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Is Topical Metformin Effective in Treatment of Melasma?

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ABSTRACT

Background: Melasma is an acquired hyperpigmentation characterized by bilateral irregular brown macules and patches over sun-exposed areas of face and less commonly, forearms. No single treatment is universally effective. It has been shown that metformin could decrease intracellular cyclic adenosine mono phosphate. Since c-AMP has a role in melanogenesis, metformin can inhibit melanogenesis resulting in a significant reduction in melanin in the basal layer. **Objective**: The aim of the present study was to evaluate the effectiveness and safety of topical metformin for melasma treatment. **Patients and methods**: A quasi-experimental (pre-post comparison study) study included 30 female cases of melasma from the Dermatology outpatient clinic of Mansoura University Hospital, during the period between March 2021 and March 2022. Included females had more than 18 years old. The metformin lotion was prepared using metformin powder and a mixture of polyethylene glycol (PEG) -6; Ethylene Glycol; PEG-32, acetyl alcohol, liquid Paraffin, Methylparaben, propylparaben, and distilled water. Participants applied one layer of metformin 30% lotion on the affected area on face at night to the morning for a period of 3 months.

Results: Melasma Area and Severity Index (MASI) score decreased gradually after successive sessions (mean 13.8, 13.7, 11.5, 11.4, 11.4, respectively), with statistically significant improvement after 2, 3 months and also 1 month after the end of treatment (P values 0.002, 0.001, and 0.001, respectively). Grades of improvement significantly increased after 1, 2 months, but became stable by the 3rd month and one month after therapy**.** After the end of therapy, 20% of participants were satisfied, 36.7% were slightly satisfied, 26.7% were poorly satisfied, and 16.7% were not satisfied. No side effects were reported. **Conclusion**: Melasma was improved after using of topical metformin with no side effects appeared. Thus, topical metformin is a new, safe, and effective for melisma treatment.

Keywords: Melasma, Metformin, Topical treatment, Quasi-experimental study.

INTRODUCTION

Melasma is an acquired pigmentary disease characterized by symmetrical hyperpigmented macules and patches over face, sometimes neck and rarely forearms, often involving females of reproductive age [(1)]. Its prevalence varies from 1.5% to 33.3% [(2,3)].

Hyperpigmentation is generally because of melanocytosis and enhanced melanogenesis due to upregulated melanin biosynthesis-related genes including microphthalmia-associated transcription factor (MITF), and tyrosine-related protein-1(TYRP1) because of many factors like genetic predisposition, UV exposure, thyroid diseases and gestation and medications like contraceptive pills and phenytoin [(4)].

Melasma treatment is a frustrating experience for physicians and patients due to its recurrent and recalcitrant nature. Several treatment modalities were tried for melasma including hydroquinone [(5,6)], Triple Therpy Combination (TCC) include hydroquinone , steroid and tretinoin [(7,8)], kojic acid, azelaic acid, arbutin, vitamin c, chemical peeling, lasers, tranexamic acid, rucinol, oligopeptides, silymarin, orchid extracts, and botanical extracts with variable success rates [(8)].

However, TCC is still standard treatment, although associated with severe side effects after long-term use. Therefore, the search for an effective therapy that achieves depigmentation with no side effects has continued. Studies demonstrated that topical metformin has melanopenic effect because of down regulation of MITF expression leading to downregulation of several melanogenic proteins including tyrosinase, tyrosinase related protein-1(TRP-1), TRP-2, and protein kinase C-beta [(9-11)].

The aim of the study was to evaluate the effectiveness and safety of topical metformin for melasma treatment.

PATIENTS AND METHODS

Study Design

A quasi-experimental (pre-post comparison study) study included 30 female cases of melasma from the Dermatology outpatient clinic of Mansoura University Hospital, during the period between March 2021 and March 2022. We included females aged more than 18 years old, who did not receive any drugs for melasma over the previous 14 days for topical therapy or 3 months for cosmetic techniques including lasers, dermabrasion, or peel. Pregnancy, lactation, females on contraceptives, phenytoin, kidney disease, and females with any other skin diseases were excluded.

METHODS

All participants were subjected to thorough history taking including personal history (age, occupation, marital status, address, pregnancy and lactation, any special habit), present history of the illness (onset, duration and course), history of precipitating factors, medical history of any systemic diseases, any history of drugs (as; oral contraception, hormonal therapy,

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phototoxic, ant seizure and anticoagulant drugs) and family history of similar condition.

The general examination for any signs of systemic diseases like thyroid diseases, cushing syndrome, adrenogenital syndrome and diabetes mellitus. While, the dermatological examination included clinical assessment of the lesion distribution (cases were differentiated into centrofacial, malar, and mandibular pattern of melasma), fitzpatrick skin phototype detection (depending on Fitzpatrick scale), wood's lamp examination (to detect lesion's type [epidermal, dermal and mixed]) and digital and dermoscopic pictures were also obtained from each patient at baseline and after the end of follow up period. By dermoscopy, melasma was considered epidermal when regular pigment network with a brown pigmentation was observed, dermal when irregular network with blue-grey pigmentation was observed and mixed when areas of both characteristics [(12)].

Metformin lotion preparation

The metformin lotion was prepared in FAB-lab and the used materials were metformin and a mixture of polyethylene glycol (PEG) -6; Ethylene Glycol; PEG-32, acetyl alcohol, liquid Paraffin, Methylparaben, propylparaben, and distilled water. The used Equipment was hotplate with magnetic stirrer, viscometer, centrifuge, and digital pH meter.

Treatment plan of melasma

The patient was asked to shake bottle and apply one layer of metformin 30% lotion on the affected area on face at night to the morning for aperiod of 3 months and sunscreen of SPF 30 was applied at the morning.

Follow Up

Assessment of the efficacy of treatment; photographs were obtained at baseline, before treatment and every month during period of treatment. Melasma severity were assessed by Melasma Area and Severity Index (MASI) as described by **Kimbrough-Green and colleagues [(9)]**.

MASI was calculated by subjective evaluation of three factors: area (A) of affection, darkness (D), and homogeneity (H), with forehead (f), right malar region (rm), left malar region (lm), and chin (c), corresponding to 30%, 30%, 30%, and 10% of face, respectively. The A is scored from 0 to 6 (0 =no affection, 1 =less than10%; 2 =10%-29%; 3 =30%-49%; 4 =50%-69%; 5 =70%-89%; and 6 =90%-100%). D and H are scored from 0 to 4 (0 =not present; 1 =slight; 2 =mild; 3 =marked and 4 =maximum). MASI score undergoes calculation by adding the sum of D and H scores, multiplied by the value of the area of:

Total MASI score = 0.3 (DF+HF) AF+ 0.3 (DMR+HMR) AMR + 0.3 (DML+HML) AML+ 0.1 (DC+HC) AC.

Where D is darkness, H is homogenisty, A is area, F is forehead, MR is right malar, ML is left malar and C is chin.

Maximum MASI is 48. MASI score was calculated before treatment and every month during period of treatment, and the % of improvement was calculated by subtracting MASI score from pre-treatment MASI score and dividing it by pre-treatment score. Grade 0: not improved; grade 1: mildly improved (1% to <25%); grade 2: moderately improved (25%-50%); grade 3: markedly improved (>50%-75%); and grade 4: near complete/complete improvement (>75%) **[(13)].** Subjective evaluation was performed by each patient depending upon satisfaction level with therapy and was scored from 0 to 4 where 0 =not satisfied; 1 =poor satisfaction; 2 =slight satisfaction; 3 =satisfaction; and 4 =high satisfaction. Patients were followed up one time every 14 weeks during treatment to evaluate improvement and observe side effects and one month later after treatment.

Ethical Consideration:

The study approval was acquired from IRB of Faculty of Medicine at Mansoura University (MS.20.02.1051). This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Confidentiality and personal privacy were respected. The researcher was available throughout the study. The research objectives were clarified to the participants' relatives individually and in groups. Collected data weren't utilized for any other purposes.

Statistical Analysis

Data were analyzed by utilizing IBM SPSS Statistics for Windows, v22.0. Armonk, NY: IBM Corp. Qualitative data were defined by utilizing numbers and percents. Quantitative data were defined by utilizing medians and means, SDs for parametric data following testing normality by utilizing Kolmogrov-Smirnov test. Quantitative data were between groups involve Parametric tests; One Sample t test utilized for comparing mean of studied parameters compared to standard reference value and Student t-test was utilized for comparison among 2 independent groups. All tests were 2-sided and a P-value < 0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the sociodemographic characteristics and clinical data of the participants. The mean age was 39.1 years, and ranged from 29 to 50 years. All studied cases were subjected to full routine laboratory assessment, only 13.3% had anemia, while the rest of them had no abnormal laboratory findings**.**

Table (1): Sociodemographic characteristics and clinical data of included patients. included in the study.

Variable	Cases (N=30)	
	Mean ± SD/ Median (Min.-Max.)	n (%)
Age (years)	39.1 ± 6.4	
Occupation (outdoors) **No** **Yes**		 12 (40%) 18 (60%)
Onset **Gradual**		 30 (100%)
Course **Stable** **Progressive**		 21 (70%) 9 (30%)
Duration (years)	5 (0.1-10)	
Associated medical disease **No** **Diabetes mellitus** **Hypertension** **Rheumatoid arthritis** **Thyroid**		 26 (86.7%) 1 (3.3%) 1 (3.3%) 1 (3.3%) 1 (3.3%)
History of exacerbation in pregnancy	**Negative**	14 (46.7%)
	Positive	16 (53.3%)
Family history	**Negative**	14 (46.7%)
	Positive	16 (53.3%)

Table 2 summarizes skin type, pattern of melisma, wood light, dermoscope finding. Mean MASI was 13.8.

Table (2): Skin type and melasma features among studied patients.

Variable		Cases n=30 (%)
Fitzpatricks skin type	**III**	10 (33.3%)
	IV	16 (53.3%)
	V	4 (13.3%)
Pattern of melasma	**Malar**	18 (60%)
	Centrofascial	12 (40%)
Woods light	**Epidermal**	10 (33.3%)
	Dermal	6 (20%)
	Mixed	14 (46.7%)
Dermoscope	**Reticular pigmentation**	30 (100%)
MASI before therapy	**Mean ± SD**	13.8 ± 5.4

MASI score decreased gradually after successive sessions, with statistically significant improvement after 2, 3 months and also 1 month after end of treatment **(Table 3).**

Table (3): MASI score at different follow up times.

Variable	MASI Level (Mean ± SD)	P-value
Before therapy	13.8 ± 5.4	
After 1 month	13.7 ± 5.5	P1 =0.24
After 2 months	11.5 ± 4.7	P2 =0.002*
After 3 months	11.4 ± 4.8	P3 =0.001*
1 month after end of treatment	11.4 ± 4.8	P4 =0.001*

P1: difference between before therapy and after 1 month value, P2: difference between before and following 2 months, P3: difference between before and following 3 months, P4: difference between before and following 1 month after end of treatment. Test used: Paired t test.

Grades of improved significantly increased after 1 and 2 months, but became stable by the 3rd month and 1 month after end of treatment **(Table 4).**

Table (4): Improvement grades of melasma at different follow up periods.

Variable	Improvement grades		P-value
	No	Mild and Moderate	
	N (%)	N (%)	
After 1 month	27 (90%)	3(10%)	P1 <0.001*
After 2 months	5 (16.7%)	25 (83.3%)	P2 <0.001*
After 3 months	5 (16.7%)	25 (83.3%)	P3 <0.001*
1 month after treatment	5 (16.7%)	25 (83.3%)	

P1: difference between 1 month and 2 months value, P2: difference between 1and after 3 months, P3: difference between 1 month and 1 month after end of treatment, Test used: Wilcoxon signed rank test and MC Nemar test.

After the treatment, more than half of the patients were satisfied or slightly satisfied **(Table 5).**

Table (5): Satisfaction grades of participants after local treatment with metformin.

Variable		Satisfaction grade N (%)
1 month after end of treatment	**No satisfaction**	5 (16.7%)
	Poor satisfied	8 (26.7%)
	Slightly satisfied	11 (36.7%)
	Satisfied	6 (20%)

Table 6 illustrates that there was no significant difference of improved grades between studied groups as regard age, outdoor work, course and duration of disease (P >0.05). Besides, there was no significant relationship between history of exacerbation in pregnancy, positive family history and presence of anemia with degree of improvement. Similarly, there was no significant relationship between improvement grade and melasma characteristics and Fitzpatriks skin type (P >0.05).

Table (6): Association between improvement grades and different variables.

Variable	Improvement Grades		P-value
	No	Mild and Moderate	
	N=5 (%)	N=25 (%)	
Age/years			
Mean ± SD	40.2 ± 4.8	38.9 ± 7.58	0.789
Outdoor work			
• No	1 (20%)	11 (44%)	0.622
• Yes	4 (80%)	14 (56%)	
Course			
Stable	3 (60%)	18(72%)	0.622
Progressive	2 (40%)	7(28%)	
Duration/years			
Median (Min.-Max.)	5 (0.5-10)	4(0.1-7.0)	0.07
Comorbidities	1 (20%)	3 (12%)	0.63
Exacerbation in pregnancy	3 (60%)	13 (52%)	0.742
Family history	3 (60%)	13 (52%)	0.742
Anemia	0 (0.0%)	3 (12%)	1.0
Fitzpatriks skin type			
III	3 (60%)	7 (28%)	
IV	1 (20%)	15 (60%)	0.321
V	1 (20%)	3 (12%)	
Pattern of melasma			
Malar	4 (80%)	14 (56%)	0.317
Centro fascial	1 (20%)	11 (44%)	
Woods light			
Epidermal	0 (0.0%)	11 (44%)	
Dermal	2 (40%)	4 (16%)	0.11
Mixed	3 (60%)	11 (44%)	
MASI before therapy			
Mean ± SD	**13.9 ± 4.98**	**13.6 ± 5.26**	0.907

DISCUSSION

Melasma is an acquired hyperpigmentation characterized by bilateral irregular brown macules and patches over sun-exposed areas of face and less commonly, forearms. It frequently affect darker skinned women, often Asian or Hispanic females, with Fitzpatrick skin types III-IV. Melasma can be induced by several factors such as sun exposure, genetic background, and sex hormones in females. No single therapy is generally effective. Combination treatments, either in double or triple combinations showed the best results in comparison with single therapy [(14)].

It was found that metformin reduce intracellular c-AMP which has a role in melanogenesis [(15)]. The aim of the work was to assess the effectiveness and safety of topical metformin as a therapy for melasma. A total of 30 female cases of melasma were enrolled in our study. They were enrolled from the Dermatology Outpatient Clinic of Mansoura University Hospital. Their mean age was 39.1 years, and ranged from 29 to 50 years, among them 60% work outdoors.

In line with our result, **Pollo *et al.*** [(16)] reported that mean age of melasma females was 39 (SD 8) years, which is comparable to the findings of **Sarkar *et al.*** [(17)] study in which mean age was 38.02 years old. This indicated that melasma often occurs in the middle-age. One of the most important findings of **Sarkar *et al.*** [(17)] study was the relationship between cooking or occupational heat exposure and melasma severity. They reported that participants who had a higher duration of exposure to cooking heat had a more severe melasma or a greater MASI score. Sun exposure was reported as a significant trigger in the majority of studies.

All of our studied cases had gradual onset, 70% had stable, 30% had progressive course. Mean disease duration was 3.4 years, ranged from 1 month up to 10 years. **Hagag and Abdallah** [(18)] reported that 40% of melasma patients had progressive course, 40% had intermittent, and 20% were stationary. Almost 81% of the cases present progressive course in a study by **Saleh *et al.*** [(15)] the mean disease duration in **Kumaran *et al.*** [(19)] study was 4.16 (SD 3.8) years.

Most of studied cases in our study had no comorbidities, while 3.3% had DM, 3.3% had hypertension, 3.3% had rheumatoid arthritis and 3.3% had thyroid disease, 53.3% had history of exacerbation in pregnancy, and 53.3% had positive family history.

Kumaran *et al.* [(19)] revealed a positive family history in only 9.9% of melasma patients, while that were in literature ranged from 33.33% to 41.7% [(20,21)].

Epidemiologic data demonstrated that melasma happens in 14.5%-56% of pregnant females and in 11.3%-46% of those on contraceptive pills [22]. A study involving 324 melasma females in 9 different countries reported melasma in 20% of pregnant females and 10% start post-menopause.

In the current work, regarding pattern of melasma, 60% had malar pattern and 40% had Centro fascial pattern. By woods light, 33.3% had epidermal, 20% had dermal and 56.7% had mixed pattern. By dermoscope, all studied cases had reticular pigmentation.

Through the Woods lamp **Navya and Pai** [23] found that 48% of patients were epidermal pattern, 40% had mixed pattern and 12% of had dermal subtype. **Jalaly *et al.*** [24] observed that epidermal subtype was the commonest subtype (55%), followed by mixed type (22.5%) and dermal type (12.5%) which was not consistent with our findings.

In our work, mean MASI before treatment was 13.8, and ranged from 2.4 to 26.4 which is quite similar to **Hassan *et al.*** [25] the mean modified MASI score at presentation was 12.3 (SD 3.4), with a range from 9 to 23. In the current study, MASI score decreased gradually after successive topical application of metformin 30% lotion for 3 monthes, we found that mean MASI score before therapy was13.8 (SD 5.4) then after one month, the mean MASI score of studied patients was13.7 (SD 5.5). After 2 months, the mean MASI score of studied patients was 11.5 (SD 4.7). After 3 months, mean MASI score was 11.4 (SD 4.8). MASI score decreased gradually after successive sessions mean 13.8, 13.7, 11.5, 11.4, and 11.4, respectively, with statistically significant improvement after 2, 3 months and also 1 month after treatment (P values 0.002, 0.001, 0.001, respectively).

Channakeshavaiah and Chandrappa [26] reported that melasma improvement after topical metformin was observed in 13 out of 20 patients. Mean MASI score significantly decreased from 7.84 (SD 5.32) to 6.71 (SD 5.04) following 8 weeks of therapy in *Group 1* (P1 =0.017). Likewise, **Abo Alsoud *et al.*** [27] assessed safety and effectiveness of topical metformin (30%) in melasma and compared its effectiveness with TCC (hydroquinone 2% + tretinoin 0.025% + fluocinolone acetonide 0.01%). They observed a reduction in melasma severity after metformin application in the majority of cases with different degrees of improvement. MASI score reduced significantly from 12.18 (SD 9.33) pre-treatment to 5.59 (SD 4.61) following 8 weeks of therapy a mean reduction percent of 55.97 (SD 16.77) in metformin group (P value 0.001).

In agreement with our result, **Mapar *et al.*** [28] showed that topical metformin (15%) significantly reduced MASI score and was safe over 3 months of use; they found that at the onset of the study, mean MASI Score in metformin group was 11.93 (SD 4.64) then following 4 weeks, it was 10.69 (SD 5.08). Following 8 weeks, mean MASI Score in metformin group was 9.44 (SD 4.65). Following 12 weeks, mean MASI of was 8.82 (SD 4.82). They found that MASI Score significantly decreased after 4 weeks in comparison with week zero (P-value 0.001), after 8 weeks in comparison with after 4 weeks (P-value 0.001) and in after 12 weeks in comparison with after 8 weeks (P-value 0.001); nonetheless, from the 12th week onwards, the alterations were not statistically significant. Finally 4 weeks after the study, MASI Score was significantly less than its value in week zero (P-value 0.001).

Lehraiki *et al.* [11] assessed the influence of topical metformin 30% on melanogenesis both in vitro and in vivo. They applied metformin on tail of mice over 8 weeks and noticed that tail depigmentation in mice. In addition, they reported an anti-melanogenic effect of metformin on reconstituted human epidermis and human skin biopsies.

In the present study, mean improvement increased with increased duration of topical application of metformin, after 1 month 3 (10%) patients demonstrated mild to moderate improvement and increased to 25 (83.3%) after 2 monthes and become stable by 3rd and 1 month after treatment 25 (83.3%).

In terms of the global improvement scale, **Channakeshavaiah and Chandrappa** [26] recorded out of 20 cases in metformin group, 1 (5%) cases demonstrated significant improvement, and 11 (55%) cases had mild improvement by after 8 weeks.

In our study, after treatment, 20% of patients were satisfied, 36.7% were slightly satisfied, 26.7% were poorly satisfied, and 16.7% were not satisfied. Satisfaction showed significant positive correlation with improvement percent, but not with age, duration or baseline MASI.

No adverse effects to metformin application were noted in our study**,** this agreed with that previously reported by **Channakeshavaiah and Chandrappa** [26]. Furthermore, no significant side effects to metformin were reported in **AboAlsoud *et al.*** [31] study.

CONCLUSION

Melasma was statistically significant improved after using of topical metformin with no side effects appeared. Thus, topical metformin is a new, safe, and almost effective for melisma treatment.

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