

Management of Melasma

Subjects: Dermatology

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Melasma is a commonly occurring pigmented skin condition that can significantly affect one's appearance, described as symmetric hyperpigmentation that presents as irregular brown to gray-brown macules on various facial areas, such as the cheeks, forehead, nasal bridge, and upper lip, along with the mandible and upper arms. Due to its complex pathogenesis and recurrent nature, melasma management is challenging and the outcomes following treatment are not always deemed satisfactory.

Keywords: melasma ; laser ; treatment

1. Introduction

Melasma, a common dermatological condition characterized by the presence of hyperpigmented patches and macules, typically manifests on the facial skin. This condition predominantly impacts adult females, particularly those with Fitzpatrick skin phototypes III to V ^[1].

So far, the exact cause of melasma remains not fully understood. Nevertheless, it is suggested that chronic exposure to ultraviolet (UV) radiation, hormonal factors in females, such as pregnancy and oral contraceptive medication, and a genetic predisposition are all factors that have been proposed to be involved in the development of melasma ^{[2][3][4]}.

The treatment of melasma continues to pose a challenge due to the limited clinical effectiveness, high recurrence rates, and the occurrence of adverse reactions associated with many of the treatments. The management of melasma typically commences with preventive measures involving sun protection followed by a range of treatments that encompass topical applications, oral therapies, chemical peels, microneedling, laser procedures, and light treatments ^{[4][5]}. The most utilized topical agent is hydroquinone, but it frequently results in irritant and allergic contact dermatitis ^[6]. Oral tranexamic acid (TA) is known to cause menstrual irregularities and may increase the risk of deep venous thrombosis ^[7]. Chemical peels, commonly used as an adjunctive therapy, often come with side effects like burning and peeling of the skin ^[8].

Laser treatments, which have arisen as a newer method, have been increasingly used in recent years. The mechanism of light selectively damaging pigment particles in pigment cells, offers precision in targeting different skin chromophores without damaging adjacent normal tissues, so it takes effect quickly and does not produce scars ^[4].

However, it is important to note that some studies have reported adverse effects, including erythema, a burning sensation, post-inflammatory hyperpigmentation (PIH), hypopigmentation, and the possibility of melasma recurrence ^{[9][10][11]}. Additionally, some studies have suggested that combining laser therapy with other treatments does not yield significantly better results compared to laser therapy alone ^[12].

2. Management of Melasma

2.1. Overview

The initial approach to treating melasma in patients generally involves addressing or removing risk factors, implementing rigorous protection against ultraviolet sun exposure, and using topical formulations designed to lighten the skin. While topical treatments may provide temporary improvement, the condition frequently recurs. Treatment principles aim to inhibit melanin synthesis pathways, reduce melanosome transfer from melanocytes to keratinocytes, and expedite pathways for melanin removal.

2.2. Preventative Practices

Photoprotection is the cornerstone of the prevention and treatment of melasma ^[13]. Exposure to sunlight has been observed to trigger and worsen hyperpigmentation in individuals with melasma. Adopting habits like minimizing sun

exposure duration, donning protective clothing to limit exposure to the sun, and diligently applying sunscreen can aid in the management of melasma. Sun protection topicals take precedence and are often employed as a supportive measure alongside other melasma treatments, as both ultraviolet (UV) and visible light can trigger prolonged hyperpigmentation across all skin types [14][15]. Due to the underlying mechanisms of melasma, depending solely on UVA/UVB protection is insufficient. Sunscreens designed for this condition should provide broad-spectrum coverage, including UVA1 and HEVL, with a high SPF for robust defense. Additionally, they should be aesthetically pleasing for regular use [13].

2.3. Topical Treatment

The mainstay of melasma treatment has historically been topical therapies, with the most utilized topical agent being hydroquinone 2–5% [6]. Other topical agents, including azelaic acid, kojic acid, and tranexamic acid, have demonstrated a substantial reduction in melasma and should be taken into consideration before opting for chemical peels or laser therapy [16]. The most effective formulation to date has been Kligman's formula, which consists of a cream base containing hydroquinone, tretinoin, and dexamethasone. This formulation has been shown to lead to improvements or even complete clearance in as many as 60–80% of treated patients and is still regarded as the gold standard in melasma treatment [17][18][19].

2.4. Systemic Treatment

Before prescribing systemic therapies, physicians should take the initiative to educate themselves and inform the patient about the appropriate dosage, potential side effects, and necessary precautions. Many systemic therapies can be used in melasma treatment, and orally administered *P. leucotomos* may provide significant therapeutic benefits for melasma, as it can be used as an adjuvant to topical treatment of melasma, particularly when used in conjunction with hydroquinone cream [20][21]. A randomized double-blind placebo-controlled clinical trial found oral polypodium leucotomos extract to be a safe and effective adjunctive treatment in combination with topical hydroquinone and sunscreen for melasma [22]. Oral tranexamic acid is increasingly being utilized due to its affordability and ease of prescription in general medical practice. A recent meta-analysis of randomized controlled trials, evaluating the use of oral tranexamic acid in adult melasma, demonstrated notable effectiveness and safety [23].

2.5. Microneedling

Microneedling, which is also referred to as percutaneous collagen induction therapy, is a minimally invasive procedure that entails the insertion of fine needles into the skin, often achieved through techniques such as stamping, needle rollers, or an electric-powered pen [24][25]. Microneedling has the potential to enhance transdermal drug delivery [26]. Additionally, the microinjuries that result from microneedling appear to activate genes related to epidermal differentiation and tissue remodeling when studied in vitro [27]. Recent studies prove microneedling combined with topical interventions to be an effective measure in melasma treatment [28][29]. In combination therapy with a 4% hydroquinone (HQ) cream and Q-switched Nd:YAG laser (QSNYL), microneedling has demonstrated superior results when compared to using topical or laser therapy alone [30][31][32]. The adverse effects associated with microneedling can range from temporary redness, a burning sensation, to pain, swelling, and bruising. It is important to note that the severity of these local reactions depends on the skills and technique of the operator [33][34].

2.6. Lasers and Light Based Therapy

2.6.1. Overview

In 1983, Anderson and Parrish introduced the concept of laser therapy for treating cutaneous disorders. Their pioneering work highlighted the distinct thermal and absorptive characteristics of pigmented structures within the skin, rendering them suitable targets for precise destruction using specific wavelengths of radiation. Importantly, this approach spared the surrounding healthy tissue. Consequently, a wide range of targets, such as unwanted hair and tattoo ink, could be effectively removed with minimal impact on the surrounding normal skin [35]. Since that milestone, light and laser therapies have been found to be applicable in numerous dermatologic and cosmetic conditions, encompassing vascular birthmarks, telangiectasias, hypertrichosis, tattoo removal, pigmented lesions, solar lentigines, lentiginous nevi, café-au-lait macules, and melasma [36].

Laser therapy has emerged as a safe alternative option for treating melasma, particularly in cases where the more conventional methods involving topical creams and chemical peels have proven less effective. A wide array of laser therapies underwent extensive examination in numerous clinical trials, revealing a diverse spectrum of treatment effectiveness and potential adverse events. Typically, the results of these trials are assessed by medical professionals or based on changes in the Melasma Area Severity Index (MASI).

2.6.2. Intense Pulsed Light (IPL)

Intense pulsed light (IPL) systems emit a range of different wavelengths between 515 and 1200 nanometer (nm). Within this spectrum of light, some of its wavelengths are selectively absorbed in the melanosomes. Another benefit of IPL technology is its multiple wavelengths that allow for the targeting of multiple layers of epidermal and dermal melasma simultaneously [37].

Based on meta-analysis from Jiarong Yi. In 2020 [38], IPL-based combination therapy for melasma can effectively reduce MASI scores and result in higher satisfaction among patients.

Typical side effects include mild erythema (skin redness) and a slight tingling sensation, which generally resolves within a day. In a few cases, some patients may encounter mild skin exfoliation due to the use of higher energy levels, but this typically heals without scarring in approximately one week [9][39].

2.6.3. Low-Fluence Q-Switched 1064 nm Nd:YAG

Q-switched lasers are known for producing high-intensity laser beams with extremely short pulse durations. Their pulse velocity is about a million times faster than that of an IPL pulse. These lasers, specifically designed to target melanin, are available in various wavelengths, including ruby (694 nm), alexandrite (755 nm), and neodymium-doped yttrium aluminum garnet (Nd:YAG; 532 nm or 1064 nm) [40]. Among patients with melasma, the 1064 nm Q-switched neodymium-doped yttrium aluminum garnet (QSNY) laser is a popular choice, often used in combination with other treatment methods. However, the use of QSNY has been associated with adverse effects such as guttate hypopigmentation and melasma rebound. It is important to note that the application of high-fluence QSNY in melasma treatment carries a risk of post-inflammatory pigmentation [41][42].

A new approach to using Q-switched lasers, referred to as low-fluence or subthermolytic Q-switched treatment, is becoming increasingly popular [37][43]. While the lasers used are the same, the fluences applied are lower compared to those traditionally used for treating other pigmented lesions. Low-fluence treatments primarily utilize the 1064 nm wavelength, which penetrates deeper into the dermis while sparing the epidermis to a greater extent. The rationale behind treating patients with melasma using subthermolytic low fluences is based on the concept that pigment disruption occurs via a photoacoustic mechanism, breaking down the pigment while preserving the keratinocytes and melanocytes from damage. Although there is typically some level of damage associated with subthermolytic Q-switched treatment, it is reported to be less than that observed with traditional photothermolytic approaches [44].

The optimal outcomes and reduced risk of recurrence are attained with this technique when it is combined with additional agents, including topical hydroquinone (HQ), azelaic acid, chemical peels like Jessner's formula, glycolic acid (GA), and systemic treatment [45]. Moreover, clinical trials involving combination using other types of lasers, such as nonablative 1550 nm erbium-doped fractional photothermolysis, pulsed dye laser (PDL) and Er:YAG (2940 nm) laser, have been documented. In a meta-analysis by CHEN et al., it was suggested that the laser combination treatment approach yields superior results compared to monotherapy. This is attributed to the fact that combination therapy operates through diverse mechanisms in treating melasma, and their effects can be attributed to a synergistic superposition [46].

Notwithstanding the favorable therapeutic effects, the recurrence rate following these procedures remains notably high, making this treatment option not sufficiently effective. Low-fluence Q-switched laser therapy, especially using an Nd:YAG laser, has displayed promising initial results. However, it necessitates multiple treatments within a relatively short treatment interval (typically weekly) and is associated with exceptionally high 3-month recurrence rates ranging from 64% to 81%. The number of required treatments is generally higher compared to other light- and laser-based treatment modalities [47][48][49] and can affect patients' compliance with the treatment. In terms of the LQSNY safety of the treatment, it has been demonstrated to induce adverse events, including erythema, transient burning, slight edema, microcrust, hyperpigmentation, hypopigmentation, and telangiectasia. Notably, guttate hypopigmentation has been reported in cases involving the combination of LQSNY with microneedling, glycolic acid, intense pulsed light (IPL), or hydroquinone, with incidence rates ranging from 5.5% to 13.6% [9][50].

2.6.4. Non-Ablative Fractionated Resurfacing Lasers (NAFL)

Four laser wavelengths are used in this category including 1440 nm, 1540 nm, 1550 nm, and 1927 nm, namely within the short-wavelength infrared spectrum of light. Non-ablative fractionated lasers mechanism of action is in the form of photothermolysis. As laser energy targeted and absorbed by water-containing tissues, it induces selective thermal damage in the form of micro-beams with a diameter of less than 400 µm and can reach up to 1000 µm in depth. This process leads to the formation of microscopic thermal zones (MTZ) that impact collagen fibers and keratinocytes. Column-

like necroses of keratinocytes, referred to as microscopic epidermal necrotic debris (MEND), develop within the epidermis. This formation enables keratinocytes and dermal components to migrate towards the stratum corneum, resulting in the removal of coagulated substances [51][52]. Immediately after the application of NAFLs on melasma lesions, melanin can be detected within MENDs within six days of treatment. Enlarged melanocytes, commonly observed in melasma lesions, remain reduced in number for up to three months after a single NAFL treatment. These findings suggest that MENDs act as “melanin shuttles”, contributing to the elimination of dermal and epidermal melanin [53][54].

The utilization of NAFLs appears to yield a more enduring clinical response compared to IPL or Q-switched laser treatments. This is particularly notable when patients undergo topical tyrosinase inhibitor treatment both before and after the laser surgery [45].

Common side effects include erythema, swelling and pain. These are typically short-term side effects lasting for 3 to 10 days, and overall, the treatment is regarded as having low downtime with a fast recovery process. Post-inflammatory hyperpigmentation (PIH) is a reported side effect in most clinical trials. The occurrence of PIH appears to be associated with the density of the microthermal zones and possibly arise as a byproduct of the heat generated during the treatment. Relapses often occur after NAFL treatments, usually noted between 3 and 6 months after treatment, which is better than IPL and Q-switched lasers, where recurrence can occur as early as 3 months after discontinuing the treatment [37].

2.6.5. Ablative Fractionated Resurfacing Lasers (AFL)

Ablative fractionated resurfacing lasers have been documented for the treatment of melasma patients [55]. Lasers such as CO₂ 10,600 nm and Er:YAG 2940 nm operate by having their light energy absorbed by water molecules in the tissue, resulting in tissue ablation [56]. Fractionated ablation creates microscopic injury zones, facilitating improved transepidermal drug delivery (TDD), extraction of transepidermal melanin, enhancement of dermal elastin tissue, neocollagenesis, basal membrane stabilization, and consequently, reduced interaction between keratinocytes and melanocytes with melanogenic dermal stimulators, leading to less noticeable pigmentation [50].

Adopting a fractionated approach minimizes epidermal injury, resulting in fewer side effects and a lower risk of dyspigmentation. However, it is not recommended to use AFLs for melasma treatment due to the significant occurrence of side effects and the likelihood of relapses. In cases where specialists do employ AFL treatments, they prefer a CO₂ laser with very low fluency, usually as part of combination therapy [57]. In a recent prospective cohort comparative study involving 40 female participants, the efficacy of a single session of low-power fractional CO₂ (10,600 nm) laser followed by Jessner's solution peeling was compared to that of Jessner's solution peeling alone. The study found that there was no significant difference between the two groups in terms of improvements in mMASI scores. Additionally, both groups were safe and effective for the treatment of melasma [58].

2.6.6. Picosecond Lasers

Picosecond lasers represent cutting-edge technology capable of generating pulses within the picosecond timeframe. The use of extremely short laser pulse durations induces melanin fragmentation through a photoacoustic mechanism rather than a photothermal one. This laser technology is highly efficient in pigment removal without causing thermal damage to the surrounding tissues. Picosecond lasers are based on light emission at various wavelengths, mainly 532 nm (KTP), 755 nm (alexandrite), and 1064 nm (Nd:YAG) [45][59].

To date, there have only been a few studies exploring the use of picosecond lasers for the treatment of melasma, some recommended its use, while others presented association with high recurrence rates. Therefore, further studies are required to evaluate the efficacy of this novel technology [57][60].

2.7. Patient Counseling

Effective management of melasma is attributed, in part, to the strength of the patient–clinician relationship. When advising patients dealing with melasma, clinicians need to collaborate with patients to identify the most suitable treatment options and establish realistic expectations for the course of the condition. In a condition that disproportionately affects individuals of color, it is crucial to employ patient-centric language that is both culturally and racially sensitive. This ensures effective communication about available treatment options, the potential for side effects, and the proper use of treatments [61].

References

1. Sheth, V.M.; Pandya, A.G. Melasma: A Comprehensive Update: Part i. J. Am. Acad. Dermatol 2011, 65, 689–697.

2. Pathak, M.A.; Riley, F.C.; Fitzpatrick, T.B. Melanogenesis in human skin following exposure to long-wave ultraviolet and visible light*. *J. Investig. Dermatol.* 1962, 39, 435–443.
3. Grimes, P.E. Melasma: Etiologic and Therapeutic Considerations. *Arch. Dermatol.* 1995, 131, 1453–1457.
4. Ogbechie-Godec, O.A.; Elbuluk, N. Melasma: An Up-to-Date Comprehensive Review. *Dermatol. Ther.* 2017, 7, 305–318.
5. Gupta, A.K.; Gover, M.D.; Nouri, K.; Taylor, S. The Treatment of Melasma: A Review of Clinical Trials. *J. Am. Acad. Dermatol.* 2006, 55, 1048–1065.
6. Nordlund, J.J.; Grimes, P.E.; Ortonne, J.P. The Safety of Hydroquinone. *J. Eur. Acad. Dermatol. Venereol.* 2006, 20, 781–787.
7. Lee, H.C.; Thng, T.G.S.; Goh, C.L. Oral Tranexamic Acid (TA) in the Treatment of Melasma: A Retrospective Analysis. *J. Am. Acad. Dermatol.* 2016, 75, 385–392.
8. Kumari, R.; Thappa, D. Comparative Study of Trichloroacetic Acid versus Glycolic Acid Chemical Peels in the Treatment of Melasma. *Indian J. Dermatol. Venereol. Leprol.* 2010, 76, 447.
9. Vachiramon, V.; Sirithanabadeekul, P.; Sahawatwong, S. Low-Fluence Q-Switched Nd: YAG 1064-Nm Laser and Intense Pulsed Light for the Treatment of Melasma. *J. Eur. Acad. Dermatol. Venereol.* 2015, 29, 1339–1346.
10. Wattanakrai, P.; Mornchan, R.; Eimpunth, S. Low-Fluence Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (1,064 Nm) Laser for the Treatment of Facial Melasma in Asians. *Dermatol. Surg.* 2010, 36, 76–87.
11. Moubasher, A.E.A.; Youssef, E.M.K.; Abou-Taleb, D.A.E. Q-Switched Nd: YAG Laser versus Trichloroacetic Acid Peeling in the Treatment of Melasma among Egyptian Patients. *Dermatol. Surg.* 2014, 40, 874–882.
12. Kim, H.S.; Kim, E.K.; Jung, K.E.; Park, Y.M.; Kim, H.O.; Lee, J.Y. A Split-Face Comparison of Low-Fluence Q-Switched Nd: YAG Laser plus 1550 Nm Fractional Photothermolysis vs. Q-Switched Nd: YAG Monotherapy for Facial Melasma in Asian Skin. *J. Cosmet. Laser Ther.* 2013, 15, 143–149.
13. Morgado-Carrasco, D.; Piquero-Casals, J.; Granger, C.; Trullàs, C.; Passeron, T. Melasma: The Need for Tailored Photoprotection to Improve Clinical Outcomes. *Photodermatol. Photoimmunol. Photomed.* 2022, 38, 515–521.
14. Lai, D.; Zhou, S.; Cheng, S.; Liu, H.; Cui, Y. Laser Therapy in the Treatment of Melasma: A Systematic Review and Meta-Analysis. *Lasers Med. Sci.* 2022, 37, 2099–2110.
15. Anvery, N.; Christensen, R.E.; Dirr, M.A. Management of Post-Inflammatory Hyperpigmentation in Skin of Color: A Short Review. *J. Cosmet. Dermatol.* 2022, 21, 1837–1840.
16. Grimes, P.E.; Ijaz, S.; Nashawati, R.; Kwak, D. New Oral and Topical Approaches for the Treatment of Melasma. *Int. J. Womens Dermatol.* 2019, 5, 30.
17. Doolan, B.J.; Gupta, M. Melasma. *Aust. J. Gen. Pract.* 2021, 50, 880–885.
18. Rodrigues, M.; Pandya, A.G. Melasma: Clinical Diagnosis and Management Options. *Australas. J. Dermatol.* 2015, 56, 151–163.
19. Sarma, N.; Chakraborty, S.; Poojary, S.; Rath, S.; Kumaran, S.; Nirmal, B.; Felicita, J.; Sarkar, R.; Jaiswal, P.; D'Souza, P.; et al. Evidence-Based Review, Grade of Recommendation, and Suggested Treatment Recommendations for Melasma. *Indian Dermatol. Online J.* 2017, 8, 406.
20. Handog, E.B.; Galang, D.A.V.F.; De Leon-Godinez, M.A.; Chan, G.P. A Randomized, Double-Blind, Placebo-Controlled Trial of Oral Procyanidin with Vitamins A, C, E for Melasma among Filipino Women. *Int. J. Dermatol.* 2009, 48, 896–901.
21. Nestor, M.; Bucay, V.; Callender, V.; Cohen, J.L.; Sadick, N.; Waldorf, H. Polypodium Leucotomos as an Adjunct Treatment of Pigmentary Disorders. *J. Clin. Aesthet. Dermatol.* 2014, 7, 13.
22. Goh, C.L.; Chuah, S.Y.; Derm, D.; Tien, S.; Thng, G.; Vitale, M.A.; Delgado-Rubin, A. Double-Blind, Placebo-Controlled Trial to Evaluate the Effectiveness of Polypodium Leucotomos Extract in the Treatment of Melasma in Asian Skin: A Pilot Study. *J. Clin. Aesthet. Dermatol.* 2018, 11, 14.
23. Feng, X.; Su, H.; Xie, J. Efficacy and Safety of Tranexamic Acid in the Treatment of Adult Melasma: An Updated Meta-Analysis of Randomized Controlled Trials. *J. Clin. Pharm. Ther.* 2021, 46, 1263–1273.
24. Hou, A.; Cohen, B.; Haimovic, A.; Elbuluk, N. Microneedling: A Comprehensive Review. *Dermatol. Surg.* 2017, 43, 321–339.
25. Alster, T.S.; Graham, P.M. Microneedling: A Review and Practical Guide. *Dermatol. Surg.* 2018, 44, 397–404.
26. Bonati, L.M.; Epstein, G.K.; Strugar, T.L. Microneedling in All Skin Types: A Review. *J. Drugs Dermatol.* 2017, 16, 308–313.

27. Schmitt, L.; Marquardt, Y.; Amann, P.; Heise, R.; Huth, L.; Wagner-Schiffler, S.; Huth, S.; Baron, J.M. Comprehensive Molecular Characterization of Microneedling Therapy in a Human Three-Dimensional Skin Model. *PLoS ONE* 2018, 13, e0204318.
28. Kaur, A.; Bhalla, M.; Pal Thami, G.; Sandhu, J. Clinical Efficacy of Topical Tranexamic Acid with Microneedling in Melasma. *Dermatol. Surg.* 2020, 46, E96–E101.
29. Bailey, A.J.M.; Li, H.O.Y.; Tan, M.G.; Cheng, W.; Dover, J.S. Microneedling as an Adjuvant to Topical Therapies for Melasma: A Systematic Review and Meta-Analysis. *J. Am. Acad. Dermatol.* 2022, 86, 797–810.
30. Tehranchinia, Z.; Saghi, B.; Rahimi, H. Evaluation of Therapeutic Efficacy and Safety of Tranexamic Acid Local Infiltration in Combination with Topical 4% Hydroquinone Cream Compared to Topical 4% Hydroquinone Cream Alone in Patients with Melasma: A Split-Face Study. *Dermatol. Res. Pract.* 2018, 2018, 8350317.
31. Ustuner, P.; Balevi, A.; Ozdemir, M. A Split-Face, Investigator-Blinded Comparative Study on the Efficacy and Safety of Q-Switched Nd:YAG Laser plus Microneedling with Vitamin C versus Q-Switched Nd:YAG Laser for the Treatment of Recalcitrant Melasma. *J. Cosmet. Laser Ther.* 2017, 19, 383–390.
32. Xu, Y.; Ma, R.; Juliandri, J.; Wang, X.; Xu, B.; Wang, D.; Lu, Y.; Zhou, B.; Luo, D. Efficacy of Functional Microarray of Microneedles Combined with Topical Tranexamic Acid for Melasma. *Medicine* 2017, 96, e6897.
33. Wu, S.Z.; Muddasani, S.; Alam, M. A Systematic Review of the Efficacy and Safety of Microneedling in the Treatment of Melasma. *Dermatol. Surg.* 2020, 46, 1636–1641.
34. Hofny, E.R.M.; Abdel-Motaleb, A.A.; Ghazally, A.; Ahmed, A.M.; Hussein, M.R.A. Platelet-Rich Plasma Is a Useful Therapeutic Option in Melasma. *J. Dermatol. Treat.* 2019, 30, 396–401.
35. Rox Anderson, R.; Parrish, J.A. Selective Photothermolysis: Precise Microsurgery by Selective Absorption of Pulsed Radiation. *Science* 1983, 220, 524–527.
36. Patil, U.; Dhami, L. Overview of Lasers. *Indian J. Plast. Surg.* 2008, 41, S101.
37. Trivedi, M.K.; Yang, F.C.; Cho, B.K. A Review of Laser and Light Therapy in Melasma. *Int. J. Womens Dermatol.* 2017, 3, 11–20.
38. Yi, J.; Hong, T.; Zeng, H.; Li, P.; Li, P.; Wang, S.; Chen, J.; Li, P.; Zhou, J. A Meta-Analysis-Based Assessment of Intense Pulsed Light for Treatment of Melasma. *Aesthetic Plast. Surg.* 2020, 44, 947–952.
39. Figueiredo Souza, L.; Trancoso Souza, S. Single-Session Intense Pulsed Light Combined with Stable Fixed-Dose Triple Combination Topical Therapy for the Treatment of Refractory Melasma. *Dermatol. Ther.* 2012, 25, 477–480.
40. TAYLOR, C.R.; ANDERSON, R.R. Ineffective Treatment of Refractory Melasma and Postinflammatory Hyperpigmentation by Q-Switched Ruby Laser. *J. Dermatol. Surg. Oncol.* 1994, 20, 592–597.
41. Kar, H.K.; Gupta, L.; Chauhan, A. A Comparative Study on Efficacy of High and Low Fluence Q-Switched Nd:YAG Laser and Glycolic Acid Peel in Melasma. *Indian J. Dermatol. Venereol. Leprol.* 2012, 78, 165.
42. TSE, Y.; LEVINE, V.J.; MCCLAIN, S.A.; ASHINOFF, R. The Removal of Cutaneous Pigmented Lesions with the Q-Switched Ruby Laser and the Q-Switched Neodymium: Yttrium-Aluminum-Garnet Laser. *J. Dermatol. Surg. Oncol.* 1994, 20, 795–800.
43. Aurangabadkar, S.J. Optimizing Q-Switched Lasers for Melasma and Acquired Dermal Melanoses. *Indian J. Dermatol. Venereol. Leprol.* 2019, 85, 10.
44. Kaminaka, C.; Furukawa, F.; Yamamoto, Y. The Clinical and Histological Effect of a Low-Fluence Q-Switched 1,064-Nm Neodymium: Yttrium-Aluminum-Garnet Laser for the Treatment of Melasma and Solar Lentigenes in Asians: Prospective, Randomized, and Split-Face Comparative Study. *Dermatol. Surg.* 2017, 43, 1120–1133.
45. Piętownska, Z.; Nowicka, D.; Szepietowski, J.C. Understanding Melasma-How Can Pharmacology and Cosmetology Procedures and Prevention Help to Achieve Optimal Treatment Results? A Narrative Review. *Int. J. Environ. Res. Public. Health* 2022, 19, 12084.
46. Chen, J.; Yu, N.; Peng, L.; Li, H.; Tang, Y.; Ou, S.; Zhu, H. Efficacy of Low-Fluence 1064 Nm Q-Switched Nd: YAG Laser for the Treatment of Melasma: A Meta-Analysis and Systematic Review. *J. Cosmet. Dermatol.* 2022, 21, 2840–2848.
47. Gokalp, H.; Akkaya, A.D.; Oram, Y. Long-Term Results in Low-Fluence 1064-Nm Q-Switched Nd:YAG Laser for Melasma: Is It Effective? *J. Cosmet. Dermatol.* 2016, 15, 420–426.
48. Xi, Z.; Gold, M.H.; Zhong, L.; Ying, L. Efficacy and Safety of Q-Switched 1,064-Nm Neodymium-Doped Yttrium Aluminum Garnet Laser Treatment of Melasma. *Dermatol. Surg.* 2011, 37, 962–970.
49. Parra, C.A.H.; Careta, M.F.; Valente, N.Y.S.; De Sanches Osório, N.E.G.; Torezan, L.A.R. Clinical and Histopathologic Assessment of Facial Melasma after Low-Fluence q-Switched Neodymium-Doped Yttrium Aluminium Garnet Laser.

50. Iranmanesh, B.; Khalili, M.; Mohammadi, S.; Amiri, R.; Aflatoonian, M. The Efficacy of Energy-Based Devices Combination Therapy for Melasma. *Dermatol. Ther.* 2021, 34, e14927.
51. Manstein, D.; Herron, G.S.; Sink, R.K.; Tanner, H.; Anderson, R.R. Fractional Photothermolysis: A New Concept for Cutaneous Remodeling Using Microscopic Patterns of Thermal Injury. *Lasers Surg. Med.* 2004, 34, 426–438.
52. Hantash, B.M.; Bedi, V.P.; Sudireddy, V.; Struck, S.K.; Herron, G.S.; Chan, K.F. Laser-Induced Transepidermal Elimination of Dermal Content by Fractional Photothermolysis. *J. Biomed. Opt.* 2006, 11, 041115.
53. Goldberg, D.J.; Berlin, A.L.; Phelps, R. Histologic and Ultrastructural Analysis of Melasma after Fractional Resurfacing. *Lasers Surg. Med.* 2008, 40, 134–138.
54. Laubach, H.J.; Tannous, Z.; Anderson, R.R.; Manstein, D. Skin Responses to Fractional Photothermolysis. *Lasers Surg. Med.* 2006, 38, 142–149.
55. de Moraes, O.O.; dos Santos Sousa, M.C.; Costa, I.M.C.; Lemos, É.F.L.; Gomes, C.M.; de Paula, C.D.R. The Use of Ablative Lasers in the Treatment of Facial Melasma. *An. Bras. Dermatol.* 2013, 88, 238–242.
56. Verma, N.; Yumeen, S.; Raggio, B.S. Ablative Laser Resurfacing. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
57. Sarkar, R.; Aurangabadkar, S.; Salim, T.; Das, A.; Shah, S.; Majid, I.; Singh, M.; Ravichandran, G.; Godse, K.; Arsiwala, S.; et al. Lasers in Melasma: A Review with Consensus Recommendations by Indian Pigmentary Expert Group. *Indian J. Dermatol.* 2017, 62, 477–482.
58. ELMORSY, E.; ABOUKHADR, N.; TAYYEB, M.; TAHA, A.A.A. Low-Power Fractional Carbon Dioxide Laser Followed by Jessner's Peel versus Jessner's Peel Alone for the Treatment of Melasma. *J. Clin. Aesthet. Dermatol.* 2021, 14, 61.
59. Chalermchai, T.; Rummaneethorn, P. Effects of a Fractional Picosecond 1,064 Nm Laser for the Treatment of Dermal and Mixed Type Melasma. *J. Cosmet. Laser Ther.* 2018, 20, 134–139.
60. Choi, Y.J.; Nam, J.H.; Kim, J.Y.; Min, J.H.; Park, K.Y.; Ko, E.J.; Kim, B.J.; Kim, W.S. Efficacy and Safety of a Novel Picosecond Laser Using Combination of 1 064 and 595 Nm on Patients with Melasma: A Prospective, Randomized, Multicenter, Split-Face. 2% Hydroquinone Cream-Controlled Clinical Trial. *Lasers Surg. Med.* 2017, 49, 899–907.
61. Sanchez, D.; McLean, E.O.; Maymone, M.B.C.; Granados, N.M.; Vashi, N.A. Patient-Provider Comparison of Dermatology Vocabulary Understanding: A Cross-Sectional Study in Patients from Minority Ethnic Groups. *Arch. Dermatol. Res.* 2020, 312, 407–412.