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The Combined use of Metformin and Adalimumab in Iraqi Psoriatic Patients

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Abstract

Psoriasis is a complicated, chronic, immune-mediated inflammatory skin disease with a hereditary basis. It is possible that metformin treatment may modulate the function of immune cells, subsequently preventing proliferation of keratinocytes KCs.

Objective: The present study attempts to find out if the addition of Metformin to biological therapy Adalimumab has the beneficial effect to relieve inflammation in moderate to severe Iraqi psoriatic patients.

Subjects and Methods: The experimental group comprises 30 patients suffering from moderate to severe psoriasis, that were randomly allocated into two groups; Group A: consist of 15 psoriatic patients treated with 40mg of Adalimumab twice monthly for 12 weeks, while Group B: contains of15 psoriatic patients treated with 40mg of Adalimumab twice monthly and a single daily dose of 850mg of metformin for 12 weeks. The psoriasis area and severity index (PASI) was used to assess the percentage improvement changes after treatment period, furthermore, serum levels for inflammatory markers, IL-17 and TNF-α were used to determine their levels by using ELISA technique before and after therapy.

Results: The two groups showed significantly decrease ($p<0.05$) after treatment when compared with patients before treatments but high significantly decrease in mean IL-17 level and TNF ($p<0.05$) after treatment with group B in which addition metformin to biological therapy .As well as to that using combination adjuvant therapy in group B result in further improvement as reported by 76 % PIC for PASI score in compared with 60% PIC after 12 weeks of treatment

Conclusion: This study demonstrates that adding a single daily dose of metformin to biological therapy has a more beneficial effect to relieve inflammation of skin associated with psoriasis

Key words: complicated, inflammation, moderate, demonstrates, combination

Introduction

Psoriasis is a chronic inflammatory condition with genetic, immunological, and metabolic etiology. The link between psoriasis and, inflammatory pathways, resulting in damage in both conditions. The good results obtained with metformin as it possesses various benefits, like decreasing cardiovascular risk, improving lipid profile, anti-inflammatory, anti-cancer and anti-aging effects; (1). Metformin can exert potent anti-inflammatory effects, irrespective of its capability of glucose control (2),(3) through inhibition and activation of several signaling pathways, such as AMPK, mTOR, and NF-kB, resulting in inhibition of keratinocyte proliferation and pro-inflammatory cytokine production; (4) . Metformin is a likely curative agent for skin inflammation diseases like psoriasis. This is because NF-κB take part in the pathogenesis of psoriasis, and compounds that particularly target NF-κB could be new curative options for psoriasis; (5)

Past studies have shown that metformin caused the inhibition of inflammatory responses through NF-κB signaling pathway in the human vascular endothelial cell. What is more, current research disclosed that by NF-κB signal pathway targeting, metformin expressed anti-proliferative activity. Therefore, metformin has a likely role in alleviating the inflammatory response in psoriasis; (6)

The crucial pathogenesis of psoriasis is interaction between keratinocytes and immune cells; (7) . It is possible that metformin treatment may modulate the function of immune cells, subsequently preventing psoriasiform eruptions, which means inhibiting proliferation of KCs; (8), (4) .

Patients and methods

This clinical study involving 30 participants (females and males) was a double blind study. The participants, whose age range was (17-72) years, mean age ± S.D (44.66± 11.99male,36.22± 11.85female) and mean BMI range (31.99±8.074male, 33.26±8.95female), were individuals with psoriasis who were attending the Mirjan Teaching Hospital in Babylon City from January 2021 - March 2022.

They willingly chose to take part in the research and provided informed consent. They had a diagnosis of moderate to severe psoriasis, and there were no other evidences of overlapping illnesses. The exclusion criteria include a positive history of any drugs that would be used in the research, more than two days of medication error, and pregnant or lactating women.

The local ethical committee provided approval for the protocol and selection criteria. The participants were randomized into two study groups and took part in a 12-week double blind study as follow:

- **Group A:** 18 patients were treated with adalimumab (40mg s.c) twice monthly + placebo; 15 patients only completed the study
- **Group B:** 16 patients were treated with adalimumab (40mg s.c) twice monthly + Metformin (850mg) daily single dose; 15 patients only completed the study.

Table 1-1. Summarized characteristics of patients

Parameter	**Group A** **n = 15**	**Group B** **n =15**
Age (years) **Mean ± S.E**	♂47.69±12.61 ♀48.00±9.89	♂47.50±14.74 ♀34.42±11.63
BMI (kg/m^2) **Mean ± S.E**	♂34.36±8.53 ♀25.50±2.12	♂34.33±6.62 ♀33.14±9.64

Every patient involved in this research was interviewed directly to achieve an evaluation of the manifestations and symptoms of their disease, their medical history, and past laboratory results. PASI was used to assess patients' outcome. In addition the sera of patients were used to determine the level of human TNF-α, IL17 by ELISA technique using the corresponding ELISA kit, The assessment was done twice, before commencing treatment and after following up the drug treatment for 12 weeks.

Results

Before enrollment in the study (zero time), all psoriatic patients demonstrated high PASI scores in two groups which indicates severe or extreme symptoms of psoriasis as shown in Table 1-2 Treatment with 40mg Adalimumab alone (group A) resulted in significant reduction in the total PASI score and about 60% percentage improvement change (PIC) after 12 weeks of treatment compared to pre-treatment value ,and by using combination adjuvant therapy of metformin with Adalimumab (group B) result in further improvement as reported by**76**% PIC for PASI score, the reduction from the pre-treatment values; were highly significant reduction.

Table 1-3 showed that there was no significantly difference in mean serum levels of IL-17 and TNF in all patient's groups at base line (zero time). Treatment with Adalimumab (20mg/twice monthly, group A) resulted in a high significant decrease in mean serum IL-17, Mean±SE was (299.06 ±31.9 pg/ml), after 12 weeks treatment, as compared to baseline value (423.45 ±49.57 pg/ml), ($p<0.05$). Meanwhile, treatment of psoriatic patients with Group B, using (Adalimumab 40mg+ Metformin 850mg) showed high significantly decrease ($p<0.05$) after treatment (266.76±30.93pg/ml) when compared with patients before treatments (462.67 ±47.03pg/ml).

The Mean ±Std. Error Mean of TNF α in group A, as presented in table 1-2 showed a high significantly decrease ($p<0.05$) after 12 weeks treatment using Adalimumab (93.37±6.91pg/ml) when compared with base line level

before treatments (115.01±4.57pg/ml). Group B (Adalimumab40mg+ Metformin850mg) showed also a high significantly decrease after treatment (73.83±4.77pg/ml) when compared with patients before treatments(106.98±7.97pg/ml).

Table (1-**2**): **Effects of Treatment with Biological Therapy and Metformin on PASI Scores:**

Group	**N**	**PASI Score Pre- Treatment**	**PASI Score Post-Treatment**	**PASI PCI**	**P- value**
A	**15**	20.79±2.71	8.86±2.06	59.68 ± 5.43	.000**
B	**15**	19.14±1.95	4.48±.84	76.28±4.55*	.000**

Each value represents Mean ± SEM; group A: patients treated with Adalimumab 40mg s.c twice monthly + placebo; B: patients treated with adalimumab 40mg s.c twice monthly + Metformin850mg daily single dose; group PIC: Percentage Improvement Changes. N: Number. * Significantly different (*P<0.05*) compared to pre-treatment value within the same group; ** Highly significant difference (*P<0.01*) compared to pre-treatment value within the same group.

Table (1-3): Effects of Treatment Metformin with Biological Therapy,

Group	**N**	**1L-17 Mean ±SE Pre- Treatment**	**1L-17 Mean ±SE Post- Treatment**	**P- value**	**TNF α Mean ±SE Pre-Treatment**	**TNF α Mean ±SE Post-Treatment**	**P- value**
A	15	423.45 ± 49.57	299.06 ± 31.9	0.000**	115.01± 4.57	93.37± 6.91	0.001**
B	15	462.67 ± 47.03	266.76± 30.93	0.001**	106.98± 7.97	73.83± 4.77	0.000**

Each value represents Mean ± SEM; group A: patients treated with Adalimumab 40mg s.c twice monthly + placebo; group B: patients treated with adalimumab 40mg s.c twice monthly + Metformin850mg daily single dose

Discussion

Psoriasis is a chronic inflammatory skin disease causing significant relapsing morbidities in the affected individual (9) .

Over years ,its generally believed that psoriasis is a complex autoimmune inflammatory disease with a genetic based (10) .The inflammatory nature of psoriasis was illustrated by a systemic and dermal secretion of cytokine such as IL-2,IL-6,IL-8,IL-17,IL-18,IL-22.IL-23,IL-24,INFγ and TNFα (11).

The cytokine secretion profile of the T-cell has been well characterized in psoriasis , Th1 and Th17 has been proved to play a major roles in the pathogenesis of psoriasis (12) ;in that Th1 differentiate is mediated by IL-12,in contrast Th-17 cells develop in the presence of IL-1 ,IL-6 and TGFα Once differentiated ,IL-23 is then required for their maintenance Th1 release mediators such as TNFα and INFα leading to vasodilators ,leukocyte and keratinocyte activation and this lead to dendritic cell activation and a cycle of inflammation (13) .Th17 cells also stimulate keratinocyte activation and proliferation through secretion of IL-17 and IL-22 could be pivotal mediator of epidermal hyperplasia (14).

Table (1-2)presents that using adalimumab in a dose of 40mg EOW in group A for 12weeks result in highly significant reduction in both IL-17 and TNFα serum level and the percentage improvement was above 29%,19% for both inflammatory markers respectively

A comparable PIC was reported using metformin alone with adalimumab for the same 12weeks studies period ,also the reduction was highly significant and the PIC for the IL-17,TNFαwere (42%,31%) respectively .

Adalimumab , a recombinant ,fully human monoclonal antibody and one of the FDA approved biological therapy for moderate to severe psoriasis against TNFα ,adalimumab block the interaction of TNFα with receptor **(15).** Adalimumab has been shown to be highly wanted by patients with psoriasis due to its profound improvement in

disease severity and favorable safety profile (16),(17),(18).Yet some patient may experience some degree of treatment fail or side effects (19), (20).

Choosing metformin adjuvant therapy ,many studies proved that metformin affect both the immune and inflammatory process in many disease such as cancer ,nonalcoholic fatty liver , polycystic ovary syndrome (PCOs) and even psoriasis (21).In a study done by Tsuji et al .metformin therapy was shown to suppress TNFα and IL-17A induced inflammatory response of keratinocytes proliferation in psoriasis by blocking NLRP3inflammasone activation in vitro and vivo (4) .

The molecular mechanism of metformin as anti-inflammatory agent could be via AMPK-dependent and AMPK-independent effect (21) .AMPK activation by metformin lead to the inhibition of mechanistic target of rapamycin (mTOR) and activation of transcription 1(STAT1),also it lead to inhibition of mTOR signaling which ultimately lead to a decrease in the levels of inflammatory cytokines IL-1B and IL-17A (22),(23). .Addition AMPK –dependent anti-inflammatory effect of metformin is via decreasing NF-kB p65 phosphorylation ,leading to lower levels of inflammatory cytokines such as TNF,IL-6 and CRP (24) . On the other hand ,The AMPK-nondependent anti-inflammatory action of metformin is via reducing the levels hypoxia inducible factor 1α and fibrosis markers without lowering intracellular oxygenation ,it also present phosphorylation of JNK,P46 and lipopolysaccharide –induced gene expression of IL-1B and TNFα (25), All these anti-inflammatory effects seems to be without AMPK activation as it reported in a study done using inducible 6-Phosphofructo-2-kinase (iPFK2)-knockdown adipocytes (21)

Metformin now is consider the focusing as the treatment patients for psoriasis due to the fact that the molecular mechanism of metformin has been progressed ,and its use has expand to include condition such as cancer ,poly cystic ovarian syndrome and others inflammatory disease (26) (21)(27).

Conclusion

Metformin may hold promise as part of adjunct therapy for treatment of plaque psoriasis ,additional prospective randomized clinical trials are needed to determine the optimal dose of metformin.

Finally the limited number included in this study , somewhat was small ,so large sample sizes and long enough duration are needed to confirm the effectiveness of metformin supplementation for plaque psoriasis

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