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Comparing the Efficacy of Topical Metformin and Placebo in the Treatment of Melasma: A Randomized, Double-blind, Clinical Trial

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Authors' contributions

This work was carried out in collaboration among all authors. Authors MAM and AAH designed the study and wrote the protocol. Author GN performed the statistical analysis, and wrote the first draft of the manuscript, managed the analyses of the study, managed the literature searches and performed the study. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Generally affecting women, melasma is the acquired disorder of hyperpigmentation, and researches are still ongoing to find an effective, fast, and low-side-effect drug treating this disease. The present study is aimed at comparing the efficacy of topical metformin and placebo in the treatment of melasma.
Methods: Sixty patients with melasma were treated in placebo and topical metformin recipient groups in a double-blind clinical trial. In addition to the demographic and laboratory findings of patients before and after the intervention, the MASI Score of patients in weeks 0, 4, 8, and 12 of the study and then one month after the study were analyzed using SPSS version 20 software.
Results: The mean age of the studied patients was 35.25 ± 7.11 years. No significant difference was observed between the phenotypes (*P*= .49) and the type of melasma (*P*= .63) in the two groups. The mean MASI score of patients at the time of being included in the study in the placebo

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group was 10.47 ± 3.08; and in the metformin group, it was 11.93 ± 4.64 (*P* = .16). Compared to the beginning of the study, the MASI scores were significantly decreased in both groups of placebo (*P* = .00) and metformin (*P* = .00) one month after the end of the study; nevertheless, no statistically significant difference was observed between the MASI Scores of two groups in any of the study periods (*P* > .05).

Conclusion: The results of the present study showed that metformin cream significantly declines the patients' MASI score and does not have any effect on patients' laboratory markers. Of course, no significant difference was observed between the MASI scores of the patients receiving metformin and the placebo group; however, the MASI score decrease trend continued until the 12th week; while in the placebo group, no significant decrease was seen after eight weeks.

Keywords: Melasma; metformin; MASI score; skin; hyperpigmentation.

1. INTRODUCTION

Melasma is a prevalent acquired disease, usually symmetric, in the form of bright to darker brown macules in areas exposed to sunlight (most cases are in the face, sometimes neck and rarely forearms). The precise incidence of melasma is not clear; however, it has been often estimated in females more than males [1]. Pigmentary disorders such as melasma, impact a person's health-related quality of life adversely. Actually A healthy normal skin is an important aspect of sense of well-being and self-confidence and also unequivocally contributes to one' positive body image. These patients experience significant amount of emotional pain and incidence of psychiatric disorders among dermatology patient varies from 30-60% and all of this problems leads to avoidant personality disorder [2] The exact etiology of melasma is unknown; nevertheless, factors like sunlight, pregnancy, thyroid disorders, phototoxic drugs, antiepileptic drugs, genetic predisposition and hormone therapy play a role in its pathogenesis [1,3].

Three clinical patterns of central, malar and mandibular are considered for melasma in accordance with the distribution of lesions. Also in the examination with the wood's lamp, the types of dermal, epidermal, and mixed are the most common types [1].

Melanocytes are specific cells in the epidermal basal layer, producing melanin and transferring it to the surrounded keratinocytes. The change of tyrosine into melanin is performed through three enzymes in melanocytes (tyrosinase enzymes, tyrosinase-related protein 1 (TRP1) and dopachrome tautomerase (DCT)). Stimulation of the melanin production is done by various factors as UV rays and α-melanocyte-stimulating hormone (αMSH). These factors result in the activation of the pathway of cAMP whose main target is the microphthalmia-associated transcription factor (MITF), *i.e*. it leads to the translation of the genes playing role in induction of the expression of MITF (the main regulator in translating the genes involved in the synthesis of melanin, such as tyrosinase , TRP1 and DCT) [4]. Metformin is a member of the biguanides family; and it is considered as a guanidine derivative. As an effective ingredient in the French Lilac (Goat's Rue) Galega afficinalis, guanidine and its isopentyl derivatives, galegine, were recognized in the early twentieth century. In Europe, this plant was used to treat thirst as well as frequent urination. In 1920, metformin was known as a blood-glucose-lowering drug and it is now used as the first line for diabetes treatment [5].

Recently, it has been indicated that metformin can reduce intracellular cAMP [6]. Since cAMP plays a role in melanogenesis, metformin seems to result in the inhibition of melanogenesis. Metformin results in a considerable decline in the melanin content in the basal layer. On the other hand, it plays a role in decreasing the tyrosinase enzyme levels, TRP-1 and TRP-2 that are the key proteins in melanogenesis. In addition, the decline in MITF expression via the cAMP-dependent pathway has been introduced as the other reason for melanogenesis inhibition by metformin [7]. These effects of metformin have only been observed in its topical use and have not been seen in systemic use of the drug. The effect of metformin has been so far studied on the treatment of skin hyperpigmentation only in animal models [8].

Since the previous studies in the context of the metformin's mechanism and its effects on animal models reveal its inhibitory role in melanogenesis, and no study has been so far conducted on humans, in this study, it was

decided to use topical metformin for the treatment of melasma in human.

2. METHODS

After obtaining a license from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code of Ethics: IR.AJUMS.REC.1397.391), sixty patients with melasma who had referred to the Dermatology Clinic of Ahvaz Imam Khomeini Hospital and were willing to participate in the study were randomly included to this clinical trial study. After obtaining their informed consent and describing the plan and the treatment's benefits and side effects in detail, they participated in the study according to the protocol provided to them. The study period was four months.

2.1 Exclusion Criteria

Pregnancy, lactation, male gender, hormone therapy (like pregnancy control pills), atrophy and telangiectasia in the site of melasma, using topical treatment for melasma in the last three months, drug allergy history, lack of patient's collaboration in regular follow up visits, Glomerular filtration rate (GFR) under 30, as well as taking drugs causing photosensitivity, such as tetracycline, spironolactone, phenytoin and carbamazepine.

2.2 The Study Procedure

The patients' history was recorded at the beginning of the study, and after careful examination with the wood's lamp, the involved area and the distribution, homogeneity and melasma type (dermal, epidermal, and mixed) were recorded. Clinical assessment of the severity of melasma was recorded by the melasma area and severity index (MASI score). Furthermore, blood tests were conducted on fasting blood sugar (FBS), lipid profile, blood urea nitrogen (BUN), creatinine before and at the end of the study. Moreover, the patients' body mass index (BMI) at the onset and end of the disease was also calculated and recorded.

At the end of the study, the patients' satisfaction of the treatment was scored from zero to ten (the highest satisfaction was indicated by 10 and no satisfaction was shown by 0).

The lesions of each patient were pictured before the treatment and at the weeks 4, 8, 12 of the treatment and four weeks after the end of treatment in a location with the same brightness and distance with fixed camera.

The patients received SPF 50 Sunscreens and randomly received the drugs previously coded by the researchers, took them twice daily for 12 weeks, and evaluated at the weeks 4, 8, 12 of the treatment, and one month after the end of it. For randomization we used Simple Random Sampling by random digits table and patients randomly divided into two groups. Patients in the case group received topical metformin 15% and those in the control group received vehicle. Both groups were recommended to take sunscreen.

Two aqueous and oil phases were used in order to prepare the metformin cream. The aqueous phase contained distilled water, metformin powder 15%, protective 0.15% (methyl paraben and propyl paraben 9:1). The oil phase is consisted of 5% stearyl alcohol, 5% bee wax, 3% spermaceti (white whale), 3% cholesterol and 23% cold cream. The aqueous and oil phases were brought to the temperature of 70°C to turn into liquid. Then the aqueous phase was added to the oil phase under the incubator in order to reach it to the congeal point. Finally, the essential oil was added to the cream.

2.3 Statistical Analysis

In the beginning of the study 87 patients enrolled to the study. During study process 27 patients excluded from the study because of several problems occurred such as: Acne, patient's worsening, using alternative treatment methods such as tranexamic acid. So due to complete the exact number of each group, we continued patient selection till reach 30 patients in each group. The mean and standard deviation were used in quantitative variables and frequency and percentage were used in qualitative variables in order to describe the data. T-test, chi-square test and regression methods were used in order to analyze data. All analyses were conducted by means of SPSS software version 20.

3. RESULTS

The patients' mean age was 35.25 ± 7.11 years and the mean age was separately 32.76 ± 6.74 in the placebo group and 37.73 ± 6.69 in the metformin group, wich is significantly higher than placebo group (P = .006).The patients mean BMI was 26.87 ± 5.89 and the mean BMI was separately 65.22 ± 15.15 in the placebo group and 72.65 ± 15.09 in the metformin group, wich is significantly higher than placebo group (P = .01). Twenty-two (36.7%) had the phonotype 3, 37 (61.7%) had phonotype 4, and 1 (1.7%) had phonotype 5, and in both groups of

placebo and metformin, the highest frequency was for phonotype 4. Furthermore, 38 patients (63.3%) were epidermal, nine (15%) were dermal and 13 (21.7%) were mixed. The epidermal type has been indicated to be the most prevalent in both groups. Testing laboratory markers revealed no statistical significant difference between the placebo and drug groups before and after intervention, and the changes in each group were not statistically significant at the end of the study, too (Table 1).

At the onset of the study*, i.e.* the week zero, the mean MASI Score of all studied patients was 11.21 ± 3.99 and between 4.8 and 24.6; and the mean MASI Score was separately 10.47 ± 3.08 in the placebo group and 11.93 ± 4.64 in the metformin group, with no significant difference between the two groups (*P* = .16).

After the fourth week, the mean MASI Score of all studied patients was 10.34 ± 4.22 and between 2.4 and 24.6; and the mean MASI Score was separately 9.98 ± 3.18 in the placebo group and 10.69 ± 5.08 in the metformin group, with no significant difference between the two groups (*P* = .52).

After the eighth week, the mean MASI Score of all studied patients was 9.56 ± 3.89 and between 2.40 and 23.10; and the mean MASI Score was separately 9.63 ± 2.98 in the placebo group and 9.44 ± 4.65 in the metformin group, with no significant difference between the two groups (*P* = .79).

After the twelfth weeks, the mean MASI Score of all studied patients was 9.22 ± 4.01 and between 1.2 and 23.10; and the mean MASI Score was separately 9.63 ± 2.98 in the placebo group and 8.82 ± 4.82 in the metformin group, with no significant difference between the two groups (*P* = .33) (Tables 2-4 and Fig. 1).

Moreover, one month after the end of treatment, the mean MASI Score of all studied patients was 9.18 ± 3.89 and between 1.2 and 23.10; and the mean MASI Score was separately 9.60 ± 2.97 in the placebo group and 8.78 ± 4.79 in the metformin group, with no significant difference between the two groups (*P* = .43).

Comparison of MASI Scores in patients in both groups separately by phonotype type was not significant in any of the MASI Scores. Moreover, no statistically significant difference was observed in the MASI Score at any investigation times in terms of the type of melasma.

Investigation of the MASI Score changes in two groups revealed that the MASI Score of patients significantly declined in the placebo group in the fourth week compared to that in the week zero (*P* = .01); and in the eighth week compared to the fourth week (*P* = .001); nevertheless, from the eighth week onwards, the changes have not been statistically significant. Of course, finally one month after the study, the patients' MASI Score was significantly less than that in the week zero (*P* = .00).

Table 1. Comparison of changes in laboratory variables 3 months after treatment (week 12) between the two groups

Variable	Group	Indices		*P*-value
		Mean	SD	
BMI	Placebo	-0.1203	0.45507	.9
	Metformin	-0.1457	1.10023	
FBS	Placebo	-1.9667	5.14268	.85
	Metformin	-1.5667	5.20400	
TG	Placebo	3.3000	43.03259	.72
	Metformin	-8.1333	72.06880	
Chol	Placebo	-1.1333	13.86569	.75
	Metformin	-4.4000	23.66811	
HDL	Placebo	0.0333	4.76686	.61
	Metformin	0.7833	6.60940	
LDL	Placebo	-2.2600	15.91661	.95
	Metformin	4.5467	21.27832	
GFR	Placebo	3.2593	24.50841	.44
	Metformin	7.4377	16.84687	

BMI, Body Mass Index; FBS, Fasting Blood Suger; TG, Triglyceride; Chol, Cholesterol; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; GFR, Glomerular Filtration Rate; SD, Standard Deviation

Table 2. Comparison of melasma area and severity index in the two groups in weeks 0, 4, 8, 12 and 1 month after study

Variable	Group	Indices		*P*-value
		Mean	SD	
Week 0	Placebo	10.4759	3.08703	.16
	Metformin	11.9300	4.64744	
Week 4	Placebo	9.9828	3.14666	.52
	Metformin	10.6900	5.08218	
Week 8	Placebo	9.7034	3.00208	.79
	Metformin	9.4400	4.65230	
Week 12	Placebo	9.6345	2.98236	.44
	Metformin	8.8267	4.82379	
After 1 month	Placebo	9.6034	2.97447	.43
	Metformin	8.7867	4.79114	

SD, Standard Deviation

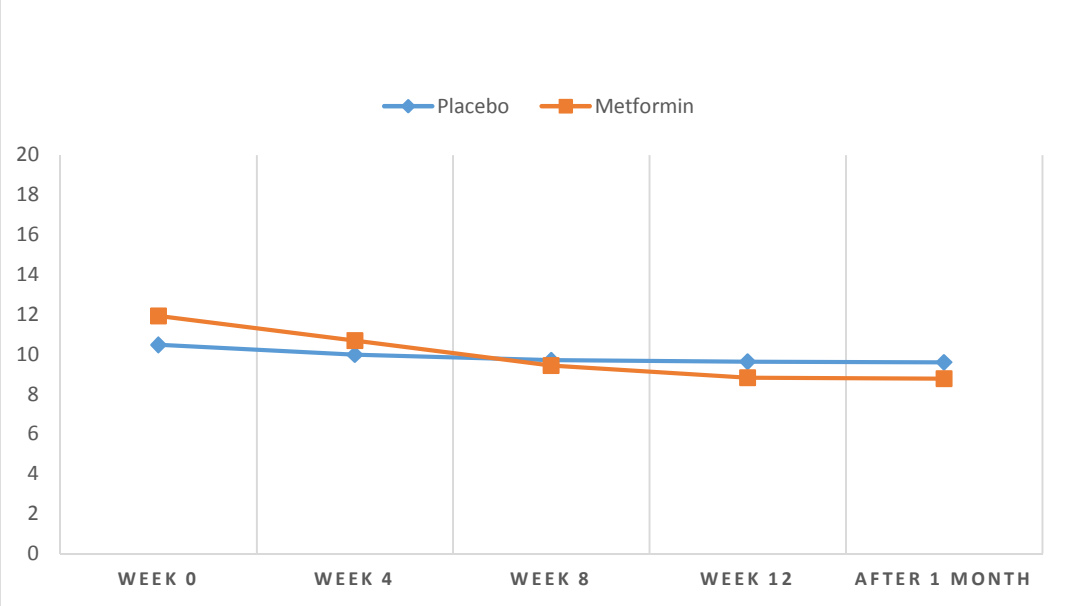

Fig 1. Comparison of MASI Score changes in two groups during the study

Table 3. Comparison of MASI score in the placebo group during the study

Rate	Time	MASI score		*P*-value
		Mean	SD	
Fourth week to zero	Week 0	10.4759	3.08703	.01
	Week 4	9.9828	3.14666	
Eighth week to fourth				.001
	Week 8	9.7034	3.00208	
Twelfth week to eighth				.098
	Week 12	9.6345	2.98236	
A month later than the twelfth				.32
	After 1 month	9.6034	2.97447	
A month later than the zero				.00

Table 4. Comparison of MASI score in the placebo group during the study

Rate	Time	MASI score		*P*-value
		Mean	SD	
Fourth week to zero	Week 0	11.9300	4.64744	.00
	Week 4	10.6900	5.08218	
Eighth week to fourth				.00
	Week 8	9.4400	4.65230	
Twelfth week to eighth				.00
	Week 12	8.8267	4.82379	
A month later than the twelfth				.32
	After 1 month	8.7867	4.79114	
A month later than the zero				.00

In addition, in the metformin group, the MASI Score of patients significantly declined in the fourth week compared to that in the week zero (P = .00), in the eighth week compared to the fourth week (P = .00) and in the twelfth week compared to the eighth week (P = .00); nevertheless, from the twelfth week onwards, the changes have not been statistically significant. Of course, finally one month after the study, the patients' MASI Score was significantly less than that in the week zero (P = .00).

Hence, one month after the study, although in both groups, the MASI Score scores significantly decreased compared to those of the week zero, in the metformin group, after eight weeks of treatment, the MASI Score also decreased significantly, while in the placebo group, the significant decrease continued until the eighth week and did not significantly change in the twelfth week (Fig. 1).

At the end of this study, it was revealed that the mean satisfaction of all the patients was 2.36 ± 2.03 and between zero and nine. The mean satisfaction separately in the placebo group was 1.06 ± 1.20 and in the metformin group, it was 3.66 ± 1.88, which is significantly higher than that of the placebo group (P = .000).

4. DISCUSSION

The present research is the first clinical study to assess the effect of topical metformin for the treatment of melasma. It was performed through the investigation of sixty patients assigned to placebo and metformin and using MASI score. As reported in the results section, the patients' age, weight, and BMI in the metformin group were significantly higher from placebo; regarding the randomly selection of patients and the lack of distortive effect on the study process, it has been an unexpected finding. The study of all laboratory markers including blood glucose, triglyceride, cholesterol, high-density lipoprotein, low-density lipoprotein, blood urea nitrogen, creatinine, as well as glomerular filtration rate indicated that in the abovementioned markers, patients had no significant difference at the onset of the study. After the end of the study, no significant difference was observed between the markers in the two groups and the recorded changes in the metformin group had not been significantly different from those in the markers in the patients in the placebo group. This finding is considerable from two perspectives. First, the patients in both groups had a consistent physiological condition at the onset of the study, which is one of the strengths of the study, indicating that the patients in the placebo and metformin groups were selected and compared with each other in conditions as closely as possible. The second and more important finding is that prescribing the topical metformin has no side effect on patients' laboratory markers, and the drug only affected the area where it is used, which is also one of the strengths of the study and the drug's efficacy without side effects.

Another valuable fundamental finding of the current study was the investigation of the patients' phonotype and melasma type that showed the majority of phonotype 4 and 3, was more phonotypes and also the MASI Score of patients with phonotype 4 was more than phonotype 3 in both groups.

The main goal and the important finding of the present study were to investigate the effectiveness of topical metformin on the patients' melasma. To this end, we examined the patients' MASI Scores. As previously indicated, at the onset of the study, there was no significant difference between the MASI Scores of patients; and they were compared at the same conditions in both groups. Investigation of the MASI scores

of the patients in the two groups showed no statistically significant difference between them in any of the MASI scores; *i.e*. the MASI Score were reduced with time and drug use in both groups and this finding could initially be due to the time period of the study; since the intervention and data collection were conducted during the second half of the year, and at that time the daily exposure to sunlight and its effect on patients are minimal compared to those in the first half of the year. Obviously, the reduction process in MASI Scores is also possible without any intervention. Further studies on each of the two groups revealed that in patients receiving placebo, their MASI Scores significantly decreased only in the fourth week of study compared to the week zero, and in the eighth week compared to the fourth week; however, this decrease was not statistically significant in the twelfth week and even one month after the treatment, no statistically significant decrease was observed compared to the twelfth week. In other words, reduction in MASI Scores happened in both groups but in patients receiving metformin, this decline was continuing while they were receiving the drug and terminated by stopping the drug, although it was not statistically significant. In contrast to metformin group, MASI Score reduction in a plcebo group continued for only 8 weeks. This finding may indicate the recommendation of continuing the drug in longer periods and significant decline of MASI Scores of patients in long-term periods; and the insignificant MASI Scores of patients in both groups may be due to the very low duration of using the drug. To achieve significant results, the drug must be prescribed for more time. Albeit, the dosage of the drug is another possible variable; however, this hypothesis cannot be investigated due to the absence of another group with a different dosage and this may be a recommendation for future studies. Although no significant difference was observed between the two groups in any of the periods, the decline trend of MASI Scores in patients receiving metformin may be consistent with the laboratory findings and animal tests of evaluation of the drug's effect on melanogenesis inhibition; since in those studies, significant statistical differences were observed. For example, the study by Miller et al. (2014) was aimed at inhibiting melanogenesis by metformin with anti-diabetic effects on mice. In that study, it was reported that the use of topical metformin caused depigmentation and decreased melanin content and melanotic genes [6].

In addition, in 2013, Miller et al [9]. performed a study on the mechanism of effect of biguanides. In order to investigate the in vivo effect, the required dosage of metformin was given to mice by gavage method. Then, glucagon was intraperitoneally injected with the required dosage. Gavage metformin led to the increased phosphorylation of acetyl carboxylase and AMPK, representing the decreased liver cellular energy. Moreover, metformin inhibited the increase, cAMP, and PKA activity as well as phosphorylation of the PKA substrate, i.e. blocking this pathway by biguanides [10]. Of course, it should be ultimately noted that patient's satisfaction of the treatment is a finding only obtained by accurate clinical studies. In the current study, patients' satisfaction with treatment in metformin group was significantly higher than that of placebo group.

In general, although the abovementioned laboratory and animal tests findings are the fundamental of clinical studies such as this one, due to the lack of sufficient studies as well as the lack of extensive clinical trials in this context, adequate documentation is not available to develop the above hypothesis and future research is required. Also it is necessary to say that using SPF 50 Sunscreens routinely may lead to decrease and improve the MASI score. Also previous studies used metformin 30% and we used 15% maybe increasing this percent lead to better results.

5. CONCLUSION

The results of the present study showed that metformin cream significantly declines the patients' MASI score and does not have any effect on patients' laboratory markers. Of course, no significant difference was observed between the MASI scores of the patients receiving metformin and the placebo group; however, the MASI Score decrease trend continued until the 12th week; while in the placebo group, no significant decrease was seen after eight weeks.

CONSENT

As per international standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

A license was obtained from the Ethics Committee of Ahvaz Jundishapur University of

Medical Sciences (Code of Ethics: IR.AJUMS.REC.1397.391)

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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