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Review

CO_2 laser therapy for management of stress urinary incontinence in women: a systematic review and meta-analysis

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Abstract

Background: Carbon dioxide (CO_2) laser therapy is an emerging treatment for women with stress urinary incontinence (SUI).

Objectives: To examine the efficacy of CO_2 laser therapy for management of SUI-related symptoms in women.

Design: A systematic review and meta-analysis of randomized controlled trials and cohort studies.

Data sources and methods: Four databases were screened until January 2023. All efficacy continuous endpoints were assessed *via* subtraction of the posttreatment from pretreatment values. The data were summarized as mean difference (MD) with 95% confidence interval (CI) using the random-effects model.

Results: A total of 15 studies with 700 patients were analyzed. CO_2 laser therapy significantly decreased the 1-h pad weights at 3 months [$n = 5$ studies, MD = −3.656 g, 95% CI (−5.198, −2.113), $p < 0.001$], 6 months [$n = 6$ studies, MD = −6.583 g, 95% CI (−11.158, −2.008), $p = 0.005$], and 12 months [$n = 6$ studies, MD = −3.726 g, 95% CI (−6.347, −1.106), $p = 0.005$]. Moreover, CO_2 laser therapy significantly decreased the International Consultation of Incontinence Questionnaire-Urinary Incontinence Short Form Scores at 3 months [$n = 10$ studies, MD = −4.805, 95% CI (−5.985, −3.626), $p < 0.001$] and 12-months [$n = 6$ studies, MD = −3.726, 95% CI (−6.347, −1.106), $p = 0.005$]. Additionally, CO_2 laser therapy significantly decreased the Pelvic Floor Impact Questionnaire scores at 6 months [$n = 2$ studies, MD = −11.268, 95% CI (−18.671, −3.865), $p = 0.002$] and 12 months [$n = 2$ studies, MD = −10.624, 95% CI (−18.145, −3.103), $p = 0.006$]. Besides, CO_2 laser therapy significantly decreased the Urogenital Distress Inventory-6 scores at 3 months [$n = 2$ studies, MD = −21.997, 95% CI (−32.294, −11.699), $p < 0.001$], but not at 6 months [$n = 3$ studies, MD = −3.034, 95% CI (−7.357, 1.259), $p = 0.169$]. Lastly, CO_2 laser therapy significantly increased the Vaginal Health Index Score at 6 months [$n = 2$ studies, MD = 2.826, 95% CI (0.013, 5.638), $p = 0.047$] and 12 months [MD = 1.553, 95% CI (0.173, 2.934), $p = 0.027$].

Conclusion: CO_2 laser therapy improved the SUI-related symptoms in women. To obtain solid conclusions, future studies should be well-designed with standardized settings, consistent therapeutic protocols, and long-term follow-up periods.

Keywords: CO_2 laser therapy, genitourinary syndrome of menopause, meta-analysis, quality of life, stress urinary incontinence

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Introduction

Stress urinary incontinence (SUI) is a gynecologic disorder manifested by urinary leak during events that associate with increased abdominopelvic pressure, such as exercising, laughing, sternutation, and coughing.[1–3] It is the most frequent subtype of urinary incontinence globally, and it is estimated to impact 35–55% of all women suffering from urinary incontinence.[4–6] Some of the causes of SUI include obesity, vaginal delivery, genetics, advanced age, pelvic surgery, pregnancy, and diabetes mellitus. Additionally, as people age, the appropriate pelvic floor structure loses nerve function, and scar tissue replaces muscle fibers.[1–3] The significant impact of SUI on quality of life imposes a psychological and heavy financial burden.[7]

Physical therapy, dietary changes, and pessary use are examples of the current non-surgical treatment options.[8,9] These treatments only temporarily relieve symptoms and are ineffective for women who have severe symptoms.[10] When these treatments are ineffective in treating SUI-related symptoms within 3–6 months, surgical intervention is recommended, particularly tension-free suburethral slings,[11] which are associated with 80–95% success rates.[12]

Laser therapy offers a less intrusive alternative for individuals experiencing mild-to-moderate SUI who prefer to avoid a more invasive surgical approach or are not suitable candidates for surgery due to contraindications.[13] Two primary categories of vaginal lasers exist: non-ablative erbium-doped yttrium aluminum garnet (Erbium:YAG) and ablative carbon dioxide (CO_2) lasers.[14] Collectively, these lasers share the common clinical need of achieving collagen remodeling in the subepithelial connective tissue/fascia, albeit through distinct mechanisms.[14] At a wavelength of 10,600 nm, Erbium:YAG laser exhibits a significantly greater water absorption capacity (about 10–15 times more than CO_2 laser). This characteristic enables a more profound secondary thermal impact, facilitating controlled heating of the targeted mucous membrane within the vaginal wall. This controlled heating occurs in the subepithelial layer without causing harm to the vaginal epithelium, promoting the contraction and remodeling of collagen fibers.[15] Conversely, CO_2 laser (operating at 10,600 nm) leads to tissue denaturation, followed by the subsequent remodeling of collagen and elastin fibers.[16] Empirical evidence supports the notion of collagen remodeling ensuing from both types of laser therapies, as revealed through histological studies.[17,18]

Indeed, CO_2 laser therapy is a relatively new treatment option for SUI. This procedure mechanistically involves the use of a CO_2 laser to stimulate collagen production and tighten the tissues around the urethra, which can help improve bladder control and reduce leakage.[19–21] Numerous studies have investigated the effectiveness of CO_2 laser therapy for management of SUI-related symptoms. However, the results have been constrained by small sample sizes, varying study designs, different follow-up times, and conflicting outcomes.[18,22–35] All in all, these study findings on CO_2 laser therapy for SUI have not been systematically and comprehensively summarized through meta-analysis. Conducting such research is of utmost importance as it can provide conclusive insights that effectively guide clinical decision-making.

The aim of investigation is to carry out a contemporary single-arm systematic review and meta-analysis of all studies that examined the efficacy of CO_2 laser therapy for the management of women with SUI-related symptoms.

Methods

We completed this unregistered investigation according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[36] and the Cochrane Handbook for Systematic Reviews of Interventions.[37]

The eligibility Patient, Intervention, Comparison, Outcome, and Study design (PICOS) criteria comprised: (i) patients: individuals with SUI, (ii) intervention: posttreatment parameters after CO_2 laser therapy; (iii) comparator: pretreatment parameters before CO_2 laser therapy; and (iv) outcomes: 1-h pad test (g), International Consultation of Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) score, Pelvic Floor Impact Questionnaire (PFIQ) score, Urogenital Distress Inventory (UDI-6) score, and Vaginal Health Index Score (VHIS) at different time points, and (v) study designs: randomized controlled trials (RCTs) and cohort single-arm studies. The exclusion criteria comprised mainly non-original studies, such as abstracts and reviews.

From inception to January 2023, we searched four information sources utilizing Scopus,

PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. We developed a relevant search strategy by combining the following keywords: ('stress urinary incontinence' OR SUI) AND (CO_2 OR 'carbon dioxide') AND (vaginal) AND (laser OR beam) AND (woman OR women OR female OR females). Supplemental Table 1 shows the exact search strategy used in each database. Additionally, we supplemented the search strategy with manual exploration of the reference lists of the recent review articles and the eligible meta-analyzed studies to decrease the probability of skipping applicable citations.

For study selection, we examined titles and abstracts and omitted the unrelated ones. Next, we performed a full-text screening of the remaining citations and checked them against our eligibility criteria. Two coauthors completed study selection and conflicts were resolved by discussion.

We assessed the quality of RCTs according to the Cochrane risk of bias tool.[38] Conversely, we assessed the quality of non-RCTs using the National Heart, Lung, and Blood Institute (NHLBI) scale for before–after (pre–post) studies with no control group.[39] The Cochrane risk of bias tool examines seven domains and scores each of them as low, high, or unclear risk of bias. The NHLBI scale for before–after (pre–post) studies with no control group examines 12 questions. As per the guidelines of the scale, question number 12 should be omitted if it is not applicable. In our meta-analysis, indeed, question 12 was not applicable as our study utilized only patient-level data. Therefore, the overall quality assessment for the non-RCTs was based on the total score out of 11, as following: poor $<50\%$, fair 50–75%, and good $\geqslant 75\%$. Two coauthors completed study quality evaluation and conflicts were resolved by discussion.

We extracted two categories of data from the included studies. The first category comprised the baseline characteristics of the included studies, such as study identifier (first author and year of publication), country, sample size, and patients' age and body mass index. The second category comprised the efficacy endpoints, namely 1-h pad test (g) at 3, 6, and 12 months, ICIQ-UI SF scores at 3 and 6 months, PFIQ-7 scores at 6 and 12 months, UDI-6 scores at 3 and 6 months, and VHIS scores at 6 and 12 months. The 24-h pad weight test is an important tool for objective measurement of urinary incontinence.[40,41] The severity of urinary incontinence is based on the pad weight and includes mild (1.3–<20 g), moderate (20–<75 g), and severe (>75 g) categories.[41] The ICIQ-UI questionnaire (range of scores: 0–21) examines reasons for SUI and its incidence, frequency, and impact on daily lifestyle; higher scores reflect worse symptoms.[42] PFIQ-7 questionnaire (range of scores: 0–100) examines how changes of bladder or urine symptoms affect the quality of life of patients; higher scores reflect worse quality of life.[43] The UDI-6 questionnaire (range of scores: 0–75) examines six domains relating to urinary frequency, urgency, urine leakage during activity, amount of urine leakage, difficulty emptying the bladder, and pain; higher scores reflect worse symptoms.[44] VHIS questionnaire examines vaginal elasticity, fluid volume, pH, epithelial integrity, and moisture using a numeric scale of 1–5. The minimum and maximum scores are 5 and 25, respectively; lower scores reflect worse vulvovaginal atrophy symptoms.[45] Two pairs of coauthors collected the data and conflicts were resolved by discussion among the pairs.

All efficacy continuous endpoints were assessed *via* subtraction of the posttreatment from pretreatment (baseline) values. We analyzed the effect sizes using the inverse-variance method and summarized them as mean difference (MD) and 95% confidence interval (CI) using the random-effects model. We judged the extent of heterogeneity of the endpoints according to Higgin's I^2 and the p value of the chi-square tests. Outcomes with $I^2 > 50\%$ or $p < 0.1$ established significant heterogeneity.[46] We performed subgroup analyses of outcomes according to the study design (RCTs *versus* non-RCTs). For all purposes, $p < 0.05$ established statistical significance. We utilized The Open Meta Analyst software for statistical analysis and generation of forest plots.

Results

Summary of the included studies

Figure 1 displays the PRISMA flowchart for literature search and study selection. Overall, 15 studies with 700 patients suffering from SUI and treated with CO_2 laser therapy met the included criteria and were analyzed.[18,22–35] Four studies were RCTs,[22,24,27,32] whereas the remaining nine studies were cohort single-arm investigations.[18,23,25,26,28–31,33–35] The included studies were conducted from 2018 to 2022 and carried out in various countries including Israel ($n = 3$), Brazil

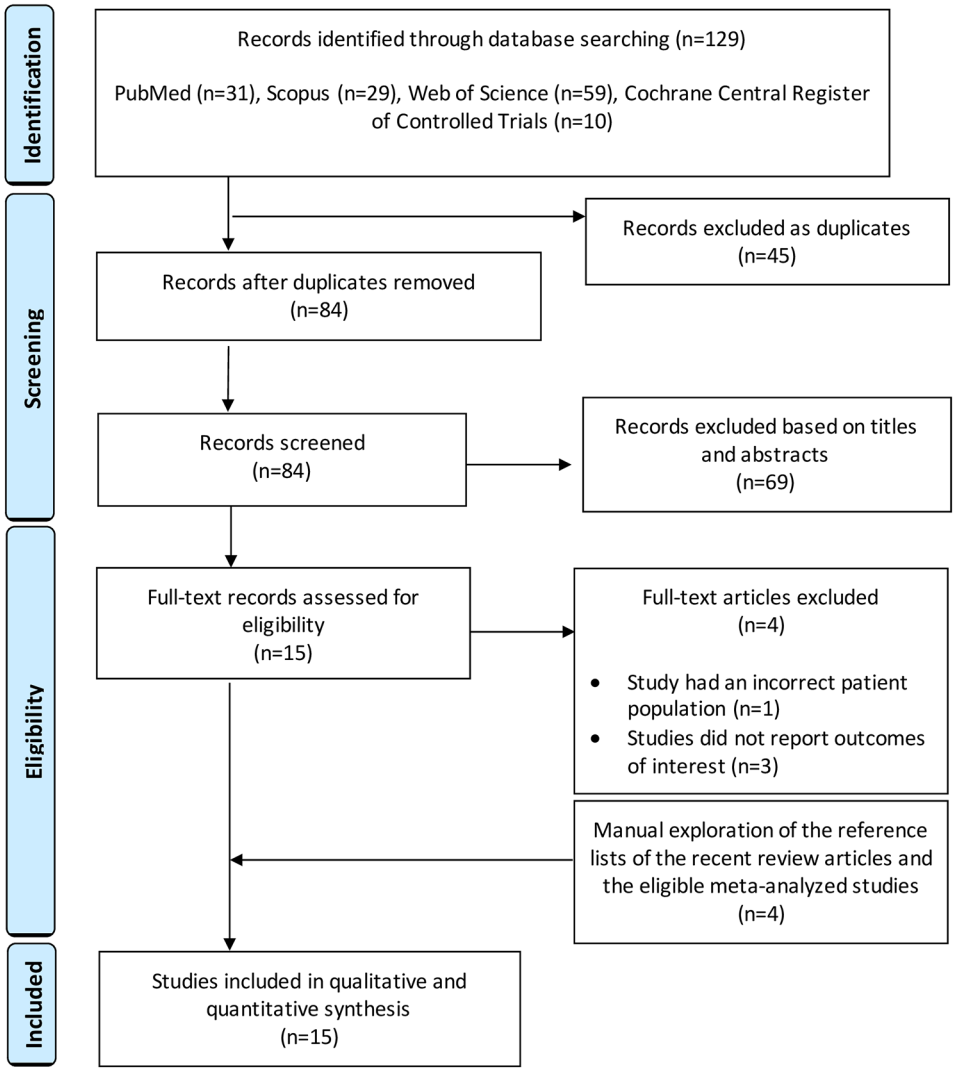

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart for literature search and study selection.

($n=2$), China ($n=2$), Taiwan ($n=2$), Australia ($n=1$), Slovenia ($n=1$), Columbia ($n=1$), Poland ($n=1$), Spain ($n=1$), and Indonesia ($n=1$). The sample sizes ranged from 10 to 161 patients and the mean age of patients ranged from 40.9 to 60.4 years old. Table 1 displays a summary of the baseline characteristics of the included studies and patients. Supplemental Table 2 shows the details of CO_2 laser therapy for management of women with SUI.

Summary of the quality assessment of the included studies

Supplemental Figure 1 displays a summary of the quality assessment of the RCTs[22,24,27,32] which were assessed according to the Cochrane's risk of bias tool. All RCTs were judged to have low risk of bias for the domains of random sequence generation, incomplete outcome data, and selective reporting. One study (Aguiar, 2020) did not have a controlled intervention, and hence the domains of allocation concealment and blinding of participants and personnel were judged as high risk of bias.[22] In the same study (Aguiar,2020), there were no adequate information about blinding of the outcome assessment, and hence the domain of detection bias was judged as unclear risk of bias.[22] For two studies (Alexander 2022 and Seki 2022),[24,32] there were no sufficient details about allocation concealment, and hence the corresponding domain of selection bias was judged as

Table 1. The baseline characteristics of the included studies and patients.

Study identifier	Country	Study type	*n*	Age (years)		BMI (kg/m²)	
				Mean	SD	Mean	SD
Aguiar, 2020	Brazil	RCT	24	57.83	5.01	NR	NR
Alcalay, 2021	Israel	Cohort	42	49.1	9.7	27.1	5.2
Alexander, 2022	Australia	RCT	49	51.5	10.6	26.5	5.1
Dabaja, 2019	Israel	Cohort	32	42.25	4.75	26.5	3.2
Franić, 2021	Slovenia	Cohort	85	38.3	10.4	30.3	8.7
Isaza, 2018	Colombia	Cohort	161	53	5.1	NR	NR
Lauterbach, 2022	Israel	RCT	63	51.8	3.5	26.5	4.2
Lin, 2018	Taiwan	Cohort	10	48.43	12.75	21.97	2.12
Long, 2022	Taiwan	Cohort	25	42.9	5.6	22.6	3.5
Nalewczynska, 2022	Poland	Cohort	59	51	10.7	26.1	3.07
Palacios, 2019	Spain	Cohort	25	51.4	9.9	NR	NR
Seki, 2022	Brazil	RCT	42	50.2	8.7	28.8	5
Zhang, 2021	China	Cohort	33	40.9	4.95	NR	NR
Moegni, 2020	Indonesia	Cohort	20	54.95	9.30	25.84	NR
Wu, 2021	China	Cohort	30	60.4	7.8	NR	NR

BMI, body mass index; NR, not reported; RCT, randomized controlled trial; SD, standard deviation.

unclear risk of bias. The quality assessment of the remaining cohort single-arm studies[18,23,25,26,28–31,33–35] was evaluated using the NHLB tool for before–after (pre–post) studies with no control group.[39] The overall quality was fair in nine studies and good in one study. Supplemental Table 3 depicts a summary of the quality assessment of the included cohort studies.

Meta-analysis

One-hour pad weight. CO_2 laser therapy significantly decreased the 1-h pad weights at 3 months [$n=5$ studies, MD = −3.656 g, 95% CI (−5.198, −2.113), $p<0.001$], 6 months [$n=6$ studies, MD = −6.583 g, 95% CI (−11.158, −2.008), $p=0.005$], and 12 months [$n=3$ studies, MD = −6.373 g, 95% CI (−9.958, −2.788), $p<0.001$]. All the pooled analyses were heterogeneous ($I^2>50\%$ and $p<0.1$) (Figure 2).

ICIQ-UI SF scores. CO_2 laser therapy significantly decreased ICIQ-UI scores at 3 months [$n=10$ studies, MD = −4.805, 95% CI (−5.985, −3.626), $p<0.001$] and 12 months [$n=6$ studies, MD = −3.726, 95% CI (−6.347, −1.106), $p=0.005$]. The pooled analyses were heterogeneous ($I^2>50\%$ and $p<0.1$) (Figure 3).

PFIQ scores. CO_2 laser therapy significantly decreased the PFIQ scores at 6 months [$n=2$ studies, MD = −11.268, 95% CI (−18.671, −3.865), $p=0.002$] and 12 months [$n=2$ studies, MD = −10.624, 95% CI (−18.145, −3.103), $p=0.006$]. The pooled analyses were homogeneous ($I^2=50.01\%$, $p=0.157$ and $I^2=42.49\%$, $p=0.187$; respectively) (Figure 4).

UDI-6 scores. CO_2 laser therapy significantly decreased the UDI-6 scores at 3 months [$n=2$ studies, MD = −21.997, 95% CI (−32.294, −11.699), $p<0.001$], but not at 6 months [$n=3$ studies, MD = −3.034, 95% CI (−7.357, 1.259), $p=0.169$]. The pooled analyses were heterogeneous ($I^2=79.44\%$, $p=0.027$) and homogeneous ($I^2=27.21\%$, $p=0.253$), respectively (Figure 5).

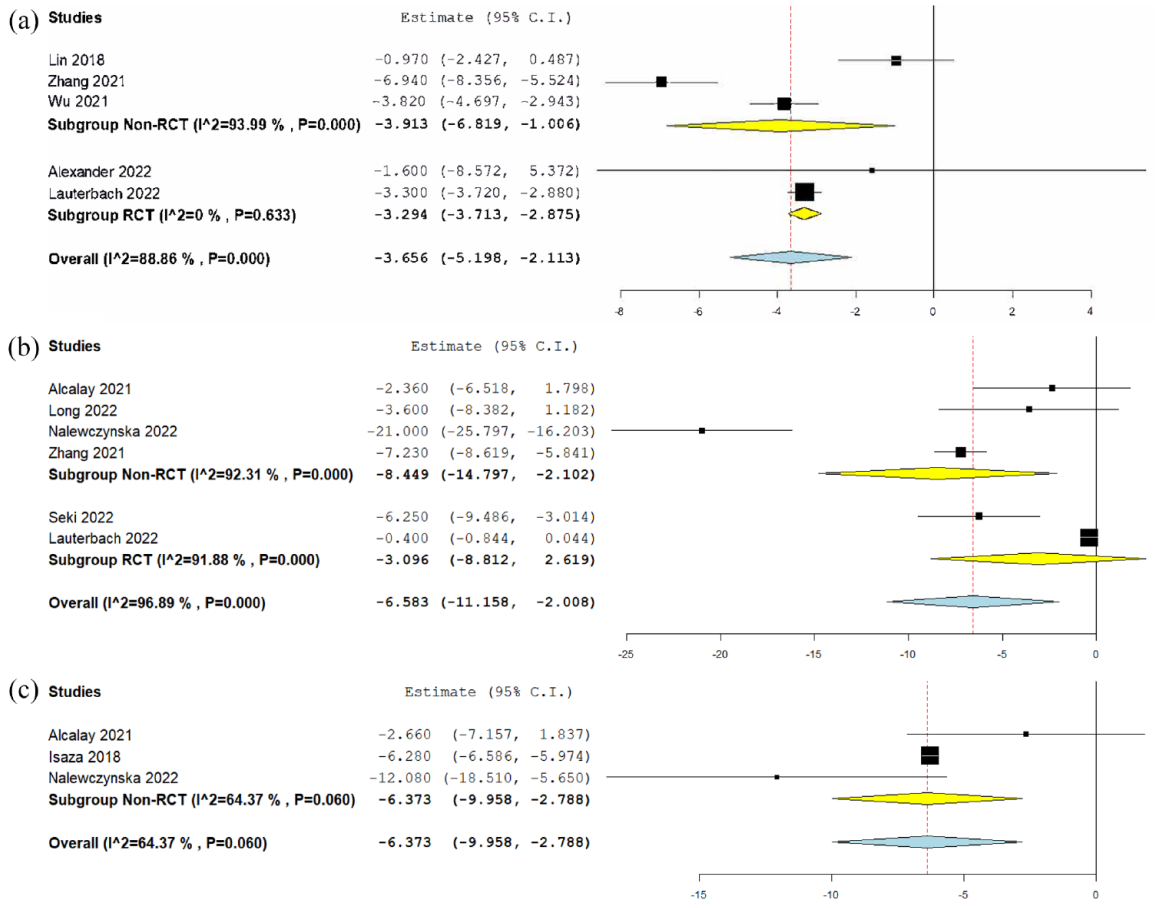

Figure 2. Meta-analysis of 1-h pad weights (g) at 3 months (a), 6 months (b), and 12 months (c).

VHIS scores. CO_2 laser therapy significantly increased the VHIS scores at 6 months [$n = 2$ studies, MD = 2.826, 95% CI (0.013, 5.638), $p = 0.047$] and 12 months [MD = 1.553, 95% CI (0.173, 2.934), $p = 0.027$]. The pooled analyses were heterogeneous ($I^2 = 79.29\%$, $p = 0.028$) and homogeneous ($I^2 = 0\%$, $p = 0.723$), respectively (Figure 6).

Discussion

This systematic review and meta-analysis aimed to scrutinize the evidence on the efficacy of CO_2 laser therapy for management of women suffering from SUI-related symptoms. Overall, 13 studies with good quality and 650 patients were included. Our results depicted that CO_2 laser therapy was effective in female patients with SUI, which was demonstrated by significant improvements in several SUI-related parameters, such as 1-h pad test, ICIQ-UI SF, PFIQ, UDI-6, and VHIS at various time points including 3, 6, and 12 months of follow-up.

SUI is a type of urinary incontinence that occurs when physical movements, such as coughing, sneezing, laughing, or exercising, put pressure on the bladder and cause unintentional urinary leakage. It is more common in women than men and can be caused by a variety of factors, including weakened pelvic muscles, hormonal changes, childbirth, obesity, and certain medical conditions.[1–3] Treatment options for SUI can include pelvic floor exercises, lifestyle changes, medications, and in some cases, surgery, or laser therapy.[8,9]

CO_2 laser therapy has emerged as a promising treatment option for SUI. The therapy involves the use of a high-energy CO_2 laser to stimulate collagen production in the vaginal tissues, which can help to strengthen the pelvic floor muscles and improve bladder control.[19–21] The procedure is minimally invasive and can be performed in a doctor's office with minimal discomfort. Advantageously, the procedure does not require a hospital stay, and patients can usually resume

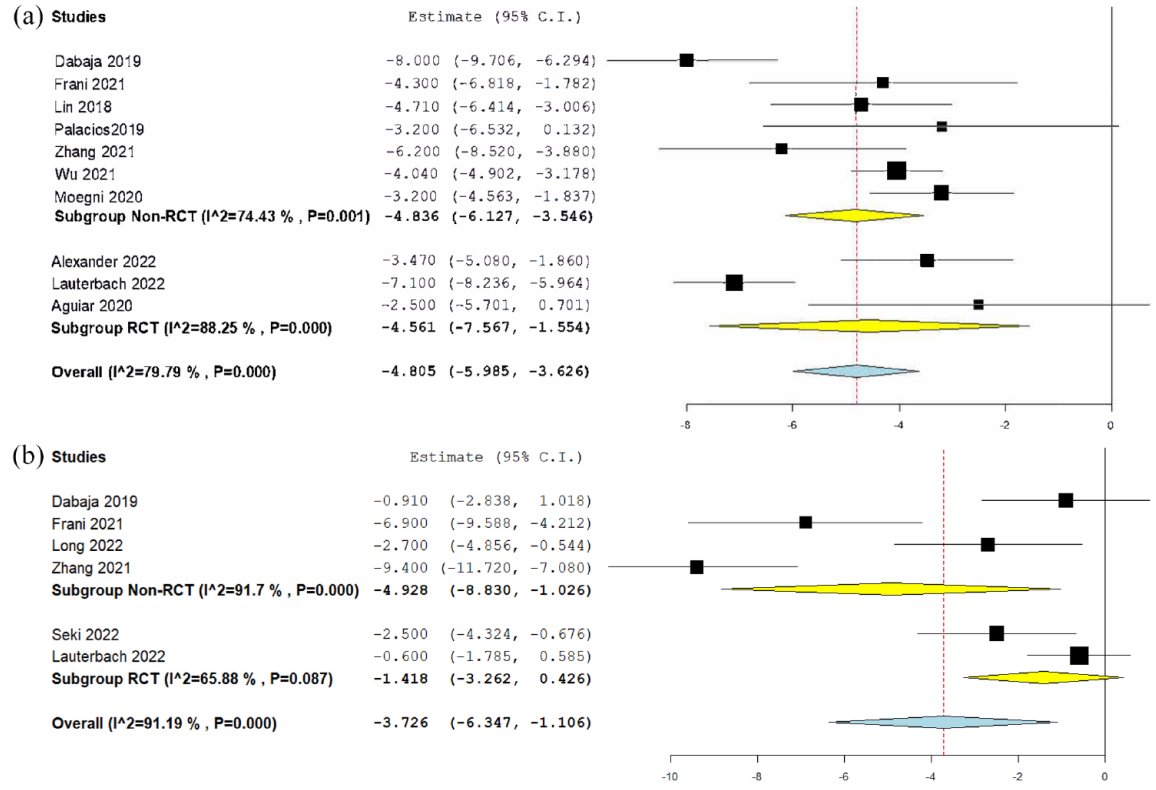

Figure 3. Meta-analysis of ICIQ-UI SF scores at 6 months (a) and 12 months (b).
ICIQ-UI SF, International Consultation Of Incontinence Questionnaire-Urinary Incontinence Short Form.

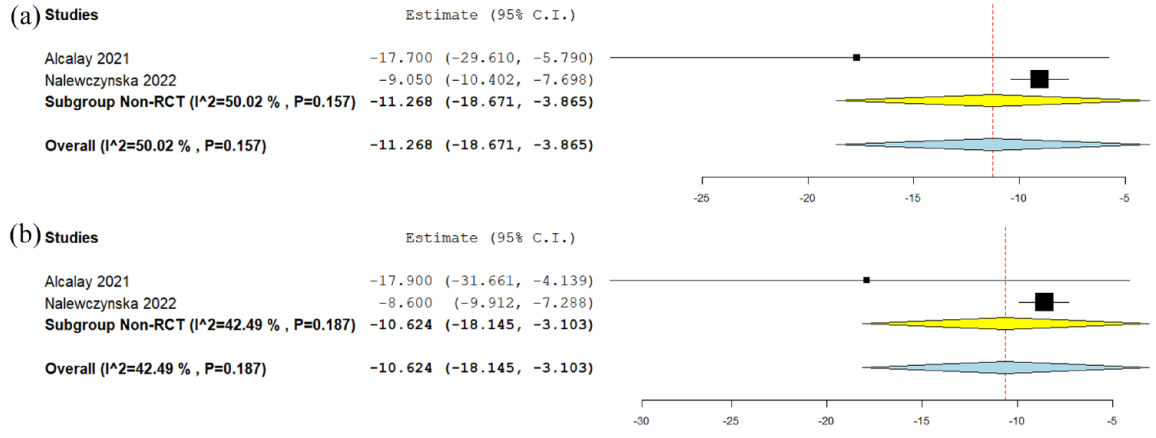

Figure 4. Meta-analysis of PFIQ scores at 6 months (a) and 12 months (b).
PFIQ, pelvic floor impact questionnaire.

their normal activities within a few days. Another benefit is that CO_2 laser therapy is relatively painless and has a low risk of complications, making it a safe option for many patients who may not be good candidates for surgery or other more invasive treatments. The findings of our meta-analysis showed that CO_2 laser therapy is effective in reducing the symptoms of SUI and improving quality of life for women who suffer from this condition. Overall, CO_2 laser therapy offers a promising alternative to traditional treatments for SUI, such as surgery or medication, and may provide relief for women who are seeking a non-invasive solution to this common condition.

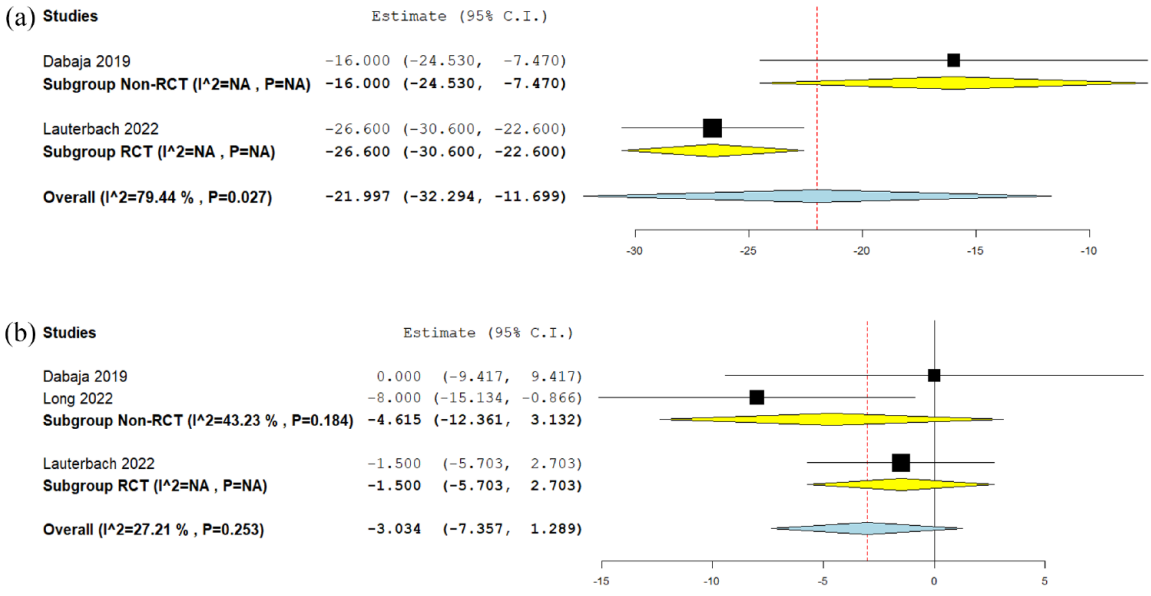

Figure 5. Meta-analysis of UDI-6 scores at 3 months (a) and 6 months (b).
UDI, urogenital distress inventory.

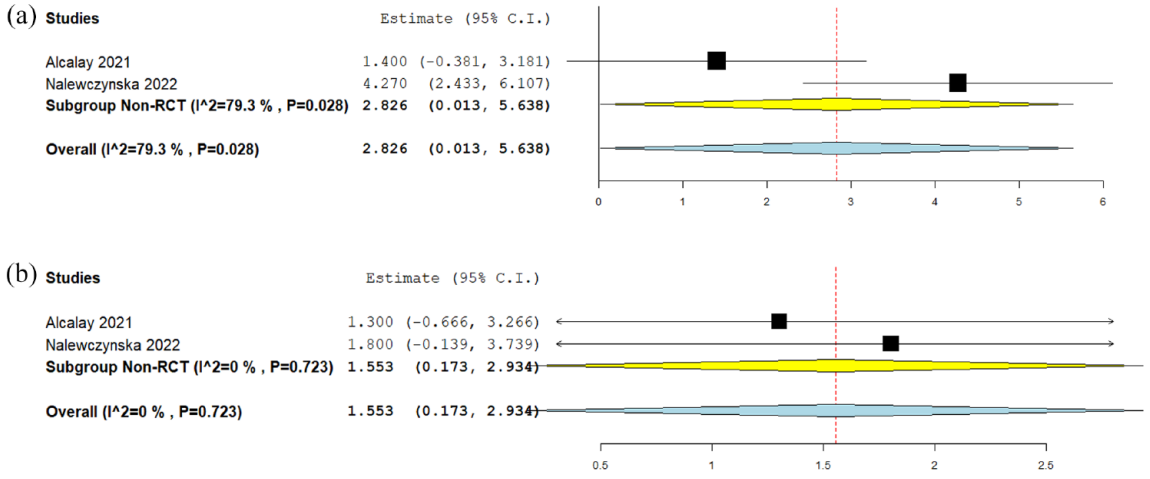

Figure 6. Meta-analysis of VHIS scores at 6 months (a) and 12 months (b).
VHIS, Vaginal Health Index Score.

Menopause is largely correlated with a wide array of urinary symptoms, such as incontinence, frequency, nocturia, urgency, recurrent infections, and dysuria. Collectively, these urinary symptoms often negatively influence the quality of life and sexual function. They additionally comprise several of the symptomatology of the genitourinary syndrome of menopause (GSM).[47–49] From a pathophysiologic perspective, GSM occurs secondary to decreased estrogenic stimulation to the vulvovaginal and/or lower urinary tracts.[50] A recent meta-analysis of 25 studies with close to 1150 patients concluded the favorable effects of vaginal CO_2 laser therapy for management of various symptoms of the GSM, such as vaginal dryness, itching, and burning, as well as dyspareunia and dysuria.[51] These favorable benefits can be ascribed to CO_2 laser-induced production of collagen in the genitourinary tract, which in turns provides tissue strength, elasticity, and lubrication.[51] Our present meta-analysis expands the utility of CO_2 laser therapy to treat women with SUI.

Notably, in 2018, the United States Food and Drug Administration (FDA) has cautioned against unfounded advertising and improper use of laser-based tools, such as CO_2 laser therapy, for treatment of various gynecological and urogynecological disorders, including SUI.[52] The FDA argued that laser therapy carries the potential for significant adverse events. The safety and effectiveness of employing laser therapy to treat these conditions remain uncertain and unsupported by established evidence. Subsequently, the International Urogynecological Association (IUGA) Committee has shared its clinical opinion on laser-based vaginal devices used to treat SUI, vaginal laxity, and GSM. The IUGA Committee concluded that to gain deeper insights into the potential benefits, risks, and effectiveness of laser therapy for SUI, well-designed case–control studies are imperative.[14] Moreover, the IUGA Committee emphasized that to endorse the therapeutic merits of nonsurgical laser-based devices within urogynecology, it is essential that substantial clinical trials establish their long-term safety, effectiveness, and complication profiles.[14] Similar opinions were also voiced by other Committees such as the American Urogynecologic Society (AUGS)[53] and the European Society for Sexual Medicine (ESSM).[54]

Our study has several notable strengths. First, we included a large number of eligible studies, which allowed us to generate highly powered findings. Additionally, most of the studies had a low risk of bias, which increases the validity and reliability of our results. Furthermore, we examined multiple outcomes and assessed efficacy at various timepoints, allowing us to determine short-term and long-term effectiveness of the intervention. Collectively, our study is the most comprehensive and up-to-date reference on the efficacy of CO_2 laser therapy for symptomatic management of women with SUI.

Despite the valuable findings of our study, there are a few limitations that must be acknowledged. The small number of studies and corresponding sample size are noteworthy shortcomings. Indeed, there is a reduced number of studies that have examined the safety and effectiveness of CO_2 laser treatment (specifically for SUI) compared to those investigating its application for GSM. In certain studies, urinary symptoms, including SUI, were considered as components of the broader symptom profile associated with GSM, and we decided to exclude them to maintain a uniform and strict inclusion criterion. Besides, some outcomes did not report the long-term efficacy of the intervention. We also observed heterogeneity across several endpoints, which could have impacted the validity of the meta-analyzed results. Moreover, some studies were single-arm investigations without randomization, which could have potentially subjected the results to selection bias. Further shortcomings include the lack of uniformity of CO_2 laser application and some studies did not provide adequate information on the technique and related parameters. Although not a mandatory requirement, however, an additional limitation comprises the lack of retrospectively recording the research protocol in the International Prospective Register of Systematic Reviews (PROSPERO); therefore, potential bias cannot be certainly excluded.

Future research comprises conducting additional, large-sized, randomized, double-blinded, controlled trials to better evaluate the efficacy and safety of CO_2 laser therapy for the management of SUI-related symptoms. Additional prospective research encompasses identification of which specific cohort of SUI women are more likely to benefit the most from administration of CO_2 laser therapy. Besides, interesting forthcoming research may compare CO_2 laser therapy with other laser-based therapies for management of SUI. The specific quantity and duration of treatment sessions, as well as the protocols for ongoing maintenance, are currently characterized by a significant degree of arbitrariness for CO_2 laser therapy in the management of SUI. Therefore, it is imperative to prospectively establish a standardized approach for these parameters and ascertain the optimal settings that can yield maximal efficacy while minimizing potential adverse effects.

Conclusion

This systematic review and meta-analysis depicted the efficacy of the non-invasive CO_2 laser therapy in improving SUI-related symptoms in women. In order to obtain solid conclusions regarding the effects of CO_2 laser therapy, future studies should be well-designed with standardized settings, consistent therapeutic protocols, and long-term follow-up periods. Furthermore, outcome evaluations should be conducted in a uniform manner to ensure the reliability of the results.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
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