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Exploring the Efficacy of Fractional Carbon Dioxide Laser as an Add-on Combination to Conventional Therapies for Treatment-Resistant Vitiligo (A Review Article)

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Abstract

Introduction: Vitiligo, a dermatological disorder that leads to depigmented skin patches, presents a significant challenge, particularly in resistant areas such as acral regions. Fractional CO2 laser therapy holds promise as an adjunct to conventional treatment, enhancing repigmentation. This review comprehensively explores its efficacy and safety in resistant-to-treatment vitiligo.

Methods: We conducted extensive database searches in PubMed, Embase, and Cochrane, focusing on English-language literature published between 2012 and 2023. We included comparative studies that met the following criteria: (1) Participants had non-segmental vitiligo, with resistant-to-treatment localization engagement; (2) The treatment involved the use of fractional CO2 laser in combination with conventional therapies; and (3) Outcomes were assessed based on the repigmentation ratio or significant difference. We excluded studies from which data from published results could not be extracted.

Results: After extensive screening of 52 articles, we finally selected five studies. The results showed that fractional CO2 laser therapy, when combined with other treatments, often shows promise in vitiligo treatment in refractory cases. Although individual responses varied, overall efficacy and safety were promising, with minimal adverse effects and no severe complications.

Conclusion: The fractional CO2 laser, when used in conjunction with conventional therapies, emerges as a promising option for treating refractory vitiligo. Large-scale randomized trials and a deeper understanding of the underlying mechanisms are vital for future progress in optimizing treatment protocols, case selection, and safety.

Keywords: Vitiligo; Resistant to treatment; Fractional CO2 laser; Fractional laser; Combination therapy.

Introduction

Vitiligo is a common skin disease with a prevalence of 0.5% to 2%.[1] In this condition, the skin turns white with the loss of melanocytes. Studies show that the level of anxiety and hopelessness and psycho-social comorbidities in vitiligo patients is significantly higher than in healthy people.[2,3] Several studies have shown that patients with vitiligo experience low self-esteem, body image issues, and social problems, which contribute to a lower quality of life.[4-8] Women, patients over 40, and people with darker skin tones may experience a greater impact on their quality of life.[9-11]

People with vitiligo lesions in acral areas may have a lower quality of life due to the visibility of the lesion. In particular, patients with lesions in visible areas of the skin tend to experience greater impairment in their quality of life.[5]

Vitiligo poses therapeutic challenges when conventional treatments face resistance. Traditional treatments have included topical corticosteroids, immunomodulators, and light therapies such as PUVA and UVB. However, these treatments often have limited success rates, leaving many patients without satisfactory solutions.[12]

Resistant vitiligo refers to cases of vitiligo that do not respond well to conventional treatment methods. Acral regions and bony prominences typically exhibit resistance to treatment.[13-16] Some studies show that they are even resistant to different treatment modalities such as medical and surgical interventions.[17,18] However, there are some therapeutic options that have shown efficacy in treating acral vitiligo. One of them includes the use of fractional CO2 laser, which has shown efficacy when used

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in combination with other modalities.[19] Various factors, encompassing diminished hair follicle density, melanocyte density, Langerhans cell density, epidermal MHCII expression, lesional SCF expression, and perilesional c-kit expression, collectively contribute to the inherent resistance of acral lesions in vitiligo to pigmentation. Topical corticosteroids, calcineurin inhibitors, and UVB therapy are the mainstay of treatment, but their prolonged use is limited due to safety concerns.[20] One study indicated that the most affected areas included the facial region (87%), succeeded by the acral area (76.3%) and extremities (59.7%),[21] so the acral involvement which is usually resistant to treatment is frequent.

Combination therapies, encompassing systemic and topical targeted approaches like microphototherapy, have emerged as a promising avenue, especially for resistant-to-treatment vitiligo.[22] In the quest to improve outcomes for individuals with resistant-to-treatment and refractory vitiligo, combination therapies have emerged as a promising approach. These therapies aim to achieve several crucial goals, including enhancing repigmentation, elevating treatment effectiveness beyond single modalities, reducing the occurrence of adverse effects, and tailoring regimens to meet the specific needs of each patient.

The fractional CO2 laser, with its ability to stimulate melanogenesis and improve drug penetration, has garnered attention as a potential add-on therapy for refractory vitiligo lesions. Its ability to stimulate the multiplication of melanocytes and promote the re-pigmentation of affected areas underscores its potential as a therapeutic solution.[23] Some studies show that adding the fractional CO2 laser before topical drugs in vitiligo treatment yielded an improvement in resistant-to-treatment lesions and increased the speed of therapy.[24,25] Fractional CO2 laser therapy is centered on its capacity to trigger the damaged skin to release inflammatory cytokines.[26] This process, in turn, fosters the proliferation and migration of melanocytes, while enhancing the absorption and delivery of therapeutic agents. It also triggers collagen, elastin synthesis, and melanocyte migration, aiding repigmentation.

While topical medications hold significant importance in dermatological treatments, the skin's complex structure and the protective nature of the outermost layer can limit their efficacy.[27] Applying the fractional CO2 laser as a component of combination therapy is a strategic choice due to its ability to induce controlled micro-injuries that result in microscopic pores within the skin. These pores significantly enhance the absorption and penetration of medications. Consequently, Fractional CO2 laser therapy presents a favourable approach for combination therapy in vitiligo treatment.

The fractional CO2 laser has been evaluated in several clinical trials for the treatment of vitiligo. One study found that the combination of fractional laser CO2 and narrowband ultraviolet B (NB-UVB) showed a good improvement in repigmentation, particularly on the trunk and in stable vitiligo cases.[28] Furthermore, a study investigating the mechanism of CO2 fractional laser treatment found that it led to a good curative effect in the treatment of vitiligo.[29] Moreover, combination therapy involving lasers, such as CO2 fractional, with topical or systemic medical treatments has shown superior efficacy and faster repigmentation compared to monotherapy.[30] Fractional CO2 laser ablation has been found to be effective in recipient-site preparation before melanocyte-keratinocyte transplant procedure (MKTP), achieving successful repigmentation outcomes.[31] A randomized controlled trial compared different recipient-site preparations before cell suspension transplantation and found that superficial full surface ablation with a depth of 144 μm using a CO2 laser was an effective method.[32] CO2 fractional laser treatment has been found to have a good curative effect in the treatment of vitiligo, with a high efficiency rate and a significant reduction in Th2 and Th17 cytokine levels.[29]

Based on the aforementioned research, the combination of the fractional CO2 laser with NB-UVB phototherapy and various conventional medications emerges as a safe and effective strategy for vitiligo treatment.

This study aimed to evaluate the effectiveness of this combined approach, with a specific emphasis on its application in treating resistant areas, such as acral vitiligo.

Methods

This paper examined existing research on the application of CO2 fractional laser technology in combination with conventional therapeutic methods for treating vitiligo, with a special focus on cases that have shown resistance to treatment. Our investigation involved an extensive search across scholarly databases such as PubMed, Embase, and Cochrane, using comprehensive search terms. We encompassed English-language literature published from 2012 to 2023. Throughout this paper, we explored various therapeutic modalities, highlighting their respective advantages and limitations. Furthermore, we analysed key studies that demonstrate the effectiveness of combination therapies. We emphasized how these integrated approaches play a pivotal role in overcoming resistance to treatment in vitiligo cases. We initially incorporated all pertinent comparative studies, either observational or experimental, encompassing randomized controlled trials (RCTs), non-randomized controlled trials, cohort studies, case-control studies, as well as case reports and case series. This comprehensive approach ensured a thorough assessment of our study.

The search formulas used for this research encompassed two distinct approaches. Search formula 1, designated for

studies related to the fractional CO2 laser, incorporated keywords such as "fractional," "carbon dioxide," "CO2," and "laser" or "lasers." Similarly, search formula 2, tailored for studies related to vitiligo, relied on keywords such as "vitiligo" in conjunction with terms like "refractory," "acral," or "resistant to treatment."

The inclusion criteria were as follows: (1) Participants had to be diagnosed with non-segmental vitiligo, (2) At least one acral or treatment-resistant area had to undergo treatment involving a combination of fractional CO2 Laser and conventional therapies, such as topical or oral corticosteroids, topical immune modulators, and phototherapies, and (3) Study outcomes had to encompass proportions of re-pigmentation measured in percentages (e.g., ≥ 75%, 75% to 50%, 50% to 25%, and < 25%). The exclusion criteria for study selection consisted of studies from which data could not be extracted from published results.

The primary focus for assessment revolved around the clinical improvement of vitiligo, primarily gauged by achieving a minimum of 50% repigmentation or a significant difference in the affected skin. Additionally, the secondary focus for assessment examined cases where treatment displayed moderate effectiveness, resulting in 25% to 50% repigmentation of the affected skin, as well as instances of limited efficacy, where treatment yielded less than 25% repigmentation or demonstrated a non-significant difference in the affected skin.

These search formulas and criteria were employed to identify and select relevant studies for the research paper, which investigated the application of CO2 fractional laser technology in conjunction with conventional therapeutic methods for treating vitiligo, with a primary emphasis on cases resistant to treatment.

Article selection was conducted by two independent researchers to minimize the potential for selection bias. In instances of any discrepancies, a third researcher was consulted to reach a consensus, thereby ensuring a robust and impartial selection process.

Results

Selection of Studies

By conducting searches across Cochrane, Embase, and PubMed databases, we identified a total of 52 articles. After the removal of 33 duplicate studies, we were left with a set of 19 articles for initial evaluation based on their titles and abstracts. Subsequently, 12 articles were excluded as they were deemed irrelevant, leaving us with 7 articles for further examination. All seven studies were readily accessible in full-text format for in-depth analysis. Following the exclusion of one non-randomized controlled trial and one study with incomplete information, a final selection of five articles was made for inclusion in this study. Tables 1 and 2 provide a comprehensive overview of the characteristics of these five included studies, including details of the interventions employed.

Review of Studies

A brief summary has been reported in Table 2.

Afify et al study[23] aimed to evaluate the effectiveness of three treatments, namely fractional CO2 laser, platelet-rich plasma (PRP), and NB-UVB, in Vitiligo. Twenty participants (45% males, 55% females) with vitiligo underwent various treatments. The results indicated significant improvements in reducing the affected surface area. Specifically, treatments with CO2 laser ($P = 0.004$), PRP ($P = 0.001$), CO2 laser combined with PRP ($P = 0.001$), CO2 laser combined with NB-UVB ($P = 0.001$), and triple therapy ($P = 0.001$) outperformed the control group. Crust formation was uncommon. The key finding of the study was that the fractional CO2 laser may offer an effective treatment option for refractory cases of non-segmental vitiligo. However, it is important to note that there were instances where the observed improvement was not statistically significant, and the study lacked a direct comparison with other treatments, which limited our ability to perform a comprehensive comparative analysis. Additionally, the study had limitations such as a small sample size and a lack of blinding which is naturally hard when using the fractional CO2 laser.

In the Cunha et al study,[25] researchers explored a novel approach for treating refractory vitiligo on the hands by combining the fractional CO2 laser with betamethasone and salicylic acid solution. The study demonstrated that this combined treatment approach was effective and safe for managing refractory vitiligo on the hands. Repigmentation rates varied among patients after treatment sessions: one patient achieved excellent repigmentation (> 75%), one showed moderate repigmentation (25%–50%), and two patients exhibited minimal repigmentation (less than 25%). Remarkably, all patients who received laser treatment showed some degree of repigmentation, while the control group (treated with betamethasone solution and SA alone) did not experience significant repigmentation. The main limitation of this research is the small number of cases studied. Therefore, further research with a larger

Table 1. General Characteristics of the Selected Studies

Authors	Date	Vitiligo subtype	Design
Afify et al[23]	2021	Non-segmental vitiligo (NSV)	Self-controlled randomized clinical trial design (RCT)
Cunha et al[25]	2017	NSV	RCT with control group
Liu et al[33]	2019	NSV	prospective, self-bilateral controlled study
Li et al[34]	2015	NSV	Prospective, randomized half-body, comparative study
Shin et al[35]	2012	NSV	Prospective and randomized half-body comparative study

Table 2. Intervention and clinical outcomes of the selected studies

Authors	Insights	Intervention	Laser Characteristics	Conclusion	Limitations
Afify et al[23]	The fractional CO2 laser may be an effective treatment option for refractory cases of non-segmental vitiligo.	- Fractional carbon dioxide laser (CO2) - Platelet-rich plasma (PRP)	Targeted patches for fractional CO2 laser treatment underwent four sessions using the FIRE-XEL fractional CO2 laser by Bison Medical, Korea. These sessions were spaced two weeks apart, and the laser was operated at 15 W with a pulse width of 1 ms, one-time overlap, square spot shape, density set at 0.5, and an energy per dot of 15 mJ.	- Statistically significant improvement in all treatment groups - No statistically significant difference in the reduction of the surface area between treatment groups	The study included a relative low sample size of 20 patients, which may limit the generalizability of the findings.
Cunha et al[25]	The study found that using the fractional CO2 laser combined with betamethasone and salicylic acid solution effectively treated refractory vitiligo.	The use of fractional CO2 laser combined with betamethasone and salicylic acid solution in the treatment of refractory vitiligo in hands	PIXEL CO2 by Alma Lasers was employed. This laser had a wavelength of 10600 nm, fluence of 100 J/cm^2, pulse duration shorter than 1 millisecond, pulse width of 500–1000 microns, and a pulse frequency of 25–500 Hz. A total of five fractional CO2 laser sessions, spaced four weeks apart, were conducted using this equipment.	- Combined treatment with the CO2 laser and betamethasone/salicylic acid is effective. - The treatment is safe for refractory vitiligo.	No specific limitation mentioned. Research with a larger patient cohort is recommended.
Liu et al[33]	Ablative fractional CO2 laser aided delivery of long-acting glucocorticoid improved the response of refractory acral vitiligo.	The use of ablative fractional CO2 laser aided delivery of long-acting glucocorticoid in the treatment of acral vitiligo	The ablative fractional CO2 laser used specifically either the AcuPulse 10600 nm CO2 laser by Lumenis Inc., Santa Clara, CA, or the KL 10600 nm CO2 laser by Jilin Province Kinglaser Co., Ltd, China. The laser treatment parameters included pulse energy settings of 10-15 mJ/cm^2 or 70-100 mJ, a scan size of 10 mm, a spot density of 100-144 spots/cm^2, and a penetration depth of 300-450 microns (upper dermis) in a 1-stack static mode.	Ablative fractional CO2 laser, topical compound betamethasone solution, and NB-UVB showed promising results in improving repigmentation in acral vitiligo, with a remarkable safety profile.	The study did not mention any specific important limitations
Li et al[34]	The study investigated the efficacy and safety of triple combination treatment for refractory vitiligo.	The experimental side underwent five sessions of the ablative fractional CO2 laser followed by topical painting of compound betamethasone solution.	A 10,600-nm fractional carbon dioxide (CO2) laser device from KL, Jilin Province Kinglaser Co., Ltd, Changchun City, China was used. Key laser parameters included a pulse energy of 70–100 J/cm^2, coverage density of 5.4%, and operation in 1-stack static mode. This fractional CO2 laser was applied at a half-month interval to the treatment side of the body.	The triple combination treatment could be used as an alternative modality for refractory vitiligo.	The study had a small sample size of 25 patients.
Shin et al[35]	The study suggests that fractional CO2 laser therapy followed by NB-UVB phototherapy could be used effectively and safely as an alternative modality for the treatment of refractory vitiligo.	The control side, on the other hand, applied topical betamethasone cream once a day.	A combination treatment was performed using a 10600 nm eCO2 laser (Lutronic Corporation, Goyang, Korea) for fractional carbon dioxide (CO2) laser therapy. Two laser sessions were conducted at a 2-month interval, with pulse energy set at 100 mJ and a spot density of 150 spots/cm^2 (static mode). This laser was used to treat half of the body, while the other half received NB-UVB therapy alone.	- Combination treatment of the fractional CO2 laser and NB-UVB is effective and safe for refractory vitiligo. - Further studies are needed to confirm the results.	The study had a small sample size, which may limit the generalizability of the findings. Additional studies with larger sample sizes are needed.

patient cohort is recommended to refine the treatment protocol and confirm the effectiveness of this innovative approach.[25]

In the Liu et al study,[33] a multicenter comparative research study included 289 participants with acral vitiligo and Fitzpatrick skin Types III and IV. Their age ranged from 25-41. Its results show the triple treatment (CO2 laser, betamethasone solution, NB-UVB) significantly outperforms the control (betamethasone cream, NB-UVB), with higher marked responses ($P = 0.009$) and overall responsiveness ($P = 0.005$). The experimental side, which received laser treatment and the topical solution, showed significantly better improvement in repigmentation compared to the control side. The overall response rate for the experimental side was 51.6%, while it was 35.8% for the control side. Remarkably, no severe adverse events were reported during the trial, highlighting the safety of this triple treatment approach. Subgroups, including older patients, both genders, and varying disease durations, benefited more from the triple protocol. The key findings show that the ablative fractional CO2 laser combined with betamethasone solution and NB-UVB is an effective and safe treatment for acral vitiligo, especially for certain patient subgroups. The limitation of the study is the lack of direct comparisons with other treatments.

The Li et al study[34] was a clinical trial involving 25 patients with refractory vitiligo. A treatment protocol combining the fractional CO2 laser, topical betamethasone solution, and NB-UVB therapy was assessed. At 3 months (M3), 40% of treatment-side patients achieved over 50% repigmentation, compared to 8% on the control side. Patient satisfaction scores were significantly higher on the treatment side (4.08 ± 2.89 vs. 1.52 ± 1.29). By 6 months (M6), 44% on the treatment side achieved over 50% repigmentation, while only 8% did on the control side. Patient satisfaction scores further increased on the

treatment side (5.12 ± 3.23 vs. 2.04 ± 1.51). Adverse events were minimal. This combined approach shows promise for refractory vitiligo treatment. The limitation of this study was its relatively small sample size and the absence of a control group for assessing the effect of CO2 laser plus NB-UVB therapy alone.

The Shin ⁋et al research[35] was a prospective, randomized half-body comparative study. The participants were ten adult patients with non-segmental vitiligo (NSV). Results of the analysis revealed that combination treatment (fractional CO2 laser followed by NB-UVB) showed 51–75% clinical improvement in 10% of the patients, 26–50% improvement in 20%, and 1–25% improvement in 20%, while NB-UVB therapy alone resulted in 1–25% clinical improvement in 20% of the patients. Therefore, combination treatment had significantly higher improvement scores by physicians and higher patient satisfaction (VAS scores) compared to NB-UVB therapy alone ($P < 0.05$). No severe adverse events were reported. The limitations of the study were small sample size, short follow-up period and lack of diversity with primarily involved patients with Fitzpatrick skin type IV.

Discussion

Vitiligo patients have a high prevalence of stress, anxiety, and depression.[36] The stress stemming from the societal stigma associated with vitiligo and the resulting impact on the patients' quality of life can potentially worsen the course of the disease.[37] Lesions located on acral areas such as the hands and feet, as well as bony prominences like knees and elbows, tend to be unresponsive to conventional treatment approaches.[38] These situations pose a formidable challenge, characterized by its unpredictable treatment outcomes, thereby necessitating the exploration of innovative therapeutic modalities. Among these, the fractional CO2 laser has emerged as a promising adjunct to conventional treatments for refractory non-segmental vitiligo.

Our review, with a focus on several clinical trials, aimed to investigate the multifaceted effectiveness, safety, and combinatory aspects of the fractional carbon dioxide laser. The findings offer hope for individuals with vitiligo, especially those with refractory or resistant-to-treat cases. Several key takeaways emerging from these studies have been brought in the following.

First, the efficacy of the fractional CO2 Laser: Fractional CO2 laser therapy appears to be a promising treatment modality for vitiligo. It consistently demonstrated repigmentation across the studies, often in combination with other treatments like NB-UVB and topical steroids. This suggests that the fractional CO2 laser may act as a stimulant for melanocyte regeneration, potentially enhancing the effectiveness of other therapies.

Second, combination therapies: The studies underscore the potential benefits of combination therapies. Whether paired with PRP, topical solutions, or NB-UVB, the fractional CO2 laser showcased improved repigmentation rates compared to individual treatments. This suggests that a multifaceted approach may be more effective in managing vitiligo, especially in cases resistant to conventional therapies.

Third, Patient Variability: It is important to note that individual patient responses to these treatments varied. Repigmentation rates ranged from minimal to excellent, highlighting the need for personalized treatment plans. Factors such as age, disease duration, and gender may influence treatment outcomes, as seen in some of the studies.

Fourth, Safety Profile: Across the studies, adverse events associated with fractional CO2 laser therapy were minimal and generally well-tolerated. This suggests that the treatment is relatively safe for vitiligo patients.

However, several limitations were common to these studies. Small sample sizes were a recurring issue, potentially impacting the generalizability of the results. Additionally, some studies lacked direct comparisons with alternative treatments, limiting the ability to definitively establish the superiority of fractional CO2 laser-based approaches.

In sum, the collective findings suggest that the fractional CO2 laser, particularly in combination with other therapies, holds promise as a treatment option for vitiligo. However, further research, involving larger patient cohorts, rigorous controls, and longer-term assessments, is required to refine treatment protocols, address patient variability, and confirm the effectiveness and safety of these innovative approaches in managing vitiligo. These studies represent steps toward improving vitiligo treatment options, but there is still work to be done to optimize outcomes for individuals with this condition.

It is worth noting that various studies conducted for different other body areas have yielded similar results. One study demonstrated the effectiveness of combining the fractional CO2 laser with NB-UVB in treating stable non-segmental vitiligo, particularly on the trunk.[28] Additionally, laser therapy, when combined with topical betamethasone solution and NB-UVB, has shown a marked to excellent improvement in white patches of vitiligo.[39] The combination therapy of the fractional CO2 laser with conventional treatments has been found to be efficient and safe, with significantly superior results compared to conventional treatments alone.[40] Additionally, the fractional CO2 laser has been studied as an adjuvant treatment with other modalities, such as tacrolimus ointment, and was found to yield mild improvement, particularly in acral areas and lesions of shorter duration.[24] The laser treatment has been shown to have a good curative effect in the treatment of vitiligo, with high efficiency and patient satisfaction.[41] Therefore, other

relevant studies in the existing literature also reported positive outcomes and efficacy of the fractional CO2 laser as an additional therapy for vitiligo. Adverse effects such as pain, burning sensation, erythema, swelling, pruritus, and hyperpigmentation have been observed, but no severe complications were reported. A case report showed the sustained efficacy and safety of the fractional CO2 laser combined with sun exposure over an eight-year period.[42] Overall, these findings suggest that the fractional CO2 laser can be a safe and effective treatment option for refractory non-segmental vitiligo, particularly when used in combination with other modalities.

The results from these five studies shed light on the diverse treatment options available for vitiligo, particularly in cases resistant to conventional therapies. However, our review is not without limitations, including the constraint of small sample sizes in some studies. Additionally, maintaining appropriate blinding during the application of CO2 laser therapy presented challenges. Further research and clinical trials are essential to confirm and refine these approaches, ultimately improving the quality of life for vitiligo patients.

Conclusion

Vitiligo exerts a considerable influence on the quality of life for the majority of patients, underscoring the significance of implementing advanced and aggressive treatment approaches encompassing various modalities, coupled with appropriate counselling and psychological support.[43] In summary, the fractional CO2 laser, when combined with conventional therapies, offers a safe and effective treatment option for refractory non-segmental vitiligo. Future research should focus on understanding the pathogenesis, potential side effects, and cost implications to enhance our understanding of this promising treatment. Furthermore, conducting additional large-scale randomized clinical trials is essential to establish its efficacy, safety, and optimal applications across various vitiligo cases. A comprehensive assessment of adverse effects is crucial for a comprehensive risk-benefit profile.

Additionally, the choice of combination therapy for vitiligo should be tailored to the patient's specific characteristics and disease stage, indicating that there is no one-size-fits-all approach to combination therapy. On the basis of the above-mentioned researches, different studies suggest that combination methods including NB-UVB phototherapy, topical calcineurin inhibitors, topical corticosteroids, topical calcipotriol and other medications in combination with the fractional CO2 laser could be used effectively and safely as an alternative modality for the treatment of vitiligo.

However, achieving a consensus on the most effective use of CO2 Fractional Laser for repigmentation in vitiligo is hindered by limitations in current clinical assessment methods, including classification, assessment approaches, outcome measures, and intervention diversity. Overcoming these constraints requires more extensive research and collaboration.

Pain, redness, swelling, peeling, crusting, pigment changes, potential scarring, and variable recovery times should be considered when undergoing CO2 Fractional Laser therapy. While this procedure has been generally safe and well-tolerated in various skin interventions[44] and we could not identify any serious side effects in our review, in the context of vitiligo, it is crucial to gather more evidence and assess potential side effects, particularly the risk of the Koebner phenomenon.

Offers for next studies: One issue that should be considered in the field of using the carbon dioxide laser is the mechanism of its effect, which requires other research. Some studies show that the mechanism of action of the fractional CO2 laser in the treatment of vitiligo involves the stimulation of melanocyte proliferation and repigmentation within vitiliginous patches.[29] The laser treatment leads to increased collagen production in the dermis, resulting in the elevation of collagen quantity and arrangement, as well as the improvement of pigmentation and texture of the skin.[23] While the precise mechanisms driving repigmentation remain elusive, several hypotheses have been proposed, including enhanced transdermal delivery of topical agents, improved phototherapy effectiveness, and the involvement of melanogenic cytokines in response to inflammation.

The other challenge which needs study is controlling dermabrasion depth to provide a safer alternative to traditional therapy. It should be noted that in our reviews, we did not find comprehensive or evidence-based guidelines regarding laser depth control. However, it is worth mentioning that in other sources, recommendations may have been made in this regard.

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