# Fractional $CO_2$ laser for the treatment of Peyronie's disease: A pilot clinical trial

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## ABSTRACT

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**KEY MESSAGES**

- Fractional $CO_2$ laser therapy may serve as a safe and minimally invasive modality in reducing penile curvature in men with chronic phase Peyronie's disease.
- At one year following initial fractional $CO_2$ laser therapy, study participants experienced a significant subjective improvement in their Peyronie's disease, as determined by the Peyronie's disease questionnaire, and objective improvement, as determined by in-office penile curvature

## INTRODUCTION

Peyronie's Disease (PD) is a fibrosing disorder of the penis characterized by fibrous inelastic plaque formation of the tunica albuginea of the corpora cavernosa. This inelastic scarring results in curvature and deformity of the erect penis.[1,2] As a consequence, afflicted men often experience significant sexual and psychological dysfunction and/or distress. It is estimated that PD affects 0.3% - 13.1% of men worldwide.[3]

Although the exact pathophysiology of PD is unknown, the disease is thought to stem from trauma or microtrauma to the penis, usually from sexual intercourse, resulting in bleeding in the subtunical spaces or resulting in tunical delamination.[4,5] In response to injury platelets release a number of cytokines including transforming growth-factor (TGF) β1, an important inducer of signaling cascades that increase collagen, proteoglycans, fibronectin, and tissue collagenase inhibitor. In patients with PD, it is hypothesized that there is a dysregulation in tissue repair. At present, available medical and surgical treatment modalities for PD have limitations. Intralesional collagenase clostridium histolyticum (CCh) is approved for the reduction of penile curvature in PD, however, its use is restricted to the United States market.[6] Other medical therapies including intralesional verapamil and interferon injections have inconsistent and modest effects, while invasive surgical management with plication or grafting can result in erectile dysfunction, penile length shortening, and penile sensory changes.[7–10]

Fractional $CO_2$ laser is a minimally invasive, ablative laser that has been shown to improve scar quality and restore tissue function in several conditions.[11,12] The $CO_2$ laser functions by using a 10,600 nm laser to target water molecules and cause thermolysis in scarred tissue. This laser is applied in a fractional pattern to create small columns of thermolysis in the scarred tissue (otherwise known as microthermal zones) between areas of healthy tissue.[11,13,14] Applying the laser in a fractional pattern ablates columns of abnormal scar tissue and in turn, allows for new collagen to form in a controlled fashion.[15] On a molecular level, fractional $CO_2$ lasers remodel scarred tissue by increasing matrix metalloproteinase 1– a collagenase – while decreasing both type 1 and type 3 procollagen and pro-fibrotic TGF-$\beta_2$.[16] This may mitigate the dysregulation in the tissue repair pathway found in PD. Although fractional $CO_2$ laser therapy has not been used in urology for the management of PD, its use in dermatology to treat a variety of scarring conditions including Dupuytren's disease (DD)[12], which is associated with PD and shares common pathophysiology[17], makes this device an attractive potential alternative to current therapies.

The objective of this open-labelled, non-randomized pilot study was to evaluate the efficacy and safety of a fractional $CO_2$ device in the management of PD.

## METHODS

### Study population

Men with chronic phase PD, defined as stabilization of symptoms/plaque for at least 3-6 months with resolution of plaque pain and older than 18 years-of-age were eligible for inclusion. Inclusion and exclusion criteria are detailed in Appendix 1**.** Patient accrual took place between September 2021 and March 2022 at a university setting. All participants provided written informed consent, and the research protocol was approved by the Clinical Research Ethics Board at the University of British Columbia (H18-02482). Study funding was through a research scholar grant from the Sexual Medicine Society of North America; patients were not charged to enrol in this study.

**Study design**

Prior to treatment, each patient underwent baseline investigations for PD. Baseline investigations included a detailed medical history, assessment of primary and secondary penile curvature at the erect state, and penile curvature measurement. Penile curvature was assessed with a goniometer after achieving at least an 8/10 rigid erection using a patient-specific dose of intracavernosal injection of trimix (alprostadil, phentolamine, papaverine). The starting dose was typically 5 units; if an adequate erection was not achieved after 10-15 minutes, the patients were re-dosed with 5-10 units up to a total of three injections. The point of maximal curvature was measured using the middle of the penile curve and the corona of the glans as reference points. A point-of-care ultrasound of the penis was also performed at the initial visit to characterize the Peyronie's plaque and exclude calcified plaque. Duplex ultrasound was not performed. None of the 5 patients required reversal of a prolonged erection with phenylephrine. All curvature assessments were performed by one urologist; repeat measures were not performed. Baseline scores from the International Index of Erectile Function-15 (IIEF-15) questionnaire and Peyronie's Disease Questionnaire (PDQ) were collected prior to or at the screening visit. The PDQ was used to assess the severity, physical, and psychosexual impact of PD. This patient-reported outcome measure (PROM) is separated into three domains: Psychological and Physical Symptoms Domain (PDQ-PD), Symptom Bother Domain (PDQ-BD), and Penile Pain Domain (PDQ-Penile Pain). The IIEF-15 questionnaire, while not specifically validated for Peyronie's patient population, was used to assess erectile dysfunction and is sub-stratified into 5 domains: Erectile Function (IIEF-EF), Orgasmic Function (IIEF-OF), Sexual Desire (IIEF-SD), Intercourse Satisfaction (IIEF-IS), and Overall Satisfaction (IIEF-OS).

Enrolled patients were then assigned to receive three laser treatments at 6 weeks intervals. Treatments were performed in a private clinic and each treatment was performed by the same experienced laser surgeon (JKR). Before treatment, the penile skin was cleansed with 2% chlorhexidine, then 30% lidocaine ointment was applied to the treatment area under occlusion for 30 minutes. Treatments were administered utilizing a 10,600nm fractional $CO_2$ laser (Fraxel Re:Pair SST Laser System, Solta Medical Inc., Hayward, CA) at settings of 70 mj (corresponding to a depth of penetration of approximately 1500 microns) and a 10-15 % tissue coverage. These laser settings were established based on experience treating hypertrophic scars and myofibroplastic conditions (e.g. burn scars, keloids, and dupuytren's contractures of the hands). Laser therapy was targeted along the length of a palpable plaque and around the point of maximal curvature. Immediately after each laser session, topical triamcinolone (10mg/cc) was applied to and massaged into the treated area. Steroids were applied as they are known to induce pathological scar regression.[18] With ablative laser therapy, its delivery to the target scar tissue is thought to be enhanced.[19] Participants were then asked to apply a petroleum product (Aquaphor) to the treated area 2-5x/day for a week post-treatment to promote healing. Study participants performed daily at-home penile modelling (bending the flaccid penis in the opposite direction of

the curve and holding it for 60 seconds, 3 repetitions, three times per day) one week after each laser treatment for 6 weeks.

At the 24- and 52-week study timepoint, a penile curvature assessment was performed. Study participants also completed the Peyronie's PDQ and IIEF-15 questionnaires. Adverse events were screened for at each study visit by physician review and patient history.

### Statistical analysis

Statistical analysis was performed using GraphPad Prism version 10.0.0 (GraphPad Software, Boston, MA). Data was reported as medians (interquartile range (IQR): Q1,Q3) or means ± standard deviation. Continuous data variables were compared and analyzed between baseline and follow-up time points using Friedman's Test and Dunn's multiple comparisons test. A power calculation has not been performed due to the nature of this study serving as a pilot clinical trial.

## RESULTS

### Patient characteristics

Five patients were enrolled and completed each of the study visits. Patient characteristics are summarized in Table 1. The median age of our patient cohort was 46.0 years old (IQR: 32.5, 55.5 years). All patients were Caucasian. Four of the five patients had a primary dorsal curvature of the penis, while one individual had a primary left curvature of the penis secondary to a Peyronie's plaque. The median duration of disease prior to laser therapy was 1.5 years (IQR:1.0, 3.5 years).

**Penile curvature measurement**

A reduction in primary penile curvature was observed in every patient. At baseline the median degree of primary penile curvature was 37.0° (IQR:33.0°, 53.0°). Twenty four weeks after the initial $CO_2$ laser therapy, the median degree of primary penile curvature had decreased to 35.0° (IQR: 23.5°, 57.0°) representing a mean difference of -4.8°± 6.2° and an overall median reduction in penile curvature of 13.2% (IQR:-2.4%, 29.9%), a non-statistically significantly reduction from baseline (p=0.62, z=1.265). (Fig. 1) However, at the 52-week time interval after initial $CO_2$ laser therapy, the median degree of penile curvature had decreased to 28.0° (IQR:17.50°, 44.0°), representing a statistically significant reduction in penile curvature as compared to baseline (p=0.03, z=2.530). (Fig. 1) The mean change in penile curvature between baseline and at 52 weeks was -11.6° ± 3.6° with an overall median reduction in their penile curvature of 24.3% (IQR: 17.0%, 47.5%).

**International Index of Erectile Function -15 questionnaire**

The median overall IIEF-15 scores were not found to be significantly different between baseline (median: 59.0, IQR: 42.5, 66.5). and at 24-week follow-up (median: 63, IQR: 54.5, 67.5 , p=0.62, z=1.265) or at week 52 (median: 60.0, IQR:53.5, 70.0, p=0.81, z=1.107).(Fig.2a) Similarly, when the IIEF–15 was assessed by its individual domains, patients were not found to have significant changes from baseline as compared to week-24 and one year follow-ups. (Fig.2b-f)

**Peyronie's disease questionnaire**

Although a significant difference from baseline (median: 26.0, IQR:15.0, 29.5) was not evident for PDQ scores at 24 weeks (median: 11.0, IQR: 9.0, 22.5, p=0.08, z=2.214) patients did report a significant improvement in their overall PDQ score at the 52-week follow-up as compared to baseline (median: 14.0, IQR: 7.0, 22.50 respectively, p= 0.03, z=2.530). (Fig. 3a) No significant differences existed within PDQ-PD when comparing baseline scores (median: 12.0, IQR:11.0,15.0) to follow-up either at 24-weeks (median: 8.0, IQR: 11.0, 15.0, p= 0.34, z=1.581) or at 52-weeks (median: 7.0, IQR: 6.0,11.0, p=0.25, z=1.739). (Fig. 3b) The PDQ-BD, showed no significant difference from baseline (median: 7.0, IQR: 4.5, 11.0) to any follow-up visit (Fig. 3c). Patients did not report any significant change in Penile Pain score. At baseline patients had a median score of 0.0 (median: 7.0, IQR: 0.0, 7.0) while, at 24- and 52-weeks of follow-up, patients reported a median score of 0.0 (IQR: 0.0, 3.5 p>0.99, z=0.9487) and 2.0 (IQR:0.0, 4.0 p>0.99, z=0.4743), respectively. (Fig. 3d)

**Adverse events**

Adverse events were screened for at every study timepoint. Four patients experienced mild penile bruising, one patient also reported skin peeling, while another experienced pruritus at the treatment area. In all cases, penile bruising, skin peeling, and pruritus were self-limiting,

resolving within 2-weeks of each treatment. There were no reports of abnormal swelling, dysuria, or infection. (Table 2)

## DISCUSSION

This is the first study to report the use of a fractional $CO_2$ laser to successfully reduce penile curvature in chronic phase PD. After a follow-up period of one year, our results suggest that fractional $CO_2$ laser is well tolerated with limited minor adverse events.

From an efficacy perspective, study participants experienced a median 24.3% reduction in their penile curvature (IQR: 17.0%, 47.5%) one year after the first laser treatment. This represented a mean change of -11.6° ± 3.58° for each patient. We believe the greatest reduction in penile curvature was seen at 1 year rather than at 24 weeks due to continued tissue remodelling which may last for a year or more following therapy.[20]

Although there are no other case reports in the urology literature, fractional $CO_2$ laser therapy has been used successfully to treat conditions similar to PD such as DD.[12] DD is a fibrosing disorder of the hand with a pathophysiology comparable to that of PD and the former has shown functional improvement after fractional $CO_2$ laser treatments.[12] Furthermore, fractional $CO_2$ laser therapy has recently been utilized in the treatment of hypertrophic scars (HTS).[21] The results of a large prospective study found these lasers were capable of correcting abnormal texture, thickness, and stiffness of HTS.[11] Furthermore, over a 30 month follow-up, the HTS were found to have continued to improve, remain stable, and not worsen.[11]

Compared to other evidence-based medical therapies for chronic phase PD such as intralesional verapamil or interferon, our initial results using a fractional $CO_2$ laser demonstrate comparable performance. Intralesional Verapamil is a well-established and tolerated treatment. In both randomized and observational studies, it has been observed to reduce penile curvature by 21.5% to 25.0%.[9,22,23] Likewise, intralesional interferon injections have been observed to reduce penile curvature by up to 27.0% in both randomized and observational studies.[24,25] However, intralesional CCh provides the greatest curvature reduction of all current medical therapies. In two large multi-institutional phase 3 randomized controlled studies (IMPRESS I and II), CCh was demonstrated to significantly reduce penile curvature by 34%, representing a mean change of −17.0° ± 14.8° per subject.[6]

Although our results demonstrated an objective improvement in penile curvature, it is not surprising that there was no significant difference in overall erectile function as determined by the IIEF questionnaire. This may be explained by the fact that every patient had good baseline erectile function that was maintained throughout the study. Within the limits of this investigation, our results pertaining to the IIEF are similar to those found in the IMPRESS I and II trials. Individually, patients in each of the IMPRESS I and II trials did not experience significant improvement in their IIEF scores at 52 weeks post intralesional CCh therapy.[6]

In our study, patients experienced a significant improvement in their overall PDQ scores a year after fractional $CO_2$ laser therapy. Interestingly, when the PDQ was sub-stratified into

PDQ-PD, PDQ-BD and PDQ-Penile Pain, there were no significant differences in the scores over the 52 weeks as compared to baseline which may be related to an inadequate sample size.

Although the men in our study did experience improvement in their PD curvature and PDQ scores, this study is not without limitations. This was a small pilot study and was not powered to estimate the true treatment effect of the fractional $CO_2$ laser in managing PD. Also, there are several confounders as this was a single arm study with no control group. As spontaneous resolution may occur in PD, the absence of a control group makes it difficult to assess if improvements in PD are truly due to laser therapy.[24,26,27] A spontaneous resolution rate of 3.2% has been documented to occur within a 8.4 month follow-up period.[28] Given that the median duration of disease in our study population was 1.5 years prior to initiating laser therapy, changes in our study are likely related to the $CO_2$ laser therapy. Another possible confounder is penile modelling. In the IMPRESS trials, it was observed that men who received a placebo injection and performed penile modelling experienced a mean reduction of penile curvature of 18.2%.[6] Furthermore, this study involves the use of topical corticosteroids. Although steroids have not been shown to improve PD as a sole agent, when used as an adjunctive pharmacologic intervention, it has been demonstrated to have an effect on PD in some studies.[29,30] With fractional $CO_2$ laser, it is hypothesized that a depot effect of the topical steroid, caused by the laser channels may have contributed to improvement in penile curvature.[19] Thus, the true effect of the fractional $CO_2$ laser may have been augmented by the use of post-treatment corticosteroid.

While we utilized the gold standard methodology for penile curvature assessment, incorporating in-office penile injections, ultrasound, and goniometer measurements, blinding to treatment was not possible and slight variation in erectile rigidity may have led to significant differences in penile curvature measurement. To mitigate the variability in curvature assessment and laser treatments, all measurements were performed by a single-experienced urologist and all treatments were performed by a single-experienced laser surgeon.

## CONCLUSIONS

Fractional $CO_2$ laser therapy may serve as a safe and novel therapy for PD. While this pilot trial was not powered to assess effectiveness, initial results were positive. There was an observed reduction in penile curvature with limited and mild associated adverse events. Based on these findings, further research is warranted to evaluate the utility of fractional $CO_2$ laser therapy in the treatment of PD before laser therapy should be incorporated into clinical practice.

***Competing interests:*** *Dr. Rivers has participated in advisory board and/or received consulting fees from Abbvie/Allergan, Bausch Health, Galderma, Leo Pharma, and MetaOptima; participated clinical trials supported by Abbvie/Allergan, Galderma, Leo Pharma, Medytox, and SaNOtise; owns stock in MedSpa Partners, MetaOptima, Pfizer; and is a co-owner/founder of*

*Riversol Skin Care Solutions Inc. Dr. Flannigan has participated in advisory board and/or received consulting fees from Boston Scientific and Coloplast; and is shareholder in Teumo health technologies Inc.*

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## FIGURES AND TABLES

**Figure 1.** A comparison of degrees of primarily penile curvature at baseline, 24 weeks and at 52 weeks following fractional $CO_2$ laser therapy. Data is presented as median (interquartile range: Q1, Q3). Medians analyzed using Friedman test. Multiple comparisons performed using Dunn's multiple comparisons test. $^{*}p<0.05$. ns: non-significant.

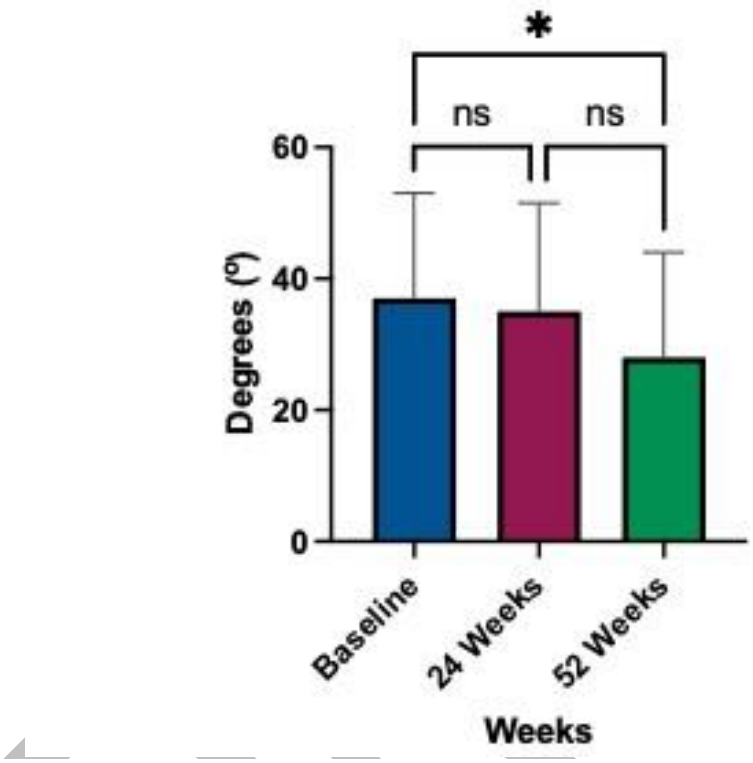


**Figure 2.** A comparison of International Index of Erectile Function-15: (a) overall score; (b) erectile function; (c) orgasmic function; (d) sexual desire; (e) intercourse satisfaction; and (f) overall satisfaction domain scores at baseline, 24 weeks, and 52 weeks following fractional $CO_2$ laser therapy. Data is presented as median (interquartile range R: Q1, Q3). Medians analyzed using Friedman test. Multiple comparisons performed using Dunn's multiple comparisons test. $^{*}p<0.05$. IIEF: International Index of Erectile Function. ns: non-significant.

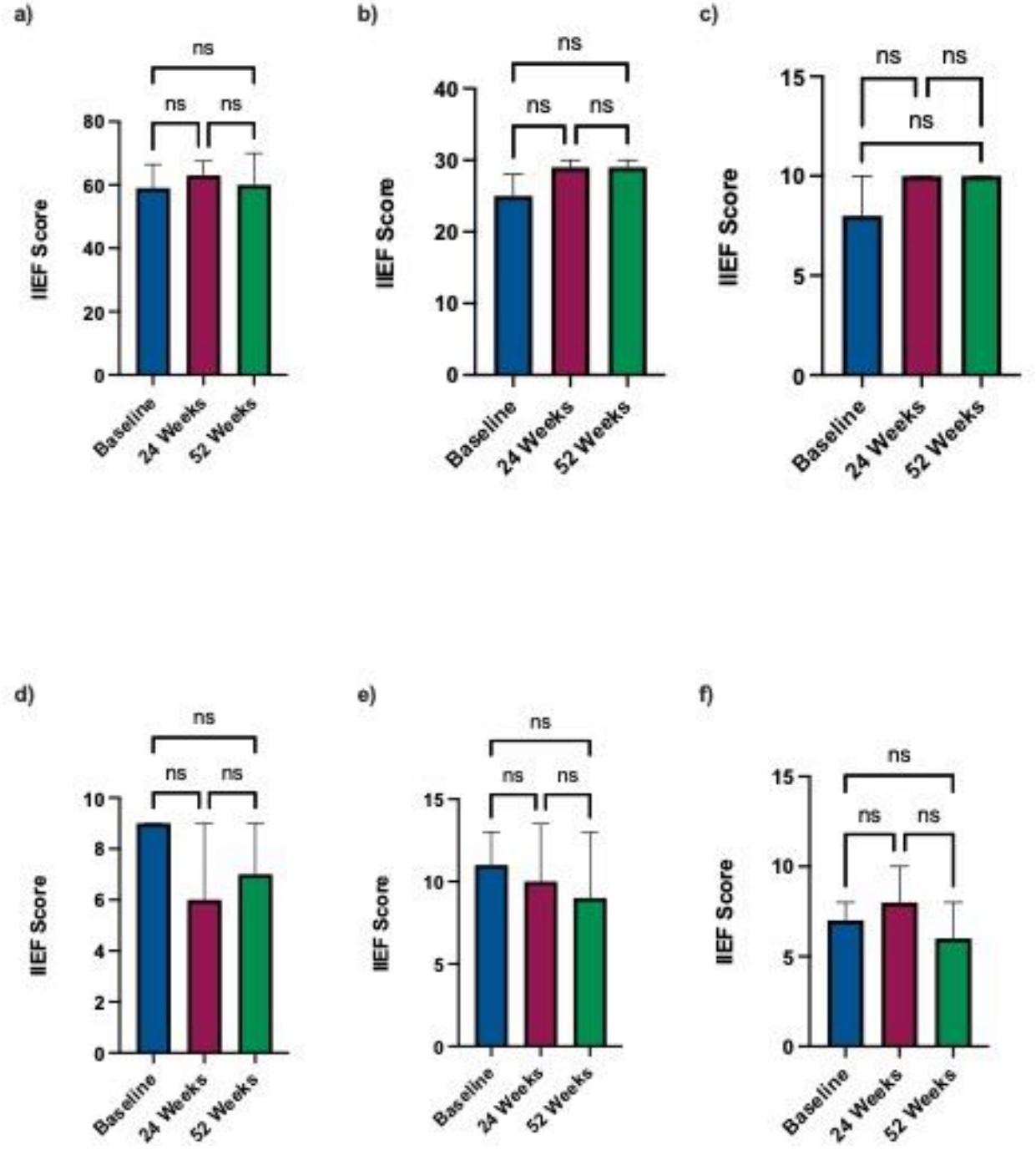
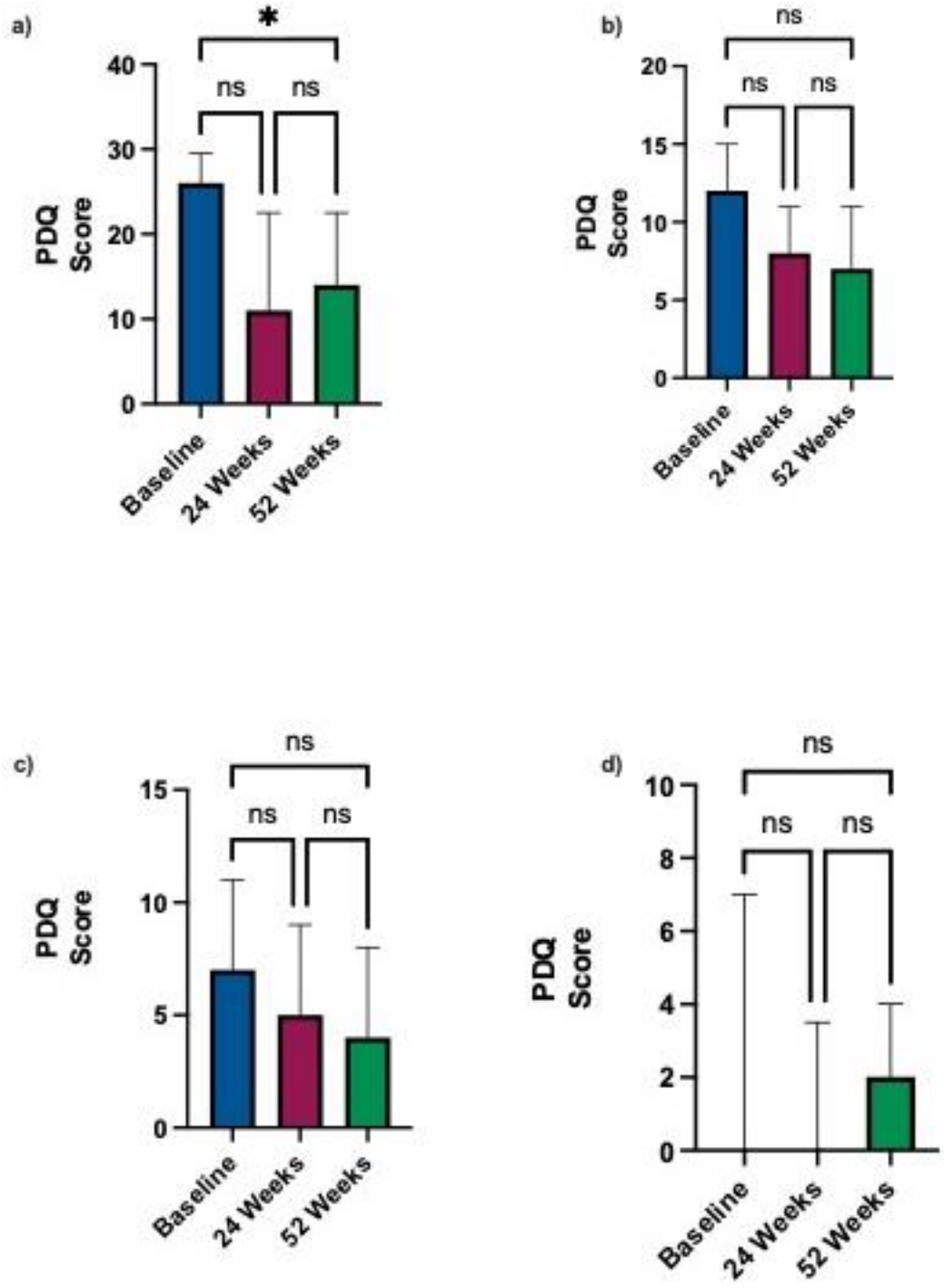


**Figure 3.** A comparison of Peyronie's disease questionnaire: (a) overall; (b) psychological and physical symptoms; (c) symptom bother; and (d) penile pain domain scores at baseline, 24 weeks and 52 weeks following fractional $CO_2$ laser therapy. Data is presented as median (interquartile rannge: Q1, Q3). Medians analyzed using Friedman test. Multiple comparisons performed using Dunn's multiple comparisons test. $^{*}p<0.05$. ns: non-significant; PDQ: Peyronie's disease questionnaire.



| Table 1. Patient characteristics | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Age** | **Duration of disease (years)** | **Primary curvature direction** | **Baseline degree of primary curve (º)** | **Primary distance of corona to maximal curvature (mm)** | **24 weeks: Degree of primary curvature (º)** | **52 weeks: Degree of primary curvature(º)** | **52 weeks: Percent reduction of penile curvature (%)** | **Baseline secondary curve direction** | **Medical comorbidities** |
| **Patient #1** | 35 | 5 | Dorsal | 36 | 70 | 35 | 21 | 41.7 | None | Hernia repair, knee surgery, tonsillectomy, tympanostomy |
| **Patient #2** | 46 | 1.5 | Dorsal | 30 | 33 | 21 | 14 | 53.3 | None | Post-traumatic stress disorder, major depressive disorder, right inguinal hernia repair, vasectomy |
| **Patient #3** | 30 | 1 | Left | 37 | 53 | 26 | 28 | 24.3 | Dorsal | Chronic headache |
| **Patient #4** | 50 | 2 | Dorsal | 53 | 34 | 46 | 44 | 17.0 | None | None |
| **Patient #5** | 61 | 1 | Dorsal | 53 | 10 | 57 | 44 | 17.0 | Left | Type 2 diabetes mellitus, ischemic heart disease, coronary artery bypass graft |

| **Table 2. Adverse events after fractional $CO_2$ laser therapy stratified by time** | | | | | |
|---|---|---|---|---|---|
| | **Adverse events (Duration)** | | | | |
| | **Week 0** ($1^{st}$ $CO_2$ laser therapy session) | **Week 6** ($2^{nd}$ $CO_2$ laser therapy session) | **Week 12** ($3^{rd}$ $CO_2$ laser therapy session) | **Week 26** (short-term followup) | **Week 52** (long-term followup) |
| Patient #1 | Mild penile bruising & skin scaling (2 weeks) | Mild penile bruising & skin scaling (2 weeks) | Mild penile bruising & skin scaling (2 weeks) | None | None |
| Patient #2 | Mild penile bruising (5–7 days) | Mild penile bruising (5–7 days) | None | None | None |
| Patient #3 | Mild penile bruising (3–4 days) | Mild penile bruising (3–4 days) | Mild penile bruising (3–4 days) | None | N/A |
| Patient #4 | None | None | None | None | None |
| Patient #5 | Mild penile bruising & pruritus (5 days) | Mild penile bruising & pruritus (5 days) | Mild penile bruising & pruritus (5 days) | None | None |

N/A: no data available.