ORIGINAL RESEARCH

A hospital based prospective assessment of the effectiveness and safety of combination therapy using metformin and MTX in the treatment of psoriasis patients with metabolic syndrome

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ABSTRACT

Aim: The aim of the present study was to evaluate the effectiveness and safety of combination therapy using metformin and MTX in the treatment of psoriasis patients with metabolic syndrome.**Material & Methods:**This study was single-blind clinical trial was conducted for the period of 6 months with 100 patient's diagnosedwith plaque psoriasis who were being treated. Allpatients met full criteria to participate in this research. This study was approved by the Board of Ethical committee.**Results:**Patients treated with the combined regimen showed measured improvement in disease status compared to those treated with MTX monotherapy. The Psoriasis Area and Severity Index (PASI) scores of psoriasis patients with metabolic syndrome using the metformin and MTX combination were significantly lower than those treated with MTX only (p<0.05). The combination treatment group also showed a significant decrease in blood sugar and triglyceride levels after 3 months (p<0.05). However, there were no significant differences in subclinical indexes between the treatment and control groups.**Conclusion:**In this treatment sample, a combination of metformin and MTX in psoriasis patients with metabolic syndrome showed positive responses and no serious side effects.

Key words: Psoriasis, metformin, methotrexate, metabolic syndrome

INTRODUCTION

Psoriasis is a chronic inflammatory condition with genetic, immunological, and metabolic aetiology that affects over 8 million people in the US.[1,2] It is considered as a severe, non-communicable disease.[3]The pathogenesis ofmetabolic syndrome in patients with psoriasis is believed tohave a connection with an increase in adipocytokines such astumor necrosis factor-α (TNF-α) and adiponectin[4,5,6].Psoriasis is a systemic disease with numerous multiorgan complications because of chronic inflammation; due to the dominant TNF-αIL-23-Th17 axis, chronic inflammation leads to dysfunctional differentiation, uncontrolled keratinocyte proliferation and neovascularization[7]. Topical treatment is used as first-line therapy or as a combination therapy depending on the severity of psoriasis. Among topical therapies used are corticosteroids, tar derivatives, calcineurin inhibitors, and vitamin D analogues[8,9]. Another therapeutic option is phototherapy with PUVA (psoralen and ultraviolet A) or UVB on its own or in combination with other therapies. Classical systemic therapy includes methotrexate, acitretinand cyclosporine, but also other systemic therapies represented by biological agents. Even with these wide therapeutic options, psoriasis cannot always be controlled [10,11,12].

A recent study demonstrated that metformin-widely used tolower blood glucose concentrations in the treatment ofdiabetes patients-may be useful in

combination withmethotrexate (MTX) for the treatment of psoriasis[13]. Biochemical indicators suggest that both drugs have thesame target: AMP-activated protein kinase (AMPK).MTX inhibits cellular DNA synthesis and is considered the"gold standard" in the treatment of psoriasis [14]. However,used in high doses over a long period of time, MTX has beenshown to cause harmful side effects to the liver (hepatotoxicity), blood, bones and lungs[15]. Therefore, this study wasconducted to evaluate the effectiveness and safety of combination therapy using metformin and MTX in the treatment of psoriasis patients with metabolic syndrome.

MATERIAL & METHODS

This study was single-blind clinical trial was conductedfor the period of 6 months with 100 patients diagnosedwith plaque psoriasis who were being treated.Allpatients met full criteria to participate in this research. This study was approved by the Board of Ethical committee.The author obtained informed consent from participants. The procedures followedwere in accordance with the ethical standards of the responsibleinstitutional committee on human experimentation and withthe Helsinki Declaration of 1975, as revised in 2013.

Diagnostic Criteria. Psoriasis diagnostic criteria: Psoriasis diagnosis is based on clinical features. Lesions areerythematous plaques with scales on the surface and suggestive characteristics are a circumscribed border, non-infiltration, sites of predilection, mild or severe pruritus andsilvery scales.

Metabolic syndrome diagnostic criteria: According to thecriteria of the National Cholesterol Education Program AdultTreatment Panel III (NCEP/ATP III) and the South AsianModified (SAM)-NCEP, the diagnosis of metabolic syndromeis established when 3 of 5 factors are present [16].

INCLUSION CRITERIA

i) Patients with both psoriasis vulgaris and metabolic syndrome between the ages of 18 and 70 years.
ii) Patients are non-alcoholic; liver and kidney functiontests are normal.
iii) Patients consent to participate in this researchstudy.

EXCLUSION CRITERIA

i) Patient is pregnant or lactating.
ii) Patient has been using systemic drugs to treat.
iii) Psoriasis-such as cyclosporine, retinoid or immunologic therapyfor one month or more.
iv) Patient has acute or chronic infection.
v) Contraindication to use metformin andmethotrexate.

METHODS. STUDY DESIGN: PROSPECTIVE, RANDOMIZED PLACEBO CONTROL STUDY WITH CONVENIENT SAMPLING. PSORIASISPATIENTS WITH METABOLIC SYNDROME WERE DIVIDED INTO TWOGROUPS:

i) Treatment group: 70 psoriasis vulgaris patients withmetabolic syndrome were treated using metformin + MTX. MTX: started with 7.5 mg/week, divided into 3 doses q12hr and sustained for threemonths (12 weeks). Metformin: 500 mg/day afterone meal.
ii) Control group: 62 psoriasis vulgaris patients withmetabolic syndrome were treated using MTX onlywith the same dosage and usage.

DATA ANALYSIS

Data were analyzed using Stata 12software. The data were analyzed using frequency,percentage, mean, standard deviationand median. $\chi 2$ is used toidentify the relationship between qualitative variables. Thegeneralized estimating equation (GEE) methodology is usedto analyze correlated data that otherwise could be modelled as a generalized linear model. For quantitative variables withnormal distribution, the student t-test was used to comparetwo mean values and analysis of variance (ANOVA) tocompare more mean values. For quantitative variables withabnormal distribution, the Wilcoxon two-sampletest was used.

RESULTS

Table 1: Research group characteristics

Variables	Experiment group	Control group	P
Age	50.5 ± 14.4	50.5 ± 8.2	0.80
Disease duration	36.4 ± 10.2	38.2 ± 14.6	0.65
PASI	22.8 ± 8.2	22.5 ± 18.6	0.90

In the experiment group, mean±SD of age was 50.5 ± 14.4 and 50.5 ± 8.2in the control group.

Table 2: Treatment results of the study and control group

After(month)	PASI(beforetreatment)(*X*±SD)	PASI(aftertreatment)(*X*±SD)	%Reduction	*p*
Study group				
1		16.4±7.5	22	0.01
2	22.8±8.2	14.6±7.2	35	0.0002
3		9.0±8.2	60	<0.001
Control Group				
1		18.2 ± 7.3	20	0.01
2	23.7 ± 9.1	14.0 ± 7.0	35	0.0002
3		10.5 ± 8.2	50	<0.001

In the study group, after three months of treatment, the mean PASI dropped by 60%.There was a statistically significant difference in PASI before and after treatment. In the control group, after three months of treatment, the mean PASI dropped by 50%. There was a statistically significant difference in PASI before and after treatment.

Table 3: AST, ALT and GGT before and after treatment of the two groups

Index	Experiment group (*n=50*)			Control group (*n*=50)		
	Before treatment	After treatment	*p*	Before treatment	After treatment	*p*
AST	34.6±22.8	32.2±20.1	0.31	24.6±10.5	26.4±8.2	0.60
ALT	39.1±30.2	40.1±45.7	0.90	26.4±17.3	30.2±14.6	0.32
GGT	40.5±35.5	42.6±25.1	0.32	25.5±15.5	40.2±20.0	0.002

There were differences in liver enzyme indexes (AST, ALT and GGT) between two groups of patients before and after treatment. However, only the GGT index in the control group showed a significant difference.

Table 4: Comparison of treatment results of two groups according to the venous blood glucose, triglycerides, HDL cholesterol and total cholesterol

Glucose (mmol/dL)	Before treatment	After 1 month	After 2 months	After 3 months
Experiment (metformin + MTX)	7.3 ± 2.8	6.4 ± 1.4	6.8 ± 1.2	6.8 ± 0.9
Control (MTX only)	6.5 ± 2.2	5.5 ± 1.1	5.9 ± 1.7	5.6 ± 1.5
Triglycerides(mmol/dL)	**Before treatment**	**After 1 month**	**After 2 months**	**After 3 months**
Experiment (metformin + MTX)	2.4 ± 1.5	2.0 ± 1.0	1.8 ± 0.9	1.9 ± 0.9
Control (MTX only)	2.8 ± 1.3	2.4 ± 1.3	2.1 ± 1.1	2.1 ± 1.1
HDL-cholesterol(mmol/dL)	**Before treatment**	**After 1 month**	**After 2 months**	**After 3 months**
Experiment (metformin + MTX)	1.1 ± 0.3	1.2 ± 0.5	1.1 ± 0.3	1.2 ± 0.5
Control (MTX only)	1.2 ± 0.8	1.1 ± 1.0	1.0 ± 0.3	1.2 ± 0.8
Total cholesterol(mmol/dL)	**Before treatment**	**After 1 month**	**After 2 months**	**After 3 months**
Experiment (metformin + MTX)	4.0 ± 1.4	4.0 ± 1.3	3.8 ± 1.1	4.0 ± 1.3
Control (MTX only)	4.8 ± 1.3	4.4 ± 1.0	4.1 ± 1.2	4.1 ± 1.2

After three months of treatment, the venous blood glucose levels of the study group and the control group markedly decreased ($p<0.05$, Student t-test). However, the change in the venous blood glucose level between two groups was insignificantly different. After treatment, the triglycerides index of both groups dropped with a significant difference. However, comparing the results of the two groups showed no statistical difference.After treatment, there was not a significant difference in the change of HDL cholesterol between the two groups. After the treatment, there was a significant difference in cholesterol change between the experiment and control groups ($p>0.05$, GEE regression). The control group total cholesterol index decreased ($p<0.05$, Student t-test) while the intervention group remained unchanged ($p>0.05$, Student t-test).

DISCUSSION

Diabetesmellitus is a chronic disease affecting over 22million people worldwide and has metabolic, inflammatory, and pathological genetic mechanisms[17,18]. A first-line treatment in type 2 diabetes, 1,1-dimethyl biguanide hydrochloride (metformin), is a biguanide that reduces hyperglycemia, prevents inflammation, normalizes lipid and carbohydrate metabolism and reduces adipose tissue[19,20]. The good results obtained with metformin as the first-line treatment of type 2 diabetes have led to its successful use in many other conditions, such as cancer (breast, endometrial, colorectal, prostate, various other tumors), nonalcoholic fatty liver disease, chronic kidney disease, metabolic syndrome, obesity, coronary artery disease, polycystic ovary syndrome, and acne. It also has anti-aging effects and improves the efficiency of

in vitro fertilization; some studies have demonstrated the benefits of metformin in patients with psoriasis[21,22].

Although there was no statistically significant difference, the GGT index of the experiment group of patients decreased after 12 weeks. In an animal clinical trial, the combination of metformin and MTX significantly reduced liver enzymes and bilirubin levels, shortened the prothrombintime and significantly reduced thrombospondin-1 concentration[23]. Additionally, histopathology of liver tissue of the group treated with metformin demonstrated a significant improvement in the liver structure. Although the necrotic lesions remained, the severity was significantly lessened. We can speculate that metformin has a protective mechanism against MTX-induced hepatotoxicity. A study by Risk *et al*. revealed a defensive action of metformin against renal toxicity from MTX chemotherapy[24]. Theantioxidant, anti-apoptotic and anti-inflammatory propertiesof metformin may serve as contributing factors to this hepatorenal protection.

Venous blood glucose levels in our experiment reduced significantly in the experiment group, which may be-explained by the hypoglycemic ability of metformin. However, when comparing the two groups, there was not a significant difference. The same pattern was observed for triglycerides, HDL, and cholesterol indexes, although there was a significant decrease intriglycerides of both groups and cholesterol in the controlgroup before and after treatment. This result is in agreement with that in the study by El-Gharabawy*et al*. as no obvious change of biochemical indexes between the test groups, including fasting blood sugar, HbA1c, total cholesterol, low density lipoproteins, high-density lipoproteins or triglycerides, was observed[25]. According to Singh *et al*., when using metformin to treat psoriasis patients with metabolic disorders, there was a statistically significant difference inblood glucose levels, cholesterol, and triglycerides (0.002, 0.001 and <0.001, respectively) before and after treatment[26].The dose of metformin may account for this difference as Singh *et al*. used a dose of 1000 mg/day. In the present study, patients only received a dose of metformin of 500 mg/day because of a lack of specific treatment guidelines, as well as precautions against hypoglycemia or adverse effects on the liver and kidneys when used with MTX.

CONCLUSION

Combination therapy using metformin and MTX has potential to substantially improve the PASI index of psoriasis patients with metabolic syndrome. Further in-depth studies with a larger sample size are necessary to evaluate the efficacy and safety of this combination.

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