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Fractionated CO2 Laser for Scar Improvement: A Review of Clinical Effectiveness and Cost-Effectiveness

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Authors: Kwakye Peprah, Suzanne McCormack

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Abbreviations

$AFCO_2L$	Ablative fractional carbon dioxide laser
BSHS-B	Burns Specific Health Scale
CO_2	Carbon dioxide
DLQI	Dermatology life quality index
DN4	Douleur Neuropathique 4 Questions
IQR	Interquartile range
POSAS	Patient and observer scar assessment scale
SD	Standard deviation
SF-36	Short Form-36
VSS	Vancouver scar scale

Context and Policy Issues

A burn is an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction, or contact with chemicals.1 The World Health organization has stated that every year burns cause an estimated 180,000 deaths, and non-fatal burn injuries are a leading cause of morbidity.1 According to the Canadian Skin Patient Alliance, more than 3,200 people were admitted to Canadian hospitals for burns in 2005 to 2006, when the latest statistics are available.2 Based on data from the Canadian Hospitals Injury Reporting and Prevention Program, the Public Health Agency of Canada identified 1,682 cases of thermal burns and scalds, representing 1.2% of injuries reported in 2013. The report did not include burns from friction, chemical or caustic agents, or direct contact with lightning, which were considered to present unique circumstances.

For survivors with severe scars, significantly diminished quality of life often persists despite traditional scar management, due to disfigurement, pain, itchiness, and contractures restraining the motion of body and joints.[3] Thus, trauma from burn injuries may continue to bother patients long after their wounds have healed and their hospital stay is over.[4] Treatment may be associated with substantial financial costs for modern health-care systems. For example, the direct costs for care of children with burns in the United States of America exceeded US$211 million in 2000, and the costs for hospital burn management in Norway exceeded €10.5 million in 2007.[1] The cost burden of burn-related treatment to the Canadian health system was not immediately available, at the time of compiling this report.

For contracted scars, surgery is the primary therapeutic approach to relieve tension and ultimately improve the range of motion of the affected areas. However, the efficacy of surgical treatment is limited to the surgical site, and the procedure is associated with considerable morbidity and high recurrence rates.[3] Non-surgical interventions that are often used in clinical practice to improve burn scar management include silicone gel preparations, the use of pressure garments, physical therapy, compression, onion extract-based products, local medical therapy, and different types of laser treatments.[3,4] The three main groups of lasers that can be used to improve scars include pulsed dye lasers and devices that use similar technology, Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers, and ablative and non-ablative fractional lasers (e.g., fractionated CO2 laser).[5]

The objective of this report is to summarize the evidence regarding the clinical effectiveness of fractionated CO2 laser for burn scar improvement and the cost-effectiveness of its use for this condition.

Research Questions

1. What is the clinical effectiveness of fractionated CO2 laser for burn scar improvement?
2. What is the cost-effectiveness of fractionated CO2 laser for burn scar improvement?

Key Findings

Evidence of limited quality from one systematic review, one randomized controlled trial and four non-randomized studies suggested that treatment of burn scars with fractionated carbon dioxide laser therapy significantly improves the scars (as assessed by Patient and Observer Scar Assessment Scale and Vancouver Scar Scale), and reduces pain, pruritus, and scar tightness, as well as improves scar-related quality of life, relative to no treatment or before treatment. Sources of uncertainty include the low or unclear quality of primary studies in the systematic review and the other included studies discussed, and lack of clarity about how the reported scores from the instruments used to measure outcomes translate into changes in function among the treated patients. No relevant evidence regarding the cost-effectiveness of fractionated carbon dioxide laser therapy for burn scar improvement was identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were CO2 lasers and burns treatment. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2014, and May 27, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with symptomatic burn scars
Intervention	Fractionated (also called fractional) CO2 Laser; ablative scar resurfacing (if CO2 fractional)
Comparator	No treatment comparator

Outcomes	Q1: Function (e.g., contracture, limited joint movement, impaired mouth or eye opening or closure, fragile skin prone to re-injury) and comfort (i.e., chronic pain, chronic itch) Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations

CO2 = carbon dioxide.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2009. Studies that were included in an already selected systematic review were also excluded.[6-9]

Critical Appraisal of Individual Studies

The included systematic review[5] was critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2),[10] while the randomized controlled trial (RCT)[11] and the non-randomized studies[3,4,12,13] were critically appraised using the Downs and Black checklist.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 240 citations were identified in the literature search. Following screening of titles and abstracts, 213 citations were excluded, and 27 potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search did not identify any additional relevant publications. Of the 27 potentially relevant articles, 21 papers were excluded for various reasons, and six reports that met the inclusion criteria were included in this review. These comprised one systematic review,[5] one RCT,[11] one controlled prospective cohort study,[4] and three uncontrolled before-and-after studies.[3,12,13] Appendix 1 presents the PRISMA[15] flowchart of the study selection process. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

One systematic review,[5] one RCT,[11] one controlled prospective cohort study[4] and three uncontrolled before-and-after studies[3,12,13] were included in this report. The systematic review[5] included 12 primary studies published between 1997 and 2016, including eight that assessed the effect of ablative fractional carbon dioxide laser ($AFCO_2L$) therapy on burn scars. Four of these eight had an uncontrolled before-and-after design, whereas four had a controlled clinical trial design which included a matched untreated scar area for comparison.

In the RCT,[11] which was published in 2019, regions of scar were randomized to treatment and control zones. The controlled prospective cohort study[4] published in 2017 also split the areas of scar into treatment and control halves; however, there was no description of how the of halves were assigned. The three uncontrolled before-and-after studies[3,12,13] were published in 2017[3,13] and 2018[12].

Country of Origin

Reviewers from Canada authored the systematic review.[5] The countries of origin of the primary studies of the systematic review[5] were not reported. The RCT[11] and one uncontrolled before-and-after study[13] were conducted in Australia, whereas the two remaining uncontrolled before-and-after studies were conducted in Egypt[3] and France.[12] The controlled prospective trial[4] was conducted in Germany.

Patient Population

The twelve primary studies of the systematic review[5] included a total of 602 patients who were diagnosed with hypertrophic scars caused by burn injuries. Eight of the studies, with sample sizes ranging between 10 and 320, assessed $AFCO_2L$ in a total of 534 patients. Five of the eight studies included a total of 52 males and 63 females aged from seven to 58 years old. The three remaining studies did not report any age or sex distribution data.

The RCT[11] included 20 adult patients with a burn-related scar affecting a minimum area of 10 cm^2 and baseline Vancouver scar scale (VSS) score of > 5. Patients had a mean age of 29 years, and a median scar age of 17 months. The controlled prospective study[4] included 10 patients with hypertrophic burn scars. The patients' mean age was 39.3 years, and the mean scar age was 12.45 years. Information about the scar sizes was not reported. One uncontrolled before-and-after study[3] included 20 patients with burn scars that measured at least 20 cm^2. The mean scar age was 12.3 years. Another uncontrolled before-and-after study[12] enrolled 24 patients (mean age 33.7 years) with hypertrophic scars and keloids resulting from second and third degree burns of the face. Another uncontrolled before-and-after study[13] enrolled 47 patients (median age 34 years) with burn scars. No information was provided in either of these studies[3,12] about the size or age of the studied scars. However, one of the studies[13] reported that the $AFCO_2L$ treatment was initiated a median of 17.9 months (IQR 10.9 to 43.1 months) after the burn.

Interventions and Comparators

In all the included studies[3-5,11-13] in this report, $AFCO_2L$ therapy was the intervention of interest. The laser wavelength used was 10,600 nm in the studies in the systematic review,[5] the RCT,[11] and three uncontrolled before-and-after studies;[3,12,13] the laser wavelength was not specified in the controlled prospective study.[4] The reported follow-up period in the primary studies of the systematic review[5] ranged from four weeks to three years. The systematic review[5] did not provide information from its primary studies about the number of treatment sessions applied to scars, or about the post-treatment care.

In the RCT,[11] scars in both the treatment and control zones were treated with back ground standard care (i.e., silicone, massage, and pressure garments). However, in the controlled prospective study,[4] the scars in the control zone were not treated at all. The target scars in the RCT,[11] the controlled prospective study,[4] and one before-and-after study[3] underwent three treatment sessions performed at intervals of four to eight weeks, whereas one single treatment session was used in two before-and-after studies.[12,13] Patients in the RCT[11] were treated under general anesthesia. In the controlled prospective study[4] and two before-and-after studies,[3,13] $AFCO_2L$ procedure was performed under local anesthetics. One study[12] did not have information about the use of anesthesia.

All the studies described post-laser treatment care. These included application of emollient and silicone dressings for two to 10 days,[11,13] compression dressing and use gentamicin for seven days,[12] topical application of panthenol 2% twice daily for four weeks[3], regular use of

sunscreen,[3] and applying of fusidic acid to wounds.[4] In one study,[13] laser-facilitated drug delivery was used to inject topical corticosteroids into hypertrophic scar lesions immediately following the AFCO$_2$L procedure. The five studies[3,4,11-13] reported follow-up durations ranging from 1.5 to 26 months.

Outcomes

Outcome measures of interest that were commonly reported by the all five studies[3-5,11,13] were the Patient and Observer Scar Assessment Scale (POSAS) and Vancouver Scar Scale (VSS). The POSAS is a validated tool for the documentation of burn scars consisting of two parts: a patient scale and an observer scale, each containing six items, scored numerically on a ten-step scale. The total score of the POSAS, tallied from the scores of each of the six items, ranges from 6 to 60 for “like normal skin” to “worst scar imaginable,” respectively. The VSS comprises four domains: vascularity (0-3 points), pliability (0-5 points), pigmentation (0-2 points), and height (0-3 points) with total score of 0 to 13, where 0 represents normal on each scale and 13 the worst case.

One study[13] evaluated changes in neuropathic pain using the Douleur Neuropathique 4 Questions (DN4) and pruritus using a modified 5-D itch scale (4-D Pruritus Scale). The DN4 questionnaire was developed to explore both sensory descriptors as well as signs related to a bedside examination. The total score is the tally of 10 items, with a cut-off value of 4/10 required for the diagnosis of neuropathic pain.[13] The 4-D Pruritus Score ranges from a minimum score of 7 (no itch) to 35 (worst itch).

Two studies assessed the improvement of quality of life after treatment with one using the Burns Specific Health Scale (BSHS-B),[13] whereas the other used the Dermatology Life Quality Index (DLQI).[4] The BSHS-B is a 40-question outcome scale designed for evaluation of burn patients in nine fields (simple abilities, hand function, affect, body image, interpersonal relationship, sexuality, heat sensitivity, treatment regimens, and work). Higher BSHS-B scores indicate better quality of life, with the maximum score of 160 being equivalent to a normal quality of life. One study,[12] which did not apply either the POSAS or VSS, assessed patients using a non-validated five-item questionnaire developed by the authors. Each item was scored on a 0 to 10 scale from poor to excellent, respectively. A final score ranging between 0 and 50 was obtained from tallying the individual scales.

Summary of Critical Appraisal

Systematic Review

The systematic review[5] had a clearly stated research objective and inclusion and exclusion criteria. The population, intervention, and control (comparator) of interest, as well as the outcome measures, were defined. The review authors searched multiple databases, with search dates ranging from 1946 (or inception) to 2016. Also, the reference lists of relevant studies were hand-searched to identify additional studies. However, the search was limited to studies published in English. Study selection and data extraction were performed in duplicate by two review authors, with disagreements between them resolved by a third reviewer. The included primary studies were listed in tabular form, with the relevant characteristics of each study. A list of excluded studies was not provided; however, the number of studies excluded and the reasons for exclusion were specified in the PRISMA flow chart illustrating the study selection process. All the primary studies in the systematic review[5] had non-randomized designs because the literature search did not identify any RCTs. The risk of bias and methodological quality of the studies were evaluated using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool, and Strengthening

the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Overall, the included studies were of low or unclear quality with a high or unclear risk of bias. There was no indication that the review methods were established before conducting the review, and it could not be ascertained whether the report had any significant deviations from a protocol. However, the risk of bias in individual studies was considered in the discussion of the results and conclusions of the systematic review.[5] The authors stated that they had no conflicts of interest to disclose.

Primary Studies

The study objectives, the patient characteristics, and the interventions of interest in all of the five included primary studies[3,4,11-13] were described clearly. While the main outcomes to be measured and the key findings of the studies were well reported by four of the studies[3,4,11,13] that used standard, validated tools to evaluate results, one study[12] inadequately described outcomes, and assessed patients using an unvalidated questionnaire developed by the authors. It is unknown if any of the studies[3,4,11-13] were adequately powered since sample size calculations were not reported in any of them. Thus, the potential for a type-2 error cannot be ruled out in any of the studies. The authors of all of the studies declared no potential conflicts relevant to the content of the studies.[3,4,11-13]

In the RCT,[11] scar areas to be treated were randomly selected by a clinician not involved with the trial, thus, minimizing selection bias. Also, all laser therapy was administered by the same clinician, to limit variability that could affect outcomes. Nine (45%) of the 20 patients initially included in the RCT[11] opted to participate in long-term follow-up while 11 patients were not included in that phase of the study. Of the nine that participated in long-term follow-up, five (55.6%) received further laser treatments (range: 1 to 4 sessions) in addition to the initial trial intervention. Thus, a high risk exists that the reported long-term outcome could have been impacted by selection bias, and the specific contribution of the initial trial therapy to the results is uncertain.

Four included studies[3,4,12,13] were non-randomized and thus were inherently likely to have more systemic biases as they lack the risk-diminishing property of randomization. In one study,[3] only patients who completed the entire treatment and follow-up protocol were included in the final analysis. Thus, the rigour associated with intention-to-treat analysis was missing. However, the impact on the results of analysing data of 17 instead of the original 20 participating patients was unclear. In two studies,[12,13] data were presented for patients after a single treatment session. Given that $AFCO_2L$ therapy often involves multiple sessions, the reported findings may not reflect real-life clinical practice. In one study[13], the $AFCO_2L$ treatment for hypertrophic scars was immediately followed by laser-facilitated injection of corticosteroids topically or into the lesions. In another study[12], the $AFCO_2L$ therapy was applied after a lipofilling surgery. Therefore, in each of these studies, it is unclear if reported results were a consequence of the laser treatment or the co-intervention.

Overall, the quality of evidence from the systematic review[5] and the primary studies[3,4,11-13] included in this report was limited.

Summary of Findings

The following paragraphs summarize the clinical effectiveness and safety of fractionated CO2 laser for scar improvement. Appendix 4 presents tables of the main clinical-effectiveness findings and authors' conclusions from the studies included in this report.

Clinical Effectiveness of Fractionated CO2 Laser for Scar Improvement

Function – POSAS

One systematic review[5] that assessed the effectiveness of $AFCO_2L$ for the treatment of burn scars reported statistically significant improvements from eight primary studies in both the patient and the observer sections of the POSAS after treatment. The follow-up duration in the primary studies was between four weeks and three years.

After follow-up durations of between six weeks and three years, one RCT[11] and three non-randomized studies[3,4,13] reported significant reductions in the overall mean POSAS score as well as the observer and patient scores of the POSAS.

Function – VSS

One systematic review[5] reported significant improvements in the mean total VSS score and/or VSS component scores from seven primary studies that evaluated the effectiveness of $AFCO_2L$ for the treatment of burn scars. However, in one primary study of the systematic review, no significant change was observed in one component (scar vascularity) of VSS. The follow-up duration in the primary studies was between four weeks and three years.

One controlled prospective study[4] and two uncontrolled before-and-after studies[3,13] also found that treatment with $AFCO_2L$ resulted in significant reductions in the total VSS after follow-up periods ranging from two to 12 months. However, one RCT[11] found that VSS assessments did not show any significant difference between treatment and control segments at six weeks or long-term (i.e., two to three years) after therapy assessments compared to pre-treatment scores.

Comfort

Pain, itching, and scar tightness

The included systematic review[5] included one primary study that reported that 96.7% of patients were satisfied with laser treatment, and had significant improvements in pain, pruritus, and scar tightness, at least two months after $AFCO_2L$ therapy. However, that study used an unvalidated questionnaire to assess patient experience and outcomes.

One RCT[11] found that patients achieved significant improvement in scar pain ($P = 0.047$) and itch ($P < 0.01$) in the treated areas (as measured by the POSAS) six weeks after treatment compared to pre-treatment.

One uncontrolled before-and-after study[13] found that pain in patients for whom $AFCO_2L$ was used for burn scars was significantly reduced after a median follow-up of 55 days, as indicated by a decrease in DN4 pain score from a median of 3.0 (IQR: 1.0 to 6.0) before treatment to 2.0 (IQR: 0.0 to 5.0; P <0.001) during the follow-up assessment. In the same study, itching, as measured by the modified 4-D Pruritus Score (maximal score 35), was reduced by 2.5 points from a median of 16.0 (IQR: 9.8 to 20.0) to 13.5 (IQR: 7.0 to 18.0; $P < 0.001$) during the same follow-up period.

Quality of life

One uncontrolled before-and-after study[13] found that the overall quality of life score on BSHS-B for patients who underwent $AFCO_2L$ treatment for scars increased significantly by 16 points compared to baseline, at a median follow-up of 55 days (IQR: 32 to 74 days) after therapy ($P < 0.001$). One controlled prospective study[4] found a significant decreased in the

negative influence of scars on the patients' quality of life as indicated by a 47.2% reduction (*P* = 0.0030) in the DLQI score from a mean (SD) baseline value of 8.900 (5.990) to 4.700 (3.335) six months after treatment.

Adverse events

One uncontrolled before-and-after study[3] reported that seven patients (29.2%) experienced pain following the laser session, lasting one to six days. The pain was described as mild in four patients (23.5%) and moderate in three patients (17.6%). One controlled prospective study[4] indicated that slight weeping, crusting, swelling, and postoperative erythema occurred but no incidence data were provided.

Cost-Effectiveness of Fractionated CO2 Laser for Scar Improvement

The literature search for this review did not identify any relevant evidence regarding the cost-effectiveness of fractionated CO2 laser for scar improvement; therefore, no summary can be provided.

Limitations

The primary studies included in the systematic review[5] were of low or unclear quality with a high or unclear risk of bias. Further, the systematic review reported study-level findings without combining data in analysis. Thus, it does not provide the benefit of effect estimates synthesized from multiple studies. Also, the systematic review[5] was limited to hypertrophic scars secondary to burn injuries. Therefore, studies were excluded from the systematic review if they examined different types of scars (i.e., hypertrophic, keloid, surgical, and so forth) and did not present results separately from results specific to hypertrophic scars secondary to burn injuries. The five primary studies[3,4,11-13] included in this report had sample sizes ranging from 10 to 47. None of the investigators performed calculations to determine whether the studies were sufficiently powered; therefore, it cannot be ruled out that the reported findings were due to chance. Although the systematic review[5] and four other studies[3,4,11,13] included in this report evaluated outcomes using validated scar-related tools (i.e., VSS and POSAS), the translation of the reported scores from these instruments into changes in function among the treated patients was unclear. Although the comparison of interest for this report was fractionated CO2 laser versus no treatment (i.e., natural history of a chronic burn score), no active comparisons with other laser modalities were identified. Thus, it is unknown how $AFCO_2L$ compares with other laser intervention such as pulsed dye lasers and Q-switched Nd:YAG lasers which are also used to improve scars.[5] The literature search for this report did not identify any relevant evidence regarding the cost-effectiveness of fractionated CO2 laser for burn scar improvement. However, the search was limited to English language documents, and it is unknown if potentially relevant articles in other languages were missed. Although the systematic review[5] was authored by reviewers from Canada, the countries of origin of the primary studies in it were not reported. The other five studies[3,4,11-13] included in this report were conducted outside Canada. Therefore, the generalizability of the findings to the Canadian context is unclear, given the potential for differences in practice patterns that might impact the interpretation of the results or the resources used to achieve them. However, the included studies enrolled patients with a diversity of age, scar types and age, prior treatment(s), and post-operative which suggests that $AFCO_2L$ may be applied to a wide range of patients, implying a good generalizability across the targeted patient population. Given these limitations, there is a need for further studies, adequately powered and using appropriate controls and tools to

assess changes in patients' function, to confirm the effectiveness of the $AFCO_2L$ modality and its cost-effectiveness for the improvement of burn scars.

Conclusions and Implications for Decision or Policy Making

One systematic review,[5] one RCT,[11] and four non-randomized studies[3,4,12,13] provided the information in this report. Data from these studies suggest that fractionated CO2 laser ($AFCO_2L$) therapy results in significant improvements to burn scars as assessed by Patient and Observer Scar Assessment Scale and Vancouver Scar Scale. However, how the scores on these instruments translated into changes in function such as reduction in contracture, limited joint movement, impaired mouth or eye opening or closure, and fragile skin prone to re-injury, was unclear. Concerning comfort, limited evidence from one primary study in the systematic review,[5] as well as one RCT,[11] and one uncontrolled before-and-after study,[13] indicates that patients treated with $AFCO_2L$ experienced significant improvements in pain, pruritus, and scar tightness. There was also limited evidence from two non-randomized studies[4,13] showing that patients with burn scars who underwent $AFCO_2L$ therapy had significant improvements in their quality of life as indicated by BSHS-B or DLQI scores.

Overall, limited evidence from the studies[3-5,11-13] included this report suggests that $AFCO_2L$ can improve comfort in patients with burn scars concerning pain, itching, scar tightness, and quality of life. However, the effects of $AFCO_2L$ therapy on function such as reducing contracture, limited joint movement, impaired mouth or eye opening or closure, and fragile skin prone to re-injury were unclear.

Sources of uncertainty included the low or unclear quality of evidence in the primary studies in the systematic and the limitations of the other included studies as previously discussed. Given the limitations, there is a need for additional rigorous research, adequately powered and using appropriate controls and tools to assess changes in patients' function in addition to the quantitative outcome measures, to confirm the clinical effectiveness of $AFCO_2L$ therapy and its cost-effectiveness for the treatment of burn scars.

No relevant evidence regarding the cost-effectiveness of $AFCO_2L$ for burn scar improvement was identified.

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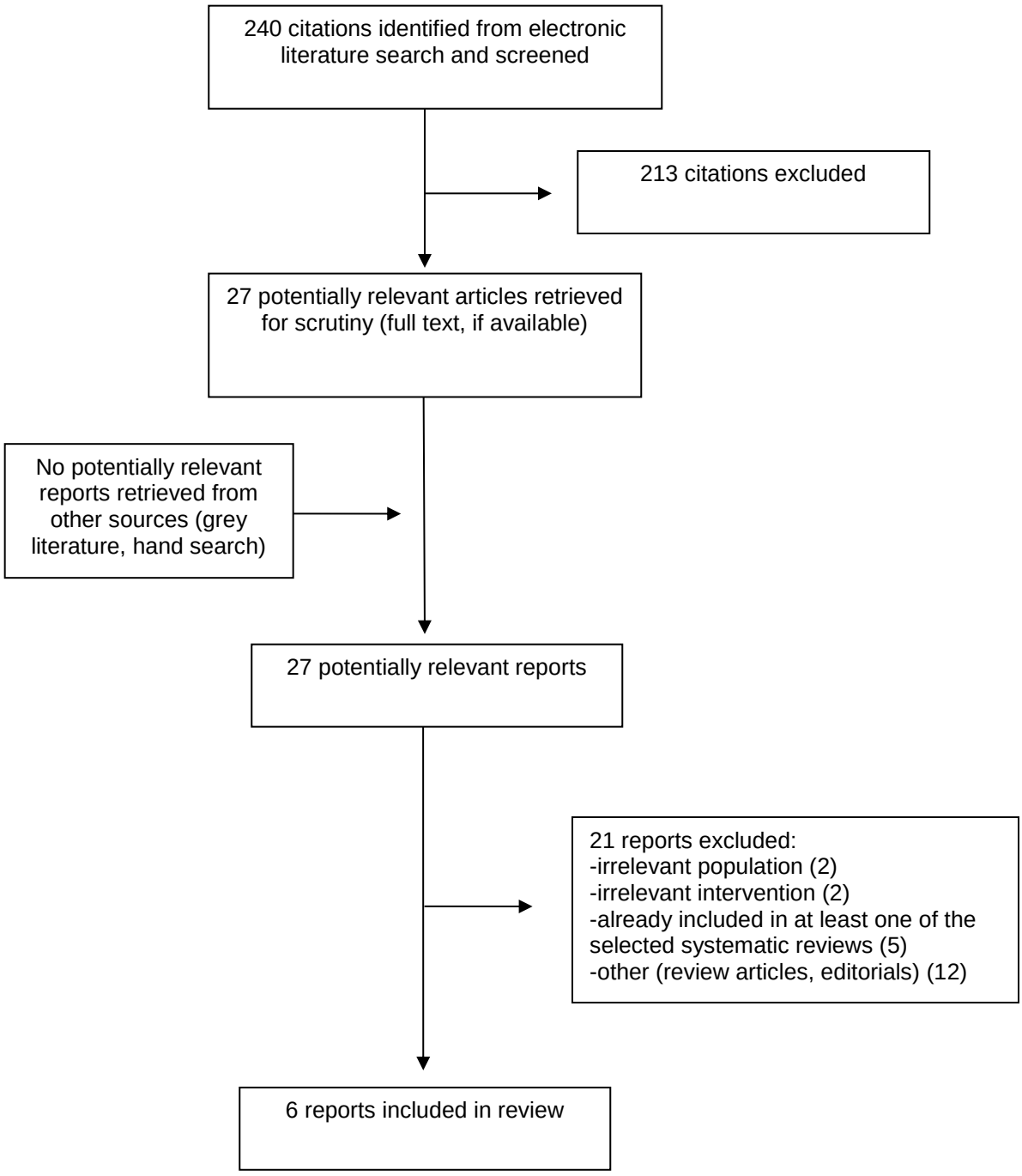
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up

Zuccaro et al., 2017[5]
 	
Canada
	Systematic review of 12 primary studies (seven before-and-after and five non-randomized controlled clinical studies), eight of which were relevant to the current report	A total of 602 patients with hypertrophic burn scars (537 treated with AFCO2 laser).
		
		Patients' age ranged from 0.5 to 77 years old.
			$AFCO_2L$ 10,600-nm (assessed in eight of the twelve primary included studies)	• VSS score
				• POASS score
				• Objective measure for
				  ○ pigmentation,
				  ○ elasticity,
				  ○ sensation in scar,
				  ○ scar thickness
				• SF-36 for health status
				• Patient satisfaction
				
				Follow-up in the primary studies ranged from four weeks to three years.

$AFCO_2L$ = Ablative fractional carbon dioxide laser; CO_2 = carbon dioxide; POSAS = patient/observer subjective; SF-36 = Short Form-36; VSS = Vancouver scar scale.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
Douglas et al., 2019[11] Australia	Randomized controlled trial (The regions of scar were randomized to treatment and control zones)	Twenty adult patients, mean age of 29 years, with a burn-related scar with a minimum scar area of 10 ×10 cm and Vancouver scar scale (VSS) score of > 5. The median scar age was 17 months (range: 6 to 341 months).	$AFCO_2L$ plus standard scar care versus Standard scar care (silicone, massage and pressure garments) alone. Patients were treated under general anesthetic; with treatment zones receiving three standardized laser treatments at four to six weeks intervals. Emollient and silicone dressings were applied to all laser treatment and control	• VSS score • Patient Scar Assessment Scale (for pain and itch) • Histological tissue analysis (e.g., for changes in collagen fibers) Follow-up was six weeks post-treatment. Long-term (two to three years) VSS assessment was reported for nine patients

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			zones for 48 hours after the procedure. Afterwards, emollient was applied twice daily to all scar areas for two weeks.	
Non-randomized Studies				
La Padula et al., 2018[12] France	Uncontrolled before-and-after prospective cohort study	Twenty-four patients with hypertrophic scars and keloids resulting from second and third degree burns of the face enrolled from November 2011 to January 2013. The mean (SD) age was 33.7 (12.6) years. They had previously received a mean of 4.3 (2 to 7) restoration operations before the first fat graft (which preceded the $AFCO_2L$).	$AFCO_2L$ (10,600 nm wavelength) following fat graft (lipofilling). Patients were allowed to wear compression dressing and use gentamicin for seven days after the procedure.	• Texture • Softness • Color • Elasticity Assessed by a five item questionnaire, each graded between 0 (poor) and 10 (excellent). The individual scores were used to obtain a final score ranging from 0 to 50. The mean follow-up was 13.5 months (range: 12 to 26 months)
El-Hoshy et. Al, 2017[3] Egypt	Uncontrolled, before-and-after, prospective study	Twenty patients (16 women and four men); with burn scars of at least $20cm^2$ and at least one year old, presenting to the outpatient clinic from March 2014 to August 2014. The mean (SD) scar age was 12.3 (8.7) years (range: 1 to 30 years)	$AFCO_2$ laser 10,600 nm. The target scars underwent three treatment sessions performed four to eight weeks apart. Topical anesthesia (lidocaine 2.5% and prilocaine 2.5%) was applied to the target area 30 to 60 minutes before the procedure, and then the area was washed off and dried properly before laser application. Post-laser home treatment included topical application of panthenol 2% twice daily for four weeks. Patients were also instructed to use sunscreen regularly	***Primary*** VSS score POSAS score ***Secondary*** Histological and histochemical evaluation of collagen and elastic fibers. Final follow-up was two months after the last laser treatment

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			(for scars in sun-exposed sites) and to avoid removal of the crust.	
Issler-Fisher et al., 2017 [13] Australia	Uncontrolled prospective before-and-after study	Forty-seven patients (13 male 34 female) with burn scars who completed at least one treatment cycle from December 2014 until February 2016. The median age was 34 years (IQR 24.5 to 48.0 years)	$AFCO_2L$ (10,600-nm wavelength) Topical anesthesia was applied to the target area before the procedure. Wound care after laser therapy included application of topical Vaseline for 7–10 days For hypertrophic scars, laser treatment was immediately followed by laser facilitated drug delivery of corticosteroids topically or intra-lesionally injected.	Objective • VSS score, • POSAS score, • Scar thickness Subjective • Pain (using DN4) • Pruritus (4-D* pruritus scale) • QoL (using BSHS-B) Final follow-up assessment was at 12 months after the last laser therapy
Poetschke et al., 2017[4] Germany	A controlled prospective cohort study (Two similarly scarred skin areas of roughly 10 × 10 cm were defined in the same individual, one of which was treated and one of which was left untreated as the internal control)	Ten patients (three male, seven female) with hypertrophic burn scars were involved. Patients' mean (SD) age was 39.3 (15.3) years, and the mean (SD) scar age was 12.45 (17.18) years.	$AFCO_2L$ (a single session). Topical anesthesia was applied to the target area before the procedure. Postoperatively, the wounds were treated with a fusidic acid containing salve and covered with paraffin gauze, sterile gauze, and dressings. Wounds were usually dry after 24 h and required no further dressing.	• VSS score, • POSAS score, • QoL (using DLQI). Follow-up was six months after treatment

$AFCO_2L$ = Ablative fractional carbon dioxide laser; BSHS-B = Burns Specific Health Scale; CO2 = carbon dioxide; DLQI= dermatology life quality index; DN4 = Douleur Neuropathique 4 Questions; IQR = interquartile range; PGA = Physician Global Assessment; POSAS = patient and observer scar assessment scale; QoL = quality of life; VSS = Vancouver scar scale.

* 4-D pruritus score is a modification of the 5-D purities scale in which the components are duration, degree, direction, disability, and distribution. In the modified 4-D version used in the study by Issler-Fisher,[13] the "distribution" component was dropped as the location of pruritus was given by the site of the scar.[13]

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of included Systematic Review using AMSTAR-2[10]

Strengths	Limitations
Zuccaro et al., 2017[5]	
• A comprehensive search for relevant literature was conducted through multiple databases, and the reference lists of relevant studies were hand-searched to identify additional studies. • The inclusion and exclusion criteria were defined, and reasons for excluding studies were provided. • Two review authors independently examined study titles and abstracts to determine which articles should be included for further review. Full-text articles were reviewed according to pre-specified selection criteria. Disagreements between reviewers were resolved by the third author. • The included primary studies were listed in a table with relevant characteristics. • The two reviewers independently extracted data using a customized data extraction form. Disagreements between reviewers were resolved by the third author. • The authors stated that they had no conflicts to disclose.	• All the included primary studies had non-randomized design, with low or unclear quality and high or unclear risk of bias. • A list of excluded studies was not provided. • It was unclear if the protocol for the systematic review was developed and registered before the review was conducted. • Selection was limited to English-language studies. Thus, potentially relevant articles in other languages could have been excluded. • The review was limited to hypertrophic scars secondary to burn injuries. Therefore, studies were excluded if they included different types of scars (hypertrophic , keloid, surgical, and so forth) but did not distinguish them from one another in the analysis using subgroups. • A clear link was not provided between the reported outcomes and change in function or comfort among treated patients.

Table 5: Strengths and Limitations of Clinical Studies using Down and Black Checklist [14]

Strengths	Limitations
Douglas et al., 2019[11]	
• The study objective, the intervention, and the main outcomes measures were defined • Inclusion and exclusion criteria were described • Scar areas to be treated in each patient were selected randomly by a clinician not involved with the trial using a random number generator. • The same clinician performed all laser treatments, thus limiting variability that could affect outcomes. • The authors declared that there was no source of financial or other support, or professional relationships, which may pose a competing interest.	• Sample size calculations were not performed. • Nine (45%) of the twenty patients initially included in the study opted to participate in long-term follow-up. Thus, a high risk exists that the reported long-term outcomes could have been impacted by selection bias driven by patients' response to initial therapy. • Of the nine patients who entered the long-term follow-up analysis, five received further laser treatments (range: 1 to 4) to the study areas in addition to the initial trial intervention. Thus, the specific contribution of the initial trial therapy to the long-term follow-up outcomes is uncertain
La Padula et al., 2018[12]	
• The objective of the study was well-defined • The interventions to be studies were described • The inclusion criteria were provided. • The authors declared that there was no source of financial or other support, which may pose a competing interest	• As a non-randomized study, it lacked the risk-diminishing property of randomization and was inherently likely to have more systemic biases • The main outcomes measures were not adequately described. • It is unknown how patients were enrolled to participate in the study. • Patients were evaluated using a questionnaire developed by the authors, which had not been validated, and without details about the items they measured.

Strengths	Limitations
	• Sample size calculations were not performed. • The $AFCO_2L$ procedure was performed after lipofilling (fat graft) in all patients. Therefore, it is unknown whether results were due to the $AFCO_2L$ therapy.
El-Hoshy et. Al, 2017[3]	
• The study objectives, the intervention, and the main outcomes measures were defined • The inclusion and exclusion criteria were provided. • The outcomes were evaluated with validated tools • Statistical approach to analyzing results were appropriate • The authors declared they received no funding for the study and had no financial conflicts relevant to the content of the article	• As a non-randomized study, it lacked the risk-diminishing property of randomization and are inherently likely to have more systemic biases. • Sample size calculations were not performed.. • The ITT population was not used in analysis. Only patients who completed the entire treatment and follow-up protocol were included in the final analysis (17/20 patients). One patient dropped out after the second treatment session due to personal issues, and two patients were not able to attend the final follow-up session. • The follow-up period (two months) was relatively short.
Issler-Fisher et al., 2017[13]	
• The study objectives, the intervention, and the main outcomes measures were defined • The inclusion and exclusion criteria were provided. • The outcomes were evaluated with validated tools • Statistical approach to analyzing results was appropriate • The authors declared they received no funding for the study and had no financial conflicts relevant to the content of the article	• As a non-randomized study, it lacked the risk-diminishing property of randomization and are inherently likely to have more systemic biases • The study did not include a control group. Therefore, the comparative effectiveness of $AFCO_2L$ therapy to other interventions is unknown • The data presented in the article were for results after one single treatment session. Given that $AFCO_2L$ procedure often involves multiple sessions, the reported findings may not reflect real-life clinical practice. • Most scars were also treated with laser facilitated steroid infiltration immediately following the $AFCO_2L$ procedure; it is not possible to determine whether the results were a consequence of the corticosteroids or the $AFCO_2L$ treatment. • Sample size calculations were not performed. • The analysis was not based on the ITT population but instead included patients who had completed at least $AFCO_2L$ treatment with at least one follow-up assessment. • The one follow-up period was relatively short (a median of 55 days (IQR: 32 to 74 days) after treatment
Poetschke et al., 2017[4]	
• The same clinician performed all laser treatments, thus limiting variability that could affect outcomes. • The study objective, the intervention, and the main outcomes measures were defined • The results were evaluated with validated tools • Statistical approach to analyzing results was appropriate • The authors declared that there was no source of financial or other support, or any professional relationships, which may pose a competing interest	• As a non-randomized study, it lacked the risk-diminishing property of randomization and are inherently likely to have more systemic biases, • Sample size calculations were not performed. • It was unclear how the reported outcomes impacted function or patients comfort

$AFCO_2L$ = Ablative fractional carbon dioxide laser.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Review

Main Study Findings	Authors' Conclusion
Zuccaro et al., 2017[5]	
Duration of follow-up after laser treatment in the primary studies of the systematic review ranged from four weeks to three years • Eight studies in the systematic review assessed the effectiveness of $AFCO_2L$ therapy for hypertrophic burn scars. • In all studies, statistically significant improvements in both the patient and the observer sections of the POSAS were reported after $AFCO_2L$ treatment. • All the studies reported significant improvements in the mean total VSS score and/or VSS component scores (pliability, height, vascularity, pigmentation), except one study that found no significant change in one component (scar vascularity). The reported *P*- values of the individual studies were between $P = 0.0002$ and $P < 0.05$. • One primary study of the systematic review stated that patients were classified within the "norm" for various health domains in Short Form-36. However further information or analysis was not provided.	"Given that most of the studies included in this review were of low quality and had a high or unclear risk of bias, the authors were unable to draw definitive conclusions regarding the effectiveness of laser therapy for hypertrophic burn scars."[5] p. 12

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Douglas et al., 2019[11]	
• Patients reported a significant improvement in scar pain ($P = 0.047$) and itch ($P < 0.01$) on the POSAS scar score only in the treated areas when compared to pre-treatment control, six weeks after treatment. • Data from long-term (up to three years) follow-up assessment of nine (45%) patients showed that the total patient POSAS scores improved significantly from pre-treatment scores in both treatment and control segments ($P = 0.004$), although no long-term differences were seen between treated and control zones. • VSS assessments did not show any significant difference between treatment and control segments at six weeks or long-term (i.e., two to three years) after therapy compared to pre-treatment scores.	"Results demonstrate that 3 treatments of $AFCO_2L$ significantly improve scar pain, itch and dermal architecture at 6 weeks post-treatment. Histological results suggest greater potential in treating immature scar. Further investigation into the timing of laser treatment could help assist treatment protocols."[11] p. 2
La Padula[12] et al., 2018	
• All the patients reported improvement in their clinical condition at the one-year follow-up assessment • On a final score scale ranging from 0 (poor) to 50 (excellent), the mean score increased from 22.6	"Laser-therapy not only improves the physical aspects of hypertrophic burn scars, but may also eliminate the need for more reconstructive surgeries."[12] p. 4

Main Study Findings	Authors' Conclusion
preoperative to 34.6 one year after the procedure. The difference was statistically significant (*P*<0.00001). Adverse event • Moderate blistering and post-inflammatory hyperpigmentation were reported in 3 (12.5 %) and 2 (8.3%) of patients, respectively.	
El-Hoshy et. Al, 2017[3]	
At the final follow-up assessment conducted two months after the last session, results were as follows: • The mean (SD) total POSAS was reduced from 65.71 (11.23) before treatment to 38.35 (9.92), with a mean (SD) percentage POSAS improvement of 27.62% (7.75%) • The mean (SD) percentage improvement in POSAS patient overall assessment score 44.44% (12.42%) • The mean (SD) total VSS was reduced from 7.76 (2.07) before treatment to 5.18 (1.1), with a mean (SD) percentage VSS improvement of 19.90% (12.17%) Adverse events • Seven patients (29.2%) experienced pain following the laser session. The pain was described as mild in four patients (23.5%) and moderate in three patients (17.6%). The pain was generally tolerable, lasting 1 to 6 days (mean: 2.71 ± 1.70 days) • Three patients (17.6%) experienced transient swelling following sessions, lasting from 1 to 3 days (mean: 2 ± 1 days). • Three patients (17.6%) developed hyperpigmentation which improved with the application of topical bleaching creams. • Two patients (11.8%) developed hypopigmentation which remained at the two-month follow-up visit.	"In conclusion, fractional CO_2 laser can be an effective and safe modality in the treatment of post-burn scars. It achieves significant change in the opinion of the patients about their scar appearance."[3] p. 7
Issler-Fisher et al., 2017[13]	
At a median follow-up of 55 days (IQR: 32 to 74 days) after treatment: • The overall POSAS-O (maximal score 10) decreased from 5.0 (IQR: 4.0 to 6.3) to 4.0 (IQR: 3.0 to 4.3; *P* < 0.001) • The Patient Score of the POSAS (POSAS-P, maximal score 60) decreased significantly from a median of 36.0 (IQR: 27.0 to 42.0) at initial assessment to a median of 23.0 (IQR: 17.0 to 32.0; *P* < 0.001) with the overall POSAS-P score (maximal score 10) improving by four points from 9.0 (IQR: 8.0 to 10.0) to 5.0 (IQR: 4.0 to 8.0; *P* < 0.001) • The VSS dropped significantly from a median of 7.0 (IQR: 6.3 to 8.8) to 6.0 (IQR: 4.3 to 7.0; *P* < 0.001) • The Observer Scar Assessment Score of the POSAS decreased from a median of 29.0 (IQR: 24.0 to 33.0) to 21.0 (IQR: 18.0 to 25.0; *P* < 0.001) • Neuropathic pain as assessed by the DN4 Pain Questionnaire (maximum 10 points) decreased from a median of 3.0 (IQR: 1.0 to 6.0) to 2.0 (IQR: 0.0 to 5.0; *P* <	"In summary, this study strongly supports previous reports that burn scars can be dramatically improved in various domains by using the CO2-AFL for scar management including texture, colour, function and wide variety of symptoms. However, to our knowledge, this is the first report that shows that CO2-AFL treatment induces strong improvements in patient quality of life. Whilst CO2-AFL does not replace reconstructive surgery; it may well decrease the extent of subsequent surgical procedures, and prepares the scar for an optimal outcome. Furthermore, treatment with the CO2-AFL provides a novel treatment modality for a holistic scar improvement, which until now has not been available. Finally, the entire rehabilitative process may be enhanced and accelerated by this treatment, which may, in turn, lead to a faster re-integration in workplace and social life of burn victims and thus presents a milestone in burn patient management."[13] p. 9

Main Study Findings	Authors' Conclusion
0.001) • Itching (pruritus) as measured by the modified 4-D* Pruritus Score (maximal score 35) was reduced by 2.5 points from 16.0 (IQR: 9.8 to 20.0) to 13.5 (IQR: 7.0 to 18.0; *P* < 0.001) • The overall QoL score for study population, as measured by the BSHS-B instrument, increased by 16 points from a median of 120 (IQR: 110 to 139) at baseline to a median of 136 (IQR: 104 to 149; *P* < 0.001).	
Poetschke et al., 2017[4]	
Six months after treatment: • The POSAS Observer Scale dropped from an initial mean (SD) overall score of 23.60 (10.09) to 13.30 (2.87; *P* = 0.0144) • The overall mean (SD) POSAS Patient Scale score was reduced from 35.20 (15.29) before treatment to 26.00 (14.68; *P* = 0.0406), representing a decline of 26.2%. • The overall mean (SD) VSS score decreased from 6.800 (1.317) at baseline to 2.200 (1.549; *P* < 0.0001) • The mean (SD) DLQI score decreased from a baseline value of 8.900 (5.990) to 4.700 (3.335), a 47.2% reduction representing a decreased negative influence of the scars on the patients' quality of life (*P* = 0.0030) • The negative impact of the scars on the patients' quality of life decreased significantly as indicated by a 47.2% reduction (p = 0.0030) in the DLQI score from a mean (SD) baseline value of 8.900 (5.990) to 4.700 (3.335) six months after treatment Adverse events • None of the patients experienced severe side effects after receiving laser treatment. Adverse events incident data were not provided.	"Fractional ablative carbon dioxide laser treatment is a safe, swift, and highly effective option for the improvement of widespread hypertrophic burn scars."[4] p. 9

$AFCO_2L$ = Ablative fractional carbon dioxide laser; BSHS-B = Burns Specific Health Scale; CO_2 = carbon dioxide; CO2-AFL = ablative fractional CO2 lasers; DLQI = dermatology life quality index; DN4 = Douleur Neuropathique 4 Questions; IQR = interquartile range; POSAS = patient and observer scar assessment scale; SD = standard deviation; SF-36 = Short Form-36; VSS = Vancouver scar scale.

* 4-D pruritus score is a modification of the 5-D purities scale, the components of which are duration, degree, direction, disability, and distribution. In the modified 4-D version used in the study by Issler-Fisher,[13] the "distribution" component was dropped as the location of pruritus was given by the site of the scar.[13]

Appendix 5: Additional References of Potential Interest

Primary Studies Included in the Selected Systematic Review

Blome-Eberwein S, Gogal C, Weiss MJ, Boorse D, Pagella P. Prospective Evaluation of Fractional CO2 Laser Treatment of Mature Burn Scars. *J Burn Care Res*. 2016 Nov/Dec;37(6):379-387.
PubMed: PM27828835

El-Zawahry BM, Sobhi RM, Bassiouny DA, Tabak SA. Ablative CO2 fractional resurfacing in treatment of thermal burn scars: an open-label controlled clinical and histopathological study. *J Cosmet Dermatol*. 2015 Dec;14(4):324-331.
PubMed: PM26260018

Levi B, Ibrahim A, Mathews K, et al. The Use of CO2 Fractional Photothermolysis for the Treatment of Burn Scars. *J Burn Care Res*. 2016 Mar-Apr;37(2):106-114.
PubMed: PM26536539

Zadkowski T, Nachulewicz P, Mazgaj M, et al. A new CO2 laser technique for the treatment of pediatric hypertrophic burn scars: An observational study. *Medicine*. 2016 Oct;95(42):e5168.
PubMed: PM27759650

Hultman CS, Friedstat JS, Edkins RE, Cairns BA, Meyer AA. Laser resurfacing and remodeling of hypertrophic burn scars: the results of a large, prospective, before-after cohort study, with long-term follow-up. *Ann Surg*. 2014 Sep;260(3):519-529; discussion 529-532.
PubMed: PM25115428