

Carboxytherapy on the treatment of managing cellulite and striae distensae: A systematic review

Carboxiterapia no tratamento de celulite e estrias: Uma revisão sistemática

Carboxiterapia en el tratamiento de la celulitis y las estrías: Una revisión sistemática

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Abstract

The use of carboxytherapy has shown excellent results in the treatment of various aesthetic conditions. The aim of this study was to investigate the effects of carboxytherapy on cellulite and striae distensae (SD). Therefore, a systematic literature review was accomplished on two databases, Medline via PubMed and Scopus, from July to August 2021. Studies that evaluated the effect of carboxytherapy on SD and cellulite were included, eight articles of all of them and that treated 299 people were included in this systematic review and the most studies classified as having low level of methodological quality. There was no consensus regarding the parameters used, but in most studies and applications were performed at a depth of 10 mm with a flow ranging from 50 to 150 mL / min. The results this intervention produced an improvement in skin aspects, with better texture, decreased severity of cellulite and SD, improved patient satisfaction, increased skin thickness, decreased edema and increased inflammatory infiltrate the number of collagen fibers. Some side effects were observed, such as transient erythema and post-inflammatory hyperpigmentation, leading to discomfort. However, all these adverse effects are transient, and patients can return to normal activities with the use of photoprotection. This review demonstrates the stimulatory effect of carboxytherapy on the symptomatology of patients with cellulite and SD.

Keywords: Striae distensae; Cellulites; Carbon dioxide; Esthetics; Systematic review.

Resumo

A utilização da carboxiterapia tem apresentado excelentes resultados no tratamento de diversas condições estéticas. O objetivo deste estudo foi investigar os efeitos da carboxiterapia na celulite e estrias. Para isso, foi realizada uma revisão sistemática da literatura em duas bases de dados, Medline via PubMed e Scopus, no período de julho a agosto de 2021. Foram incluídos estudos que avaliaram o efeito da carboxiterapia nas estrias e celulite. Foram incluídos nessa revisão oito artigos que trataram 299 pacientes, sendo a maioria dos estudos classificados como de baixo nível de qualidade metodológica. Não houve consenso quanto aos parâmetros utilizados, mas na maioria dos estudos e aplicações foram

realizadas em profundidade de 10 mm com fluxo variando de 50 a 150 mL/min. Os resultados desta intervenção produziram uma melhora nos aspectos da pele, com melhor textura, diminuição da severidade da celulite e estrias, melhora da satisfação do paciente, aumento da espessura da pele, diminuição do edema e aumento do infiltrado inflamatório e aumento do número de fibras colágenas. Alguns efeitos colaterais foram observados, como eritema transitório e hiperpigmentação pós-inflamatória, levando ao desconforto. No entanto, todos esses efeitos adversos são transitórios e os pacientes podem retornar às atividades normais com o uso de fotoproteção. Esta revisão demonstra o efeito estimulador da carboxiterapia na sintomatologia de pacientes com celulite e estrias.

Palavras-chave: Estrias; Celulites; Dióxido de carbono; Estética; Revisão sistemática.

Resumen

El uso de la carboxiterapia ha mostrado excelentes resultados en el tratamiento de diversas afecciones estéticas. El objetivo de este estudio fue investigar los efectos de la carboxiterapia sobre la celulitis y las estrías. Para ello, se realizó una revisión sistemática de la literatura en dos bases de datos, Medline vía PubMed y Scopus, de julio a agosto de 2021. Se incluyeron estudios que evaluaron el efecto de la carboxiterapia sobre las estrías y la celulitis. En esta revisión se incluyeron ocho artículos que trataron a 299 pacientes, y la mayoría de los estudios se clasificaron como de bajo nivel de calidad metodológica. No hubo consenso en cuanto a los parámetros utilizados, pero en la mayoría de los estudios y aplicaciones se realizaron a una profundidad de 10 mm con un flujo que oscilaba entre 50 y 150 ml/min. Los resultados de esta intervención produjeron una mejora en el aspecto de la piel, con mejor textura, disminución de la severidad de la celulitis y estrías, mejora en la satisfacción del paciente, aumento del grosor de la piel, disminución del edema y aumento de la el infiltrado inflamatorio, y un aumento en el número de fibras colágenas. Se han observado algunos efectos secundarios, como eritema transitorio e hiperpigmentación posinflamatoria, que provocan molestias. Sin embargo, todos estos efectos adversos son transitorios y los pacientes pueden volver a sus actividades normales con el uso de fotoprotección. Esta revisión demuestra el efecto estimulante de la carboxiterapia sobre los síntomas de los pacientes con celulitis y estrías.

Palabras clave: Estrías distensas; Celulitis; Dióxido de carbono; Estética; Revisión sistemática.

1. Introduction

Carbon dioxide (CO₂) therapy or most commonly carboxytherapy has been used since 1932 and it refers to the administration of CO₂ with therapeutic proposals (El-Domyati et al. 2021). The mechanism of action of carboxytherapy is not well understood yet. However, it is believed that injection of carbon dioxide induces changes in the microcirculation, including vasodilatation and consequently the enhancement of local blood supply, stimulation of neoangiogenesis and increase of local metabolism (Matsumoto et al. 2018). Once in contact with tissues, CO₂ reacts with water molecules, and molecular carbonic acid is formed and, as consequence a decrease of pH is observed. As a consequence, a lower pH produces an increase of oxygen release from haemoglobin, a reduction of divalent calcium ions and the split of carbonic acid to H⁺ a HCO³⁻, resulting in calcium hydrogen carbonate, sodium hydrogen carbonate and potassium hydrogen carbonate formation (Matsumoto et al. 2018; Patel et al. 2021).

Based on these molecular and physiological modifications, carboxytherapy has become one of the most effective therapeutical interventions for dermatological and aesthetic proposals (Kroumpouzou et al., 2021). There are plenty of evidences demonstrating the positive results of carboxytherapy on the treatment of arteriopathies and ulcers, hypertrophic and keloid scars, alopecia, post liposuction conditions, wrinkles and for decreasing body fat (Lokhande, & Mysore, 2019; Jamshidian-Tehrani et al., 2020). For example, El-Domyati *et al* (2020) (demonstrated that carboxytherapy was able of producing facial rejuvenation and improving some aspects of wrinkles. Also, Ferreira, Haddad e Tavares (2008) described the increase of of the index of collagen remodeling induced by intradermal injections of CO₂.

In addition, carboxytherapy has been widely used to treat cellulite and striae distensae (SD) or stretch marks. Cellulite is caused by excessive stretching of the skin, with a dermal damage and it is characterized by a visible linear scar (Pianez et al. 2016). The appearance of cellulite is multifactorial and it is related to an altered dermal connective tissue framework, involving the components of extracellular matrix (ECM) especially fibrillin, elastin, fibronectin and collagen (Mitts et al., 2005). Its appearance is relate d to a genetic predisposition, mechanical stress, hormones especially corticosteroids (both topical and systemic) and lifestyle (Lokhande & Mysore, 2019). Moreover, SD is characterized by skin atrophy with elongated form,

sometimes wavy, elevated, flat or depressed, but always soft and depressive. The color of SD can be pale or bluish when recent, and pearly white towards the end. When touched, they seem soft with a relative emptiness as if the skin was over a mobile and fleeting plan (Lokhande & Mysore 2019; Podgórna et al., 2018).

Many treatments for cellulite and SD have been reported including creams and electrophysical agents such as higher power lasers and radiofrequency therapy (Lokhande & Mysore, 2019). In addition, the positive effects of carboxytherapy as an effective therapeutical approach for these affections have also been highlighted (Rawlings, 2006). The mechanisms of action of carboxytherapy on the treatment of cellulite and SD is based on the stimulation of blood circulation and increase of oxygen release from oxyhaemoglobin by the presence of CO₂, activating the synthesis of collagenase, elastin and hyaluronic acid by stimulation of fibroblast function, which seems to improve the aspect of cellulite and SD (Rawlings, 2006).

Although all the positive results of carboxytherapy for the treatment of cellulite and SD, its use is still controversial. However, to the best of the authors' knowledge, no systematic review has evaluated the effects of carboxytherapy on the aspects and symptomatology of related to cellulite and SD. In this context, the aim of this study is to systematically review the literature investigating the effects of carboxytherapy on cellulite and in SD.

2. Methodology

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Liberati, et al. 2009) orientations. Medline via PubMed and Scopus were searched, the following search strategy was developed at PubMed database and was modify according to each database requirement: (("carbon dioxide") OR ("carboxytherapy")) OR ("carbon dioxide therapy")) AND (("cellulite") OR ("striae distensae")).

The search was performed from June to August of 2021. Articles were selected based on the titles, abstracts and full papers meeting the eligibility criteria. This systematic review was registered on the online international prospective register of systematic reviews (PROSPERO) of the National Institute for Health Research (under the number CRD42021275984). Furthermore, articles included in this review had their methodological quality assessed by the PEDro scale Physiotherapy Evidence Database.

Study type

Articles that used carboxytherapy as a main intervention to treat cellulite and SD were selected. It is important to emphasize that it was not possible to perform a meta-analysis due to the heterogeneity of the primary studies.

Inclusion criteria

The following inclusion criteria were considered:

- Articles written in English.
- Only studies reporting the treatment of cellulite or SD with carboxytherapy were considered.
- Control group could be a group without any treatment or a group with the use of a different treatment modality.
- The outcomes of the articles included had to evaluate photographic register and any skin assessment and report of interventions.

Exclusion criteria

- Studies were excluded if they included only *in vitro* and *in vivo* studies.
- Systematic reviews, meta-analysis and case reports.

- Follow-ups and conference abstracts.

Outcomes Assessment

Data were extracted from included studies by 2 reviewers using standardized forms. The study database included basic characteristics of qualified studies (first author, published date, country), characteristics of the subjects (age, gender), interventions, characteristics of the parameters of carboxytherapy application and the use of other therapeutical interventions. The outcome measures comprised digital photography and self-reported assessment.

Study selection

Two reviewers (CCSM and ACMR) independently analyzed title, abstracts and full paper versions of the studies and selected the potential studies according to the inclusion and exclusion criteria. After each step (title, abstract, full paper analyses), reviewers joined in a consensus meeting to check the agreement of including all the selected papers. Two reviewers (PGV and JRP) evaluated methodological quality of the papers with the PEDro. The PEDro scale assesses the methodological quality of the articles, using a ranging from 0 to 10 (0 being the lowest and 10 the highest methodological quality).

3. Results

The flow diagram demonstrates the search strategy used in the present study (Figure 1). Forty nine articles were retrieved from the database Scopus, 32 from PubMed, 49 from Web of Science, 24 from Cochrane and 7 from Google Scholar (in a total of 161). Then, the duplicated records were excluded ($n = 53$). Twenty-eight full-text articles were assessed for eligibility and 16 studies were excluded. Additionally, 8 studies were excluded for other reasons and finally, 9 studies were included and analyzed in this systematic review (El-Domyat, 2021; Pianze, 2016; Podgóma, et al. 2018; Sultan, 2018; Elmorsy, et al. 2021, Ahmed, & Mostafa, 2019; Eldsouky, & Ebrahim, 2018; Hodeib et al., 2018).

The general characteristics of patients, experimental groups and analyses from the included articles in the present review are summarized in Table 1. Six studies are from Egypt (El-Domyat, 2021; Elmorsy et al., 2021, Ahmed, 2019; Eldsouky, & Ebrahim, 2018; Hodeib, et al. 2018; Farouk et al., 2022), 1 from Brazil (Pianez, 2016), 1 from Poland (Podgóma, et al. 2018) and 1 from Singapore (Lee, 2010). Participants, with Fitzpatrick skin types I to IV, were included in the studies, aging from 13 to 50 years. Studies recruited only female volunteers. The number of sessions ranged from 3 (Podgóma, et al. 2018; Ahmed, & Mostafa, 2019; Eldsouky, & Ebrahim, 2018) to 8 sessions (El-Domyati, et al. 2021, El-Din et al., 2021 Pianez, 2016). All studies used carboxytherapy as intervention group. No study presented a negative control group and 3 used other types of treatments as the comparative group such as radiofrequency, PRPs application and mesolipolysis (Ahmed, & Mostafa, 2019; Eldsouky, & Ebrahim, 2018; Hodeib, et al. 2018).

Considering the methods used to evaluate the effects of carboxytherapy, clinical examination was used for 4 works (El-Domyat, 2021; Elmorsy, 2021 Eldsouky, & Ebrahim, 2018; Farouk, et al. 2022). Clinical assessment was based on a five-point scale (none = 0%, mild = 1 - 25%, moderate = 26 - 50%, good = 51 - 75% and very good = 76 - 100%) and evaluation of size, stage (color), depression or elevation, and skin texture (Elmorsy, et al. 2021; Ahmed, 2020) evaluated the improvement in width and texture. Patients were evaluated for their degree of improvement (by measuring the width of the largest striae before and after treatment) as follows: mild, moderate and excellent improvements.

Also, digital photographs were used for 7 studies, using the following score: -1 = worse, 0 = no change, 1 = weak (1–24% improvement in striae), 2 = moderate (25–49% improvement in striae), 3 = good (50–74% improvement in striae) 4 = excellent (75–100% improvement in striae). Pianez, (2016) evaluated cellulite grades by digital photographs with a digital

camera following the score: 0= no alteration; I= skin affected area is smooth while the subject is standing or lying, but the alterations to the skin surface can be seen by pinching the skin or with muscle contraction (visible changes with skin clamping or muscle contraction); II= the orange peel aspect of the skin or mattress appearance is evident when standing, and III= the alterations described in grade or stage II, are present together with raised areas and nodules (visible changes associated with nodules). Podgorna et al., (2018) used 3 photos in a standing position and 3 independent evaluators compared clinical changes. Farouk et al., (2022) compared photographs before and after treatment using the Global Aesthetic Improvement Scale (GAIS) - 5 means very much improved (optimal cosmetic result), 4 means much improved (marked improvement in appearance from initial condition but not completely optimal for this patient, a touch-up would slightly improve the result), 3 means improved (obvious improvement in appearance from the initial condition but touch-up or retreatment is indicated), 2 means no changes (appearance essentially the same as the original condition) and 1 means worse (appearance is worse than the original condition).

Also, scales were used by 3 authors (Elmorsy, et al. 2021; Elmorsy,2021 Eldsouky, & Ebrahim, 2018; Farouk, et al. 2022). Eldsouky et al., (2018) classified the degree of cellulite using a grade varying from 0 to 3. Also, the number of SD (0 = no striae signs, 1 = 1–4 striae, 2 = 5–10 striae, 3 = more than 10 striae) was used as a method of evaluation. The color of the SD was also applied following the scale 0 = no redness, 1 = ink, 2 = dark red and 3 = purple.

Another method used by 2 authors was the perception of patients after the treatment (self-reported analysis) (Elmorsy, et al. 2021; Ahmed, 2019). In these studies, each participant was asked to rate the overall satisfaction with the treatment 1 month after the last session using the criteria: “unsatisfied,” “slightly satisfied,” “satisfied,” or “very satisfied but only satisfied” or “very satisfied. In another study (Farouk, et al. 2022) the perception of patients after the treatment was evaluated by Likert Satisfaction Scale (1=very unsatisfied, 2=unsatisfied, 3=neither satisfied nor unsatisfied, 4=satisfied, 5=very satisfied).

Histological evaluation and histomorphometry were used by El-Domyati et. al (2021), Ahmed and Mostafa (2019) and Hodeib et al. (2018). Ahmed and Mostafa (2019) performed a 3-millimeter punch biopsy from the treated region and manufactured laminae (which were stained with hematoxylin- HE- and eosin, Verhoeff-Van Gieson and orcein). The slides were histologically evaluated considering histopathological changes and efficacy of treatment. El-Domyati et al (2021) used histological laminae stained with HE and performed a histometric analysis, measuring the epidermal thickness. Furthermore, Hodeib et al (2018) used histological laminae for measuring the area of SD.

El-Domyati et. al. (2021), also used 3D skin analysis of the topography which evaluates texture, scars, skin color and redness as well as pigmentation in a seamless manner. Pianez et al (2016) used ultrasound examination.

Also, circumference measurements were performed by Eldsouky e Ebrahim (2018) and Lee, (2010) recorded the thigh circumference measurements of both thighs before and after the treatment. Lee, (2010) measured the weight, abdominal and thigh circumference at baseline and after each treatment session. Elmorsy et al (2021) measured the width and length of the SDs. Moreover, Podgorna et al. (2018) used Cutometer and Lee, (2010) used ultrasound analysis.

Table 1 – General characteristics of patients, experimental groups and analyses.

Authors	Country	N. of participants/ Gender	Age	Characteristics	Control or other treatment group	Analyses
Farouk, Mahmoud & Hafiz, (2022)	Egypt	30/ Female	19-45y	Skin phototypes III and IV	No control group	Digital photography Global Aesthetic Improvement Scale (GAIS) Patient's satisfaction
Elmorsy et al (2021)	Egypt	40/ Female	20-35y	*	Fractional carbon dioxide (CO2) laser	Clinical examination Digital photography of SD; Measurement of SD width and length; Atwal scoring system
El-Domyati et. al. 2021	Egypt	20 / Female	18- 39y	Fitzpatrick skin types III to IV	No control group	Clinical evaluation 3D skin analysis Hystological evaluation and histomorphometry
Eldsouky and Ebrahim (2018)	Egypt	48 / Female	38.19±9.63	*	Group A: carboxytherapy Group B: mesolypolisis	Cellulite grading scale Thigh circumference measurements of both thighs
Ahmed & Mostafa (2019)	Egypt	45 / Female	20-41 y	*	Group A: carboxytherapy Group B: Intradermal injection of PRP. Group C: Tripolar radiofrequency device	Evaluation of photographs Patient's satisfaction Histopathological assessment
Hodeib et al (2018)	Egypt	20/ Female	17-40 y	*	Group A: PRP injection Group B: carboxytherapy	Digital photography Histological assessment
Podgorna et al (2017)	Poland	15/ Female	22-40 y	*	No control group	Cutometer Digital photography
Pianez et al (2016)	Brasil	10 / Female	13-35 y	Fitzpatrick skin types III to IV	No control group	Cellulite grades by inspection Digital photography Ultrasound
Lee (2010)	Singapore	101/female	20-50 y	Fitzpatrick skin types III to IV	No control group	Weight, abdominal, and thigh circumference measurements Ultrasound measurement of subcutaneous fat thickness

y: years; * Data not available in the study. Source: Authors.

Table 2 shows the parameters of carboxytherapy treatment. Related to the way of application, all the authors injected CO₂ intradermally and most of them in the angle of 45°. The depth of application ranged from 2 mm to 13 mm (Lee, 2010). CO₂ flow varied from 50 ml/min to 300 ml/min (Elmorsy, et al. 2021; Eldsouky, & Ebrahim, 2018;). Number of sessions were from 3 to 8 (Podgórna, et al. 2018; Pianze, 2016), in a treatment duration of 3 weeks to 6 months (Farouk, et al. 2022; Podgórna, et al. 2018). Some authors compared the effect of carboxytherapy with other treatments such as CO₂ Laser, mesotherapy, tripolar radiofrequency device. Furthermore, carboxytherapy was more commonly applied at the regions of SD and cellulite.

Table 2 - Protocols and parameters of Carboxytherapy used by the studies.

Authors	Way of application	Depth of application	CO ₂ flow	Number of sessions	Associated or other treatment	Area of application	Duration of treatment
Farouk, Mahmoud & Hafiz, (2022)	Intradermal injection directly into the striae with an angle of 15	2-mm depth	0.1–0.3 mL	6 sessions with 4-week intervals	*	Abdomen, arms, thighs, breasts, and buttocks	6 months
Elmorsy et al (2021)	Injected intradermally directly into the stretch mark with a 45° needle	*	50 to 80 mL/min	6 sessions	CO ₂ Laser	Injections were about 3–5 cm apart according to the filling of the striae	12 weeks
El-Domyati* et. al. (2021)	Injected intradermally using carboxy-gun, connected to CO ₂ cylinder	3 mm depth	*	8 sessions every 2 weeks	*	Areas with cellulite lesions	4 months
Eldsouky and Ebrahim	30 gauge/0.3 × 13 microlance needle (45°)	10–13 mm	50 to 300 ml/min	One time per week for six consecutive weeks	Mesotherapy	Thighs, below a planetangent to the apex of Scarpa’s triangle (femoral triangle) for both the right and left thighs	6 weeks
Ahmed & Mostafa (2019)	Injected superficially and intradermally	*	50 mL/min to deliver 3 mL of CO ₂ (5 to 9 mins per session)	5 sessions every 1 week	Intradermal injection of PRP and Tripolar radiofrequency device	Areas with cellulite lesions	*
Podgorna et al (2017)	Injected intradermally	1 mm	20–40 mL	3 sessions	*	Areas with striae distensae	3 weeks
Hodeib et al (2018)	Injected superficially and intradermally	*	100 mL with flow rate 80-150 cc/min.	4 sessions each every 3-4 weeks	Platelet-rich plasma (PRP)	Areas with cellulite lesions	4 months
Pianez et al (2016)	Injected intradermally using carboxy-gun, connected to CO ₂ cylinder	10 mm	80 mL of gas with a flow rate of 80 mL/min	8 sessions every 7 days weeks	*	4 in the gluteal area and six in the posterior thigh	2,5 months
Lee (2010)	30 gauge,/0.3x 13-microlance needles	10 to 13 mm.	50 to 100 ml/min	5 sessions at 1- to 2-week intervals	*	abdomen and thigh	2 months

cc= cubic centimeter. Source: Authors.

In table 3, it is possible to observe the results of all analysis and the outcomes presented in the papers in this systematic review. All the studies demonstrated that carboxytherapy was effective in attenuating the signals of cellulite and SD 8. In 4 studies, digital photographs showed that carboxytherapy presents improvement in skin texture, decrease in the grade of cellulite morphological improvement with respect to the subcutaneous tissue, fibrotic septa and aspects of the dermis-related cellulite. Also, ultrasound analysis demonstrated an improvement of the subepidermal thickness (Lee, 2010). Self-reported results showed that 60% of the patients showed excellent improvement, 20% showed good improvement and 20% showed moderate improvement (Elmorsy, 2021). Also, it was demonstrated that 93.3% of patients treated with carboxytherapy was satisfied with the treatment (Ahmed & Mostafa, 2019). Thus, a study demonstrated that 20 patients (66.7%) were satisfied, 4 patients (13.3%) were neither satisfied nor unsatisfied, 3 patients (10%) were very satisfied and 3 patients (10%) were unsatisfied with carboxytherapy (Farouk, 2022). Four studies used histological and histomorphometry analysis and observed that the mean width and the mean length were significantly lowered after the treatment. Furthermore, morphological and architectural improvement of the epidermis, increase in the mean epidermal thickness and formation of collagen and elastin in the dermis (Eldomyat, 2021). Furthermore, a decrease in oedema and inflammatory infiltrate and an increase in the number of collagen fibers in the treated groups with carboxytherapy was also observed (Ahmed & Mostafa, 2019). Also, circumference measurement determined reduced values of thighs and statistically significant improvement in skin elasticity in 15 women with SD triae distensae (Ahmed, 2019). In all patients, the analysis of the results demonstrated a significant difference between the pretreatment and post-treatment values (Ahmed, 2019).

Table 3 - Results after the intervention, outcomes and adverse effects.

Author	Digital photographs results	Self-reported results/circumference	Histological and histomorphometry	Circumferences/skin elasticity	Outcomes
Farouk, Mahmoud& Hafiz, (2022)	18 patients showed improvement (60%) 10 patients (33.3%) showed much improvement 2 patients (6.7%) showed no changes No patients showed worsening or very much improvement	20 patients (66.7%) were satisfied 4 patients (13.3%) were neither satisfied nor unsatisfied 3 patients (10%) were very satisfied 3 patients (10%) were unsatisfied, No patient was very unsatisfied	*	*	Carboxytherapy is an effective and safe therapeutic option with no significant side effects
Elmorsy et al (2021)	12 patients (60%) showed excellent improvement. 4 patients (20%) good, and the same number were moderately improved	60% of the patients showed excellent improvement, 20% showed good improvement and 20% showed moderate improvement	Mean width was significantly lowered from (5.90 ± 1.85) mm before treatment to (4.20 ± 1.55) mm mean length was lowered from (7.3 ± 1.1) mm before treatment to (5.25 ± 0.94) mm after treatment.	*	Carboxytherapy is an effective and safe therapeutic toolfor SD
El-Domyati et. al. (2021)	Improvement in skin indentation index (Large, medium and small) and skin texture	*	Morphological and architectural improvement of the epidermis; increase in the mean epidermal thickness; formation of collagen and elastin in the Dermis	*	Marked improvement in management of SD, with minimal downtime.
Eldsouky and Ebrahim (2018)	Statistically significant differences between cellulite grade after treatment with marked reduction in the number of grade III patients after treatment	*	*	Reduced values of thighs	Carbon dioxide therapy is presenting a new hope for treatment of cellulite owing to the absence of toxicity, no major side effects,
Ahmed & Mostafa (2019)	*	Results of satisfied patients were 93.3% for carboxytherapy and radiofrequency;	Compared to untreated tissues, there was an increase in the thickness of the epidermis with formation of rete ridges. The dermis showed decrease in the. Decrease in edema and inflammatory infiltrate. Increase in the number of dermal; collagen fibers.	*	Effective clinically and histopathologically in treating striae with minimal, transient side effects
Podgornna et al (2017)	*	*		Statistically significant improvement in skin elasticity in 15 women with SD triae distensae. In all patients, the of the ability of the skin to return to normal state demonstrated a significant difference between the pretreatment and post treatment values	*
Hodeib et al (2018)	The response of treatment (grading scale) was mild in 4 patients (20%), moderate in 10 patients (50%), marked	*	Improvement and fibronectin-stained area after treatment	*	Carboxytherapy is an effective, safe, and novel method for the treatment of striae

	in 5 patients (25%), and excellent in only 1 patient (5%).									
Pianez et al (2016)	Statistically significant reduction in the aspect of cellulite; morphological improvement with respect to the subcutaneous tissue, fibrotic septa, and aspects of the dermis-related cellulite.	*	*	*						Improve of the severity of cellulite at the buttocks and posterior thighs of healthy women.
Lee (2010)	Ultrasound evidence of decreased subepidermal thickness	*	*				Significant reduction in upper, mid, and lower abdomen circumference occurred			Confirming that carboxytherapy is safe and effective

Source: Authors.

Table 4 - Methodological quality evaluation of studies with technical specifications by Pedro scale.

Study	Random allocation	Concealed allocation	Comparable at baseline	Blinding subjects	Blinding therapists	Blinding assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimate and variability	PEDro Score ^a
Farouk, Mahmoud & Hafiz, (2022)	0	0	1	0	0	1	0	0	0	1	3
Elmorsy et al (2021)	1	1	1	0	0	1	1	0	1	0	6
El-Domyati et. al (2021)	0	0	1	0	0	0	1	0	0	0	2
Elsouky and Ebrahim (2018)	1	0	1	0	0	1	1	0	1	0	5
Ahmed & Mostafa (2019)	1	0	1	0	0	1	1	0	1	0	5
Hodeib et al (2018)	1	0	1	0	0	0	1	0	1	0	4
Podgorna et al (2017)	0	0	1	0	0	0	1	0	0	0	2
Pianez et al (2016)	0	0	1	0	0	1	1	0	0	0	3
Lee (2010)	0	0	0	0	0	1	1	0	0	0	2

^a The PEDro scale scores range from 1 to 10. Source: Authors.

4. Discussion

This systematic review investigated the literature about the effects of carboxytherapy on the treatment of cellulite and SD. The results showed that this therapeutical intervention produced an improvement of the aspects of the skin, decrease of the grade measuring the severity of the cellulite and SD, improvement of the satisfaction of the treated patients, increase in the thickness of the epidermis, decreased edema and inflammatory infiltrate and increase in the number of collagen fibers. Also, reduced values of the circumference of different parts of the body were observed such as thighs. Moreover, the authors evaluated female volunteers, aging from 13 to 50 years, with different number of sessions and using different parameters.

Authors used different ways to evaluate the effects of carboxytherapy, but mainly digital photos and scales to compare the data before and after treatment and patient self-reported perception.

Cellulite and SD are common complaints in the area of aesthetic medicine and dermatology and it is related to multiple factors (Oakley & Patel, 2021). In this context, carboxytherapy has been highlighted as one of the most effective noninvasive therapy for these affections, aiming of stimulating blood flow, improving the skin's elasticity and reducing the appearance of cellulite and SD (Leibaschoff et al., 2018).

The site of application of carboxytherapy in the papers is concentrated in the area of occurrence of both skin affection (El-Domyat, 2021; Pianze, 2016; Podgórna, et al. 2018; Elmorsy, et al. 2021; Ahmed & Mostafa, 2019; Hodeib, et al. 2018; Lee, 2010). Also, many different ways of evaluation were used such as clinical evaluation, digital photos and scales. Cellulite and SD rating scales and photographs have been used for many authors in the literature, providing qualitative and quantitative data measurements (Young & Dibernardo, 2018). In spite of some limitations, scales are important tools for evaluating some clinical and histopathological aspects of cellulite and SD, including qualitative measure of severity (Rossi & Vergnanini, 2000; Emanuele, 2013). Although the importance of the use of scales in this field, many of them do not have a patient-reported component, which is highly recommended (Luebberding et al., 2015). It is important to highlight that some of the works in this review used the perception of patients after the treatment or self-reported analysis as a way of evaluating the effects of carboxytherapy (Ahmed & Mostafa, 2019; Elmorsy, et al. 2021; Farouk, et al. 2022). Furthermore, histological evaluation and histomorphometry were also used (El-Domyat, 2021; Ahmed, & Mostafa, 2019 & Hodeib, et al. 2018) describing important aspects of tissues after the treatments such as the presence of inflammatory process, collagen fibers and epidermal thickness. 3D skin analysis measuring the skin topography (El-Domyati, et al. 2021, El-Din et al., 2021 El-Din et al., 2021) and ultrasound, measuring dermis, fibrotic septa and adipose tissue used by some authors of this review are also important tools of evaluation, such as digital photos. However, Young and Dibernardo (2021) points out that there is still a need for developing more accurate techniques for assessing cellulite and SD severity.

Moreover, a wide range of carboxytherapy parameters were used by the different authors. It is evident that the use of proper parameters of carboxytherapy is essential to reach key structures to obtain the success of the treatment and inadequate parameters can cause tissue damage (Almeida, et al.2020) . However, for carboxytherapy, the ideal parameters of application in the clinical settings is not well established yet and many controversies still remain (Khat & Leibaschoff, 2018; Eldsouky & Ebrahim, 2018). Regarding, the infusion speed of the CO₂, authors administrated CO₂ in a velocity of 50 ml/min to 300 ml/min (Khat & Leibaschoff, 2021; Ahmed & Mostafa, 2021). For most of the treatments, superficial (intra-dermal) injections require smaller gas volumes, i.e., 0.5-3 ml per injection spot, at a velocity of 30-40 ml/min. Superficial subcutaneous injections require 1-5 ml and deeper subcutaneous 5-50 ml per injection spot. Angles of insertion vary from 15-30° for superficial layers, 45° for superficial subcutaneous tissue, and 90° for deeper tissue (Oliveira et al., 2020).

Regarding the period of treatment and the number of sessions, there is no consensus among the authors. Number of sessions varied from 3 to 8 (Podgórna, et al. 2018; El-Domyat, 2021; Pianze, 2016) with an interval of 1 to 4 weeks between the

sessions. The number of applications is dependent on the indication as well as the treated locality and in general it is necessary to repeat the application once or twice a week (Hodeib et al., 2018).

As it can be seen in table 3, carboxytherapy produced positive effects in managing and attenuating the signals of cellulite and SD, with improvement in skin texture (El-Domyati, et al. 2021, El-Din et al., 2021; Hosam El-Din et al., 2021), a decrease in the grade of cellulite (Pianze, 2016; Hodeib, et al. 2018) and improvement of the general aspect of cellulite and SD (Pianez,2016; Podgórna, et al. 2018; Elmorsy, et al. 2021; Ahmed & Mostafa, 2019; Elmorsy,2021 Eldsouky, & Ebrahim, 2018; Hodeib, et al. 2018; Farouk, et al. 2022; Lee, 2010; El-Domati, 2020). Also, histological analysis demonstrated that carboxytherapy improved the subcutaneous tissue, fibrotic septa and aspects of the dermis-related cellulite (Pianez, 2016) and the ultrasound demonstrated evidences of decreased subepidermal thickness (Lee, 2010). Other important findings are related to the self-reported results, demonstrating that most of the patients considered the improvement after carboxytherapy as “excellent”. Also, it was demonstrated that 93.3% of patients treated with carboxytherapy was satisfied with the treatment (Ahmed & Mostafa, 2019).

One of the main modifications produced by carboxytherapy is the improvement of microcirculation function, increasing blood flux and tissue oxygenation (Oliveira, 2020). Moreover, it activates fibroblasts and consequently, increase collagen and elastin formation and deposition (Maia-Figueiró, et al. 2012). For example, El-Domyati, et al (2021) demonstrated an increase in collagen remodeling after 4 month of treatment in patients with SD. All of these modifications could explain the positive effects of carboxytherapy on cellulite and SD. Moreover, some side effects were seen such as transient erythema and post inflammatory hyperpigmentation, leading to the discomfort. However, all these adverse effects are transients and patients could return to normal daily activity with the use of photoprotection.

Furthermore, it is important to highlight a limitation of the present study related to the methodological quality of the included studies. The works included in the present review were not double-blinded being the evaluators or clinician aware of the interventions and groups.

5. Conclusion

In conclusion, this review demonstrates the stimulatory effect of carboxytherapy on the symptomatology of patients with cellulite and SD. However, there is no consensus about the parameters used by the different authors, making it difficult to compare the results. Also, the methodological quality of the study could be considered low. Further studies are necessary, considering a higher scientific rigor, especially for the description of all parameters and a higher sample size, in order to clarify the effects of this promising therapeutical intervention in order to define better protocols for treating both skin affections.

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