RESEARCH ARTICLE

The Effect of Metformin and Biological Therapy on Insulin Resistance in Iraqi Psoriatic Patients

Ghadah Ali Al-Oudah[1*], Mohammed K. Al-Hattab[3], Ahmed S. Sahib[4], Shaimaa M. Mohammed[2]

[1]*Department of Pharmacology, College of Pharmacy, University of Mustansiriyah, Mustansiriyah, Iraq*
[2]*Department of Pharmacy, Al-Mustaqbal University College, Hilla, Iraq*
[3]*Department of Dermatology, Hammurabi medical college, University of Babylon, Babylon, Iraq*
[4]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Kerbala, Kerbala, Iraq*

Received: 20th December, 2023; Revised: 15th January, 2023; Accepted: 28th February, 2023; Available Online: 25th March, 2023

ABSTRACT

Psoriasis refers to a medical condition involving long-term inflammation, high insulin resistance, obesity and a likelihood of cardiovascular disease.

Objective: This paper attempts to find out if the addition of metformin to biological therapy has the beneficial effect of increasing insulin sensitivity in moderate to severe Iraqi psoriatic patients.

Subjects and Methods: The experimental group comprises 24 patients suffering from moderate to severe psoriasis. They were randomly selected into two groups: group A comprises 13 psoriatic patients treated with 40 mg of adalimumab twice monthly for 12 weeks. While group B contains 11 psoriatic patients treated with 40 mg of adalimumab twice monthly and a single daily dose of 850 mg of metformin for 12 weeks. The psoriasis area and severity index (PASI), glycosylated hemoglobin (HbA1c), body mass index (BMI), as well as insulin-resistance parameters, which include fasting blood glucose (FBG) and fasting serum insulin (FSI) are estimated for each patient before and after completion of therapy.

Results: The two groups showed a significant reduction in insulin resistance. Nonetheless, group B showed greater reduction. Furthermore, the PASI score of the two groups exhibited improvement, but group B exhibited a higher percentage improvement than group A, and the difference was significant ($p < 0.05$).

Conclusion: This study demonstrates that adding a single daily dose of 850 mg of metformin has a more beneficial effect on insulin resistance (IR) in psoriasis patients than using only biological therapy.

Keywords: Cardiovascular disease, Insulin, Metformin, Psoriasis.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.1.35

How to cite this article: Al-Oudah GA, Al-Hattab MK, Sahib AS, Mohammed SM. The Effect of Metformin and Biological Therapy on Insulin Resistance in Iraqi Psoriatic Patients. International Journal of Drug Delivery Technology. 2023;13(1):224-227.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Psoriasis (Ps) is an immune-mediated disease of inflammation that affects the skin and is associated with keratinocyte hyperproliferation and T lymphocyte inflammation.[1,2] Psoriasis has a global prevalence of 2–3% of the world's population.[3] Patients with psoriasis have a 20 to 50% prevalence of metabolic syndrome; also, they are at least two times more likely to suffer from metabolic syndrome (MS) than people without psoriasis.[4] Usually, a chronic systemic inflammatory disease triggers other comorbid conditions.[5] The metabolic syndrome manifests atherogenic dyslipidemia, intolerance of glucose, hypertension, and central obesity. It can strongly predict non-alcoholic fatty liver disease, cardiovascular diseases, lymphoma, anxiety, diabetes, depression, and stroke, which have all been linked to psoriasis.[6-8] It is known that several inflammatory cytokines involved in the pathogenesis of psoriasis (e.g. Interferon, TNF, IL-6, IL-8, IL-12, IL-17, IL-19, and IL-23) take part in the MS's cascade of hypertension, dyslipidemia, and insulin resistance.[9] The chronicity and autoimmune nature of psoriasis involve an active inflammatory process that interacts with heredity and environmental influences in the different aspects of disease initiation, development, flare, and response to therapy.[3] Overproduction of pro-inflammatory mediators can cause angiogenesis, systemic insulin resistance, increased oxidative stress, hypercoagulation and circulatory endothelial dysfunction; these are frequent hallmarks seen in inflammatory diseases, such as psoriasis.[10]

Insulin resistance means a reduction in sensitivity to the metabolic effects of insulin.[11] It has been confirmed by many studies that metformin has an anti-inflammatory effect and

**Author for Correspondence: gada.awab@uomustansiriyah.edu.iq*

Table 1: Descriptive Statistics for study groups

Group ID	N	Age Mean ± Std. Error	BMI Mean ± Std. Error
A	13	48.6154 ± 3.41666	33.746 ± 2.431
B	11	40.7273 ± 4.99107	33.0545 ± 2.26292

reduces IR (12), (13), (33). In Tsuji *et al.'s* research, treatment with metformin was confirmed to suppress TNF-α- and IL-17A induced inflammatory responses of keratinocytes proliferation in psoriasis via blocking NLRP3 inflammasome activation *in-vitro* and *in-vivo*.[14]

AIM OF STUDY

To determine if addition of metformin to biological therapy produces increased benefits in treating insulin sensitivity in moderate to severe psoriatic patients.

SUBJECTS AND METHODS

This prospective double-blind clinical trial involved a period of over 12 weeks of follow-up of 24 patients with chronic plaque psoriasis and clinical indication with biological treatment in the Department of Dermatology, Merjan Teaching Hospital, Babylon city, Iraq. The study took place from March 2021 to December 2021. Two groups of participants were randomly formed: group A comprises 13 psoriatic patients treated with 40 mg of adlimumab twice monthly for 12 weeks, while group B contains 11 psoriatic patients treated with 40 mg of adlimumab twice monthly and a single daily dose of 850 mg of metformin for 12 weeks as an adjuvant therapy.

The fasting serum insulin levels of every patient that visited the psoriasis clinic in our institution were analyzed after measurement by electrochemiluminescence immunoassay (ECLIA) using Cobas e 411 Roche Diagnostic, Germany. HbA_{1C} concentrations were analyzed with Cobas®c 111 analyzer. Measurement of fasting blood glucose level was done by Accu-Chek® Performa, Germany.

Insulin Resistance Catalogs

The calculation of the homeostasis model assessment (HOMA-IR) of the groups was done in accordance to this formula:

HOMA-IR = glucose (mmol/L) x insulin (mIU/L)/22

by the appropriate software. The PASI scores of all patients were determined to evaluate the severity of disease.

Exclusion criteria:

Patients who fall into the following categories were excluded: diabetes mellitus, pregnant women, and COVID patients.

Statistical analysis

Absolute and relative frequencies were employed to represent categorical data. Also, arithmetic mean and standard deviation have been employed to describe numerical data in case of normal distribution. In other cases, median and interquartile range boundaries were used (SPSS software version 26). Statistical significance was assumed as $p < 0.05$.

RESULTS

With reference to HOMA-IR, both groups showed significant improvement in IR ($p < 0.05$), as present in Table 2.
Figure 1 presents the mean HOMO-IR for group A patients before and after the administration of adlimumab therapy.

Figure 2 presents the HOMA-IR for group B patients before and after treatment with adlimumab and metformin.

Figure 3 is related to the percentage improvement in PASI score. It shows that there is a more significant improvement in Group B patients compared with patients of Group A, as indicated by the medians of Group A and Group B, which were 66 and 82.94%, accordingly, $p < 0.05$. Table 3 as well as Figure 3 express the median percentage improvement for the study groups.

A statistically significant level of PASI percentage improvement is $p < (0.05)$ (independent non–parametric sample).

Table 2: Baseline characteristics of patients according to groups (dependent samples) t–test paired

Test	Group A			Group B		
	Pre Mean ± Std. Error Mean	Post Mean ± Std. Error Mean	*p-value*	pre Mean ± Std. Error Mean	post Mean ± Std. Error Mean	*p-value*
FBS	89.15 ± 5.54	83.77 ± 4.89	0.42	85.09 ± 4.55	82.91 ± 3.49	0.47
FSI	16.08 ± 2.3	16.75 ± 2.40	0.52	16.68 ± 2.09	13.34 ± 1.40	0.063
Hba1c	5.22 ± 0.29	5.58 ± .39	0.22	5.36 ± .20	4.81 ± .37	0.128
HOMO-IR	3.83 ± 0.59	3.59 ± .06	0.001*	3.41 ± .35	2.73 ± .28	0.007*

* Significant difference ($\alpha < 0.05$)

Table 3: PASI percentage improvement according to disease severity Mann-Whitney test

Assessment tool	N	Group A			N	Group B			
		median before treatment	median after treatment	median percentage improvement change		median before treatment	median after treatment	median percentage improvement change	Asymp. sig. (2-tailed)
PASI	13	13.5	4.2	66.00	11	17.0	3.1	82.94	0.04*

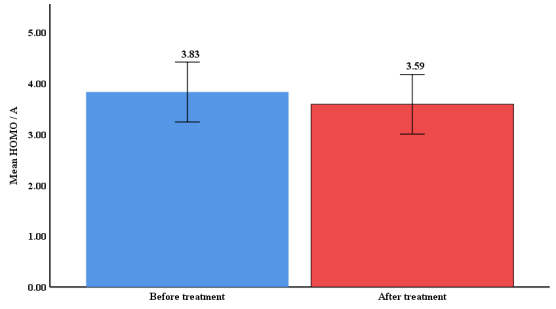

Figure 1: HOMO-IR before and after treatment for Group A

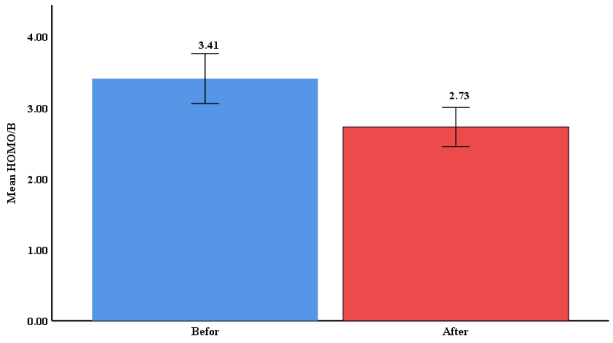

Figure 2: HOMO-IR before and after treatment for Group B.

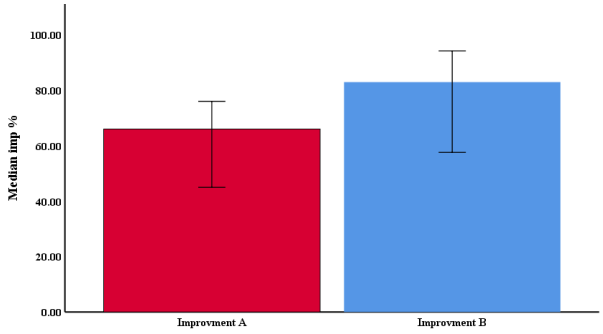

Figure 3: The median percentage improvement of PASI score for group A and group B.

DISCUSSION

This study confirms that when metformin is added to biological therapy, there is a great improvement in IR in comparison with the use of biological therapy alone. In addition, a reduction in PASI score is achieved after 12 weeks of follow-up.

Psoriasis refers to a long-term inflammation disorder associated with hyper proliferation and inflammation of the keratinocyte (15–18). Such a multisystem chronic disease is usually associated with comorbidities such as obesity, diabetes, metabolic syndrome and arthritis.[19]

The disorder has a pathophysiological basis, and serum TNF, IFN-, IL-6, IL-8, IL-12, IL-17, and IL-18 levels were considerably higher in patients with psoriasis.[10,15] Also, oxidative stress is majorly involved in disease development.[16,19-21]

Metformin is used as a first-line antidiabetic medication in the treatment of diabetes mellitus (DM). It does not produce hypoglycemia; instead, it lowers serum glucose level by inhibiting hepatic glucose synthesis and improving peripheral tissue sensitivity to insulin. It also has weight-loss benefits, with T2D, improves lipid profile and reduces cardiovascular risk.[22-24] The molecular mechanism of metformin has progressed, and its use has expanded to include conditions such as cancer, polycystic ovarian syndrome, and other inflammatory diseases.[25,26] The pathophysiological processes of psoriasis include hyperproliferation and aberrant differentiation of epidermal keratinocytes. Further, metformin also influences the immune cell and inflammatory processes. The principal technique of psoriasis treatment focuses on preventing excessive keratinocyte proliferation.[27] In this regard, metformin suppresses TNF and IL-17A-induced inflammatory responses in keratinocytes in vitro via inhibiting NLRP3 inflammasome activation. Also, oral metformin significantly reduced IMQ-induced psoriasis-like inflammation.[14] Furthermore, metformin has the potential to lower the effects of IL17 and IL23, such as anti-inflammatory and immunomodulatory activities, resulting in psoriatic lesion improvement and a reduction in skin inflammation symptoms.[28]

Metformin works by activating AMPK in the extracellular signal-related kinase$_{1/2}$ signaling pathway, causing cell cycle arrest and, thus, cell proliferation suppression, which improves psoriasis.[29] Metformin also modulates the function of T-cell and dendritic cell; their interaction with keratinocyte cells is crucial in the pathogenesis of psoriasis.[30] In psoriasis, however, oxidative stress and DNA/RNA damage are the primary pathogenic factors.[20] In relation to this, metformin acts to modulate antioxidant enzymes, such as catalase and glutathione (GSH); also, it promotes autophagy in human keratinocyte.[14,31] In a study by Chengxin Li *et al.,* metformin was found to reduce ROS level and inhibit proliferation; also, it results in the activation of FOXO transcription factor, which is a focused player in cell proliferation and antioxidant decrease.[32]

CONCLUSION

These findings provide a rationale for using metformin as an anti-inflammatory, antioxidant and/or immune modulator for treating moderate to severe psoriasis. Nonetheless, a large scale clinical trial is required.

REFERENCES

1. Kanda N, Hoashi T, Saeki H. Nutrition and psoriasis. International journal of molecular sciences. 2020 Jul 29;21(15):5405.
2. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. International journal of molecular sciences. 2019 Mar 23;20(6):1475.
3. Nestle MDF, Daniel HK, M.D, Ph.D., and Jonathan Barker, M.D. Mechanisms of Disease Psoriasis. The new england journal of medicine. 2009;361;5 nejm.org july 30,:361:496-509.
4. Gisondi P, Fostini AC, Fossà I, Girolomoni G, Targher G. Psoriasis and the metabolic syndrome. Clinics in dermatology. 2018 Jan 1;36(1):21-8.
5. Krueger JG, Brunner PM. Interleukin-17 alters the biology of many cell types involved in the genesis of psoriasis, systemic inflammation and associated comorbidities. Experimental Dermatology. 2018 Feb;27(2):115-23.

6. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. The Lancet. 2007 Jul 21;370(9583):263-71.
7. Dhara S, Dasgupta A, Rout JK, Banerjee U, Dasgupta S, Ghosh A. Clinico-biochemical correlation between psoriasis and insulin resistance. Indian Journal of Clinical Biochemistry. 2015 Jan;30:99-103.
8. Boehncke W-H, Schön MP. Psoriasis. The Lancet. 2015; 386(9997):983-94.
9. Sterry W, Strober BE, Menter A, International Psoriasis Council. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. British Journal of Dermatology. 2007 Oct 1;157(4):649-55.
10. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators of inflammation. 2005 Oct 24;2005(5):273-9.
11. Polic MV, Miskulin M, Smolic M, Kralik K, Miskulin I, Berkovic MC, Curcic IB. Psoriasis severity—a risk factor of insulin resistance independent of metabolic syndrome. International Journal of Environmental Research and Public Health. 2018 Jul;15(7):1486.
12. Pala L, Barbaro V, Dicembrini I, Rotella CM. The therapy of insulin resistance in other diseases besides type 2 diabetes. Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity. 2014 Sep;19:275-83.
13. Bjornstad P, Schäfer M, Truong U, Cree-Green M, Pyle L, Baumgartner A, Garcia Reyes Y, Maniatis A, Nayak S, Wadwa RP, Browne LP. Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus: randomized controlled trial. Circulation. 2018 Dec 18;138(25):2895-907.
14. Tsuji G, Hashimoto-Hachiya A, Yen VH, Takemura M, Yumine A, Furue K, Furue M, Nakahara T. Metformin inhibits IL-1β secretion via impairment of NLRP3 inflammasome in keratinocytes: implications for preventing the development of psoriasis. Cell death discovery. 2020 Mar 4;6(1):11.
15. Sanchez AP. Better Understanding the Immunopathogenesis of Pso-riasis. Clin Res Dermatol Open Access. 2017;4(1):1-2.
16. Stanescu AM, Simionescu AA, Florea M, Diaconu CC. Is metformin a possible beneficial treatment for psoriasis? A scoping review. Journal of Personalized Medicine. 2021 Mar 30;11(4):251.
17. Sabat R, Philipp S, Höflich C, Kreutzer S, Wallace E, Asadullah K, Volk HD, Sterry W, Wolk K. Immunopathogenesis of psoriasis. Experimental dermatology. 2007 Oct;16(10):779-98.
18. Khalil MA, Alta'ee AH, Al-Sultany HA, Al-Hattab MK. Vitamin D3 level and its receptor of patients with psoriasis: a case control study. EMBJ. 2018;13:150-4.
19. Branisteanu DE, Pirvulescu RA, Spinu AE, Porumb EA, Cojocaru M, Nicolescu AC, Branisteanu DC, Branisteanu CI, Dimitriu A, Alexa AI, Toader MP. Metabolic comorbidities of psoriasis. Experimental and Therapeutic Medicine. 2022 Feb 1;23(2):1-7.
20. Borska L, Kremlacek J, Andrys C, Krejsek J, Hamakova K, Borsky P, Palicka V, Rehacek V, Malkova A, Fiala Z. Systemic inflammation, oxidative damage to nucleic acids, and metabolic syndrome in the pathogenesis of psoriasis. International journal of molecular sciences. 2017 Oct 25;18(11):2238.
21. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. The lancet. 2005 Apr 16;365(9468):1415-28.
22. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. New England Journal of Medicine. 1998 Mar 26;338(13):867-73.
23. Jia Y, Lao Y, Zhu H, Li N, Leung SW. Is metformin still the most efficacious first-line oral hypoglycaemic drug in treating type 2 diabetes? A network meta-analysis of randomized controlled trials. Obesity Reviews. 2019 Jan;20(1):1-2.
24. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005 Oct 25;112(17):2735-52.
25. Marshall SM. 60 years of metformin use: a glance at the past and a look to the future. Diabetologia. 2017 Sep;60(9):1561-5.
26. Kristófi R, Eriksson JW. Metformin as an anti-inflammatory agent: a short review. Journal of Endocrinology. 2021 Sep 1;251(2):R11-22.
27. Rahman M, Alam K, Zaki Ahmad M, Gupta G, Afzal M, Akhter S, Kazmi I, Jalees Ahmad F, Anwar F. Classical to current approach for treatment of psoriasis: a review. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2012 Sep 1;12(3):287-302.
28. Al-Saedi HF, Al-Zubaidy AA, Ramadhan MA, Mohammad HA. Effect of metformin gel against imiquimod induced psoriasis in mice. Int J Res Pharm Sci. 2019;10(2):795-802.
29. Li W, Ma W, Zhong H, Liu W, Sun Q. Metformin inhibits proliferation of human keratinocytes through a mechanism associated with activation of the MAPK signaling pathway. Experimental and therapeutic medicine. 2014 Feb 1;7(2):389-92.
30. Lin X, Huang T. Oxidative stress in psoriasis and potential therapeutic use of antioxidants. Free radical research. 2016 Jun 2;50(6):585-95.
31. Apostolova N, Iannantuoni F, Gruevska A, Muntane J, Rocha M, Victor VM. Mechanisms of action of metformin in type 2 diabetes: Effects on mitochondria and leukocyte-endothelium interactions. Redox biology. 2020 Jul 1;34:101517.
32. Li C, Zhang L, Liu X, Huang M, Wang R, Zhu W, Li Y, Shen L, Xie F, Wang W, Song C. Metformin prevents the psoriasis under hyperlipidemia via activation of the FOXO3.
33. Kamenova P. Therapeutic potential of metformin in normal glucose tolerant persons with metabolic syndrome. Biotechnology & Biotechnological Equipment. 2020 Jan 1;34(1):30-7.