoriatic arthritis (CASPAR) with a score >3 points. Additionally, other parameters such as weight, height and waist circumference, body mass index (BMI) (kg/m²) and blood pressure were also measured. The status of PsA was determined by the following standard indexes: the Bath Ankylosing Spondylitis Disease Activity Index, Disease Activity Score 28 (DAS 28) and the health assessment questionnaire. Furthermore, metabolic syndrome was determined via the International Diabetes Federation (IDF) 2004 and the National Cholesterol Education Program Adult Panel III (NCEP ATP III) (NCEP ATP III) 2001. All patients were treated with oral methotrexate (7.5 mg/kg) weekly for three months. Before the collection of samples a written informed consent was obtained from each participant and ethical approval was granted by the ethics committee of the Mazandaran University of Medical Sciences, Pardis Unit, Ramsar, Iran.

Inclusion and exclusion criteria

In this study, PsA was diagnosed and confirmed by expert rheumatologists based on the CASPAR. Subjects with other inflammatory rheumatic diseases, myocardial infarction (MI), stroke, hyperglycemic status different from diabetes mellitus type 2 e.g. hyperthyroidism and hyperglicaeimc, renal insufficiency, lung or liver or retroperitoneal fibrosis as well as patients who took anti-inflammatory drugs (NSAIDs or corticosteroids) were excluded from the study.

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 ± 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±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

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±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±30.2                             | 101.3±22.8                             | 0.024   |
| Total cholesterol (mg/dL)        | 165.7±26.9                             | 166.5±33.2                             | 0.881   |
| HDL (mg/dL)                      | 39.6±7.7                               | 42.8±6.2                               | 0.005   |
| LDL (mg/dL)                      | 98.7±22.7                              | 104.6±22.7                             | 0.059   |
| CRP                              | 100% negative                          | 100% negative                          | 0.21    |
| ESR (mm/hour)                    | 24.2±17.9                              | 23.5±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±0.9% before and 5.9±0.9% after methotrexate therapy (P=0.250). However, HbA1c levels in PsA patients without metabolic syndrome were 5.6±0.4 % and 5.7±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. Additionally, previous reports have indicated that HbA1c as the primary screening tool for glucose intolerance and the major predictive factor for cardiovascular events. 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.

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.
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. Arch Dermatol Res 2007;298:321.
4. Channaul 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, Charlton 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 biomarker levels and the dynamic changes in coronary plaque characteristics after statin therapy. Circ Cardiovasc Imaging 2017;10:e005934.
8. Boscarno 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 Metab 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 Proc 2006;81:1615-20.
14. Pereira RMR, de Carvalho JF, Bonfá E. Metabolic syndrome in rheumatological diseases. Autoimmun Rev 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. Cardiometabolic 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. Prodanovich 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 systemic anti-inflammatory drugs: implications for the utility measures (the HUl2,HUl3, SF-6D , and the EQ-5D) and disease-specific instruments (the RAOQoL and the HAQ) in rheumatoid arthritis. Soc Sci Med 2005;60:1571-82.
21. Tarigher 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.
22. 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.
23. Taylor W, Gladman D, Hellwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheumat 2006;54:2665-73.
24. Cohen AD, Giltutz H, Henkin Y, et al. Psoriasis and the metabolic syndrome. Acta Dermato-venereol 2007;87:506-9.
25. Johansson H, Mclnnes Lb, Sattar N, et al. Cardiovascular and metabolic risks in psoriasis and psoriatic arthritis: pragmatic clinical management based on available evidence. Ann Rheum Dis 2012;71:480-3.
26. 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.
27. 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.
28. 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.
29. Perdan-Pirkmajer K, Pirkmajer S, Pirkmajer K, Pirkmajer S, et al. Prevalence of the metabolic syndrome in patients with moderate to severe psoriasis treated with systemic anti-inflammatory drugs: A Danish real-world cohort study. J Intern Med 2013;270:147-57.
30. Johansson H, Mclnnes Lb, Sattar N, et al. Cardiovascular and metabolic risks in psoriasis and psoriatic arthritis: pragmatic clinical management based on available evidence. Ann Rheum Dis 2012;71:480-3.
31. Chali Y, 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, Pirkmajer K, Pirkmajer S, et al. Prevalence of the metabolic syndrome in patients with moderate to severe psoriasis treated with systemic anti-inflammatory drugs: A Danish real-world cohort study. J Intern Med 2013;270:147-57.
35. Wu JJ, Rowan CG, Bebchuk 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.