Type of the Paper (Systemic Review)

The Effectiveness of Metformin Lotion in The Treatment of Melasma: A Systematic Review

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Abstract:

Introduction: Melasma is a form of acquired chronic symmetrical focal hypomelanosis that impacts areas exposed to the sun, particularly in female cases. Metformin lotion is commonly used to reduce melanin synthesis in patients with melasma by topical administration.

Aim of the study: To assess metformin lotion's safety and clinical efficiency in managing melasma.

Methods: This review included three studies that met the inclusion and exclusion criteria for patients with melasma. The patients were all females, and their ages ranged from childbearing to adulthood. The quality of the included studies was generally good.

Result: After the search and screening three studies met the inclusion criteria for our review. Results show that According to mMASI after treatment of metformin lotion, it is effective in the treatment of melasma.

Conclusions: Melasma can be effectively treated by metformin.

Keywords: Melasma; Metformin; Treatment.

1. Introduction

Melasma is an acquired pigmentary disorder usually a symmetrical macule or patch of bright to dark brown in women during the childbearing period [1].

It is multifactorial, with pathogenesis including a transaction of keratinocytes, pole cells, quality guideline irregularities and expanded vascularization [2].

UVB illumination likewise increments plasmin creation by keratinocytes. This protein prompts more elevated levels of arachidonic corrosive and melanocyte-stimulating hormone and hence animates the melanin amalgamation pathway [3].

Topical metformin has melanogenic action, as it downregulates the expression of microphthalmia-associated transcription factor (MITF) This results in the inhibition of the transcriptional activity of melanogenic proteins including protein kinase C–beta, tyrosinase, tyrosinase-related protein 1 (TRP-1), tyrosinase-related protein 2 (TRP-2) [4].

As of late it has been demonstrated that metformin was displayed to diminish intracellular degrees of cyclic adenosine monophosphate (c-AMP). It assumes a part in melanogenesis, metformin brings about an extensive decrease in the melanin content in the basal layer. Likewise, it assumes a part in diminishing the tyrosinase compound levels, TRP-1 and TRP-2 which are the vital proteins in melanogenesis and decline MITF articulation using the c-AMP-dependent pathway. These impacts of metformin have just been seen in its skin use and have not been seen in the frame of mind of the medication [5].

2. Methods

2.1. Search strategy

This is a systematic review performed according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines [6]. A literature search for potential studies published was done using PubMed, Cochrane, Embase, Scopus, Medline and CINAHL. The details of the search include “melasma; treatment; metformin”.

Inclusion criteria

Patients with melasma in the childbearing period (18 to 50) years old.

Exclusion criteria

- Patient with foundational sicknesses that cause hyperpigmentation as hyperthyroidism.
- Patients under treatment cause hyperpigmentation as hostile to epileptic medications.

- Patient on oral prophylactic pills and pregnant ladies.
- Patient with PCO.

2.2. Study selection

Both entire full-text and abstracts underwent conventional, blind review. Selected publications' references to pertinent studies were reviewed for potential inclusion. The Excel program was utilized. Moreover, any differences among scholars were settled by senior contributors before final clearance.

2.3. Data extraction

Before screening, the search results from each database were pooled and duplicates were eliminated. Initial screening of the title and abstract was done, full texts of chosen articles were retrieved, eligibility was double-checked using a predetermined eligibility form, and data was collected using a predefined form. The study was done in about 120 patients and all using metformin was effective for the treatment of melasma.

2.4. Bias risk assessment, quality, and validity of included studies

The author evaluated the included studies for quality and bias risk, including using the Newcastle-Ottawa Scale.

2.5. Statistical analysis

For continuous outcomes, when at least two studies were available, mean differences or mean changes from baseline were pooled and expressed as mean differences (MDs). We used the odds ratios (ORs) with 95% confidence intervals (CIs) as the common effect estimates for binary outcomes. We pooled study estimates using the inverse variance method for a fixed-effects model if there was no significant heterogeneity among the studies. However, a random-effects model was used if substantial clinical or statistical heterogeneity was observed [7]. Statistical heterogeneity was assessed using Cochran's Q test, with $p < 0.10$ [8]. The degree of heterogeneity was estimated using I2 and tau-squared ($\tau 2$) statistics, in which the heterogeneity was investigated as low (I2 75.0%, $\tau 2 = 0.16$) [8, 9]. Statistical tests were two-sided, with a $p < 0.05$. All analyses were conducted using the STATA software (version 16.0; StataCorp, Stata Statistical Software. College Station, TX: United States).

2.6. Definitions

- ***Melasma:*** It's an acquired pigmentary disorder usually a symmetrical macule or

bright to dark brown patch in women during childbearing [1].

- ***Metformin:*** An antidiabetic agent was approved by the U.S. Food and Drug Administration (FDA) in 1994 for treating type 2 diabetes. It has melanogenic action, as it downregulates the expression of microphthalmia-associated transcription factor (MITF), so used in the treatment of melasma.
- ***Hyperthyroidism:*** It happens when the thyroid gland makes too much thyroid hormone. This condition is called overactive thyroid, as well.
- ***Diabetes:*** It's a condition that happens when your blood sugar (glucose) is too high. It develops when your pancreas doesn't make enough insulin or any at all.

3. Results

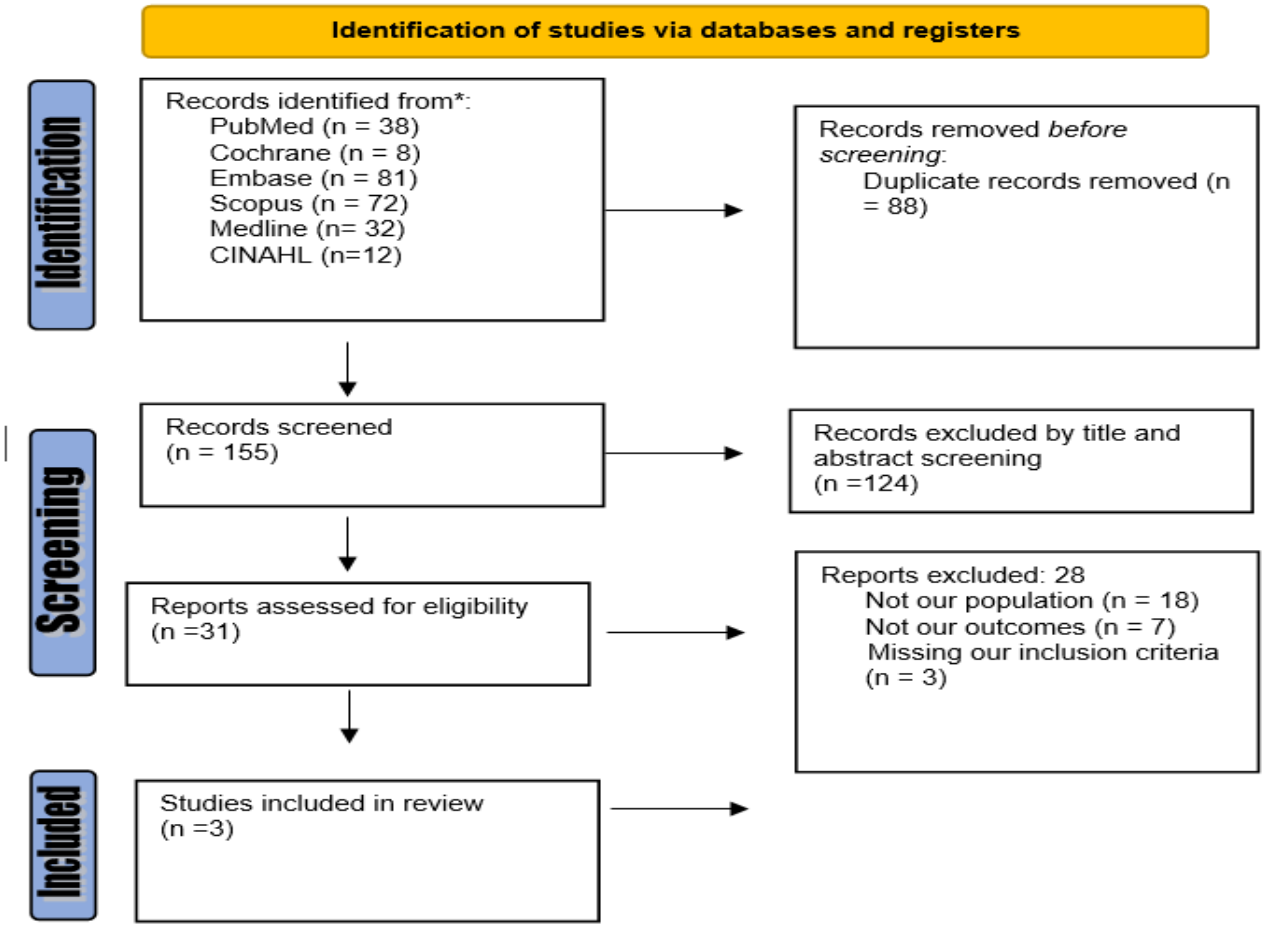

Figure 1: The PRISMA Flow diagram of the literature search process.

Our review includes three articles that match our criteria. One of them Mapar et al., (2019) led a pilot study for the treatment of melasma in sixty patients [10], Channakeshavaiah et al., (2020) directed a concentrate on 40 patients [11], and AboAlsoud et al., (2022) 20 patients complaining of melasma were included [12] (**Tables 1, 2**).

Table 1: Summary of included studies.

Study ID	Country	Study Design	Study Population	Selection criteria	Conclusion points
Mapar et al., 2019 [10]	Iran	Double-blind clinical trial.	Melasma patients were referred to the Ahvaz Imam Khomeini Hospital's Dermatology Clinic.	***Exclusion:*** • GFR under 30. • Atrophy and telangiectasia in the melasma site. • Topical treatment in the recent three months. • Drug allergy history. • Pregnancy or breastfeeding. • Male gender. • Hormone therapy (such as pregnancy control pills). • Photosensitive drugs like tetracycline, spironolactone, phenytoin, and carbamazepine.	• Metformin cream considerably lowers patients' MASI scores without affecting laboratory markers. • MASI scores of the metformin patients and the placebo group did not differ significantly; however, the MASI Score fall trend persisted until the 12th week, and the placebo group did not exhibit a discernible decline after eight weeks.
Channakeshavaiah et al., 2020 [11]	India	A prospective randomized controlled study	Patients with melasma aged more than 18 years.	***Inclusion:*** • Patients >18 years. • With melasma but didn't use any topical treatment, systemic steroids, or cosmetic procedures including laser, or dermabrasion.	• The topical metformin. Is a new, safe, and nearly equally effective treatment for melasma as TCC is

				• Didn't use peels for at least two weeks. ***Exclusion*** • Patients with acne vulgaris or rosacea. • Pregnant or breastfeeding women. • Oral contraceptive users. • Phenytoin users. • Renal failure patients. • Allergic to the trial drugs.	
AboAlsoud et al., 2022 [12]	Egypt	A randomized controlled trial	Patients diagnosed with melasma.	***Inclusion:*** • Only adults over 18. • Had not received cosmetic procedures. • Had not used topical or systemic melasma therapy for one month; • Had not undergone laser ablation, dermabrasion, or peels in the previous three months.	• Metformin cream is a potentially helpful and safe treatment for melasma.

Table 2: Bias Risk Assessment Using Newcastle - Ottawa Scale.

Study ID	Country	Year	Journal	Newcastle - Ottawa scale
Mapar et al., 2019 [10]	Iran	2019	J Pharm Res Int	Good quality
Channakeshavaiah et al., 2020 [11]	India	2020	Journal of Cosmetic Dermatology	Good quality
AboAlsoud et al., 2022 [12]	Egypt	2022	Journal of Cosmetic Dermatology	Good quality

4. Discussion

Melasma, often known as a grey-to-brown patch, is a cosmetic ailment that affects the face and can be emotionally upsetting. Treating melasma is a difficult assignment for a dermatologist because its cause is uncertain [13].

Clinical examination is sufficient for the diagnosis of melasma; biopsy is usually unnecessary. Utilizing colorimetry, mexametry, the modified MASI (mMASI) score, the Melasma Area and Severity Index (MASI) score, or the mMASI score, one can estimate the extent of melasma [14].

Topical agents such as triple combinations of hydroquinone, tretinoin, and corticosteroid, nonsteroidal demeaning creams containing (azelaic and kojic acid), and superficial chemical peels comprising (glycolic acid, trichloroacetic acid, and lactic acid) are among the numerous forms of therapy for melasma.

Also, Q-switched Nd: YAG laser, Alexandrite laser, Er: YAG laser, Fraxel laser and intense pulsed light (IPL) systems are used in the treatment of melasma [15].

Sun protection and the use of broad-spectrum, efficient sunblock with higher SPF and UVA absorbency factors are the most crucial components of the treatment [6].

Metformin, an oral hypoglycemic medication, exhibits topical melanogenic activity. This condition is explained by a decrease in the accumulation of c-AMP and the phosphorylation of c-AMP responding element-binding protein. Consequently, the expression of MITF, the master gene of melanogenesis, as well as other melanogenic proteins including tyrosinase, TRP-1, and TRP-2, is diminished. Furthermore, metformin suppresses melanogenesis by directly impeding diacylglycerol and protein kinase C-β, which is a link to melanosomes [16].

5. Conclusions and relevance

This systematic review suggests that metformin lotion is an efficient and promising therapeutic modality for treating melasma.

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