

## THE EFFICACY OF FRACTIONAL CO<sub>2</sub> LASER TREATMENT FOR THE TREATMENT OF OVERACTIVE BLADDER SYNDROME IN MENOPAUSAL WOMEN- A THREE MONTH PILOT STUDY

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### ABSTRACT

#### BACKGROUND

Overactive bladder syndrome (OABS) is a common disorder that encompasses urgency, frequency, and nocturia. Various methods of therapies have been utilized worldwide. Despite progresses, it remains a formidable challenge. Laser treatment has emerged to reliably treat the symptoms complex. This study was intended to evaluate the effect of fractional CO<sub>2</sub> laser on the main symptoms of OABS.

#### MATERIALS AND METHODS

A prospective pre- and post-intervention pilot study was conducted on 31 female subjects recruited from a general hospital in Tehran, Iran. They were treated with 3 laser applications at one-month interval using the intravaginal fractional micro-ablative CO<sub>2</sub> laser. The study measures were urgency, frequency, nocturia, leakage, International Consultation on Incontinence Overactive Bladder (ICIQ-OAB), Urogenital Distress Inventory Short Form (UDI-6), and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), which were examined at baseline and every month thereafter up to the end of the laser treatment sessions.

#### RESULTS

The findings indicated that statistically significant differences occurred in the ICIQ-OAB score and urgency during treatment sessions as compared to the baseline ( $p < 0.05$ ). Laser therapy led to marked improvements in the UDI-6 score only at month 3 ( $p = 0.001$ ). Nocturia, frequency, leakage, and PISQ-12 score did not ameliorate upon laser administration ( $p > 0.05$ ).

#### CONCLUSION

In this pilot study, it was found that fractional CO<sub>2</sub> laser could be effective in the amelioration of some OABS symptoms in menopausal women. Further investigations with a larger sample size and long-term follow-ups are required to substantiate these preliminary findings.

#### KEY WORDS

Fractional CO<sub>2</sub> Laser, Menopausal Women, Overactive Bladder Syndrome, Sexual Function.

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#### BACKGROUND

Overactive bladder syndrome OABS is described by the International Continence Society as a chronic disease characterized by urinary urgency, with or without urgency urinary incontinence (UUI), usually with frequency as well as nocturia, in the absence of urinary tract infection (UTI) or other obvious pathology.<sup>(1)</sup>

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Recent evidence put light on the fact that OAB represents considerable clinical and economic impacts to the US. Also, it appears along with depression, dementia, diabetes, hypertension, and osteoporosis.<sup>(2)</sup> It carries deleterious influences on the quality of life of patients and yielded a prevalence of 12–17.4%.<sup>(3)</sup> In women, the number of the patients is on the rise with the aging of the population owing to the functional and structural changes in the bladder related to ischemic processes and menopause,<sup>(4)</sup> and hovers around 30% over the age of 65 years.<sup>(5)</sup> Elevated sensitivity of bladder afferents in the urothelial/sub-urothelial layer of the bladder, enhanced involuntary contractions of the detrusor muscle or abnormal central nervous system processing of bladder afferent signaling constitute the OAB spectrum.<sup>(6)</sup> It has been shown that symptoms of OAB have negative effects on sexual health. These patients have reported reduction of sexual activity and enjoyment, with

rate of decline in sexual quality of life being 23%.<sup>(7)</sup> More to the point, OAB is found with lower scores in overall health, quality of life, psychological well-being, sexual satisfaction, besides work productivity as opposed to patient controls.<sup>(8)</sup> In OAB, the onset of urgency incontinence is more likely to be followed by frequency and urgency owing to detrusor over activity. It has been shown detrusor over activity carries more effects on sexual function than urodynamic stress incontinence.<sup>(9)</sup> The influence of OABS symptoms on sexual function in women has been investigated in several studies.<sup>(9)</sup> Findings have highlighted an association between sexual activity and OAB. Given marked effects of OAB upon the sexual health of women, it is proposed to pay more attention to sexual problems while treating patients with OABS.

A variety of treatment methods, either surgical or non-surgical, are recommended for OAB, such as lifestyle changes, bladder training, pelvic floor muscle exercises, pharmacotherapy, and electrical stimulation/neuromodulation. These treatments differ in degrees of invasiveness and monetary investment, as well. Despite these therapeutic options, how to treat or manage OABS and associated adverse events is still challenging.

Fractional CO<sub>2</sub> laser has been observed with safety and remodeling tissue features in different body regions, namely the skin of the face, neck, and chest.<sup>(10-12)</sup> A previous study showed that exposure of vaginal specimens obtained from reconstructive pelvic surgery to fractional CO<sub>2</sub> led to connective tissue remodeling without any marked damage or adverse effects.<sup>(13)</sup> This emerging technology has been effective in the topical remodeling of connective tissue, in addition to the synthesis of new collagen, elastic fibers, and many components in the extracellular matrix, which positively contribute to the undesirable vaginal alteration caused by climacteric estrogenic fall and notable diminution of associated symptoms.<sup>(14)</sup> Recent findings have highlighted marked improvements in OAB symptoms of patients with vulvo-vaginal atrophy as a result of three-session treatment with fractional CO<sub>2</sub> laser, suggesting its effectiveness and safety for overcoming OAB symptoms in post-menopausal women.<sup>(15)</sup> In the light of these preliminary efforts, the present study was intended to evaluate the effect of fractional CO<sub>2</sub> laser on the main symptoms of OABS, including frequency, urgency, nocturia, leakage, and others by the ICIQ-OAB and UDI-6 in a sample of female patients admitted to a general hospital in Tehran, Iran.

## MATERIALS AND METHODS

This prospective pre- and post-intervention pilot study was carried out between January 2016 and December 2017. The study protocol was given an approval from Medical Research Committee, Tehran University of Medical Sciences (Ethical code: IR.TUMS.IKHC.REC.1395.1672). An informed written consent was obtained from all women enrolled in the study.

This study included postmenopausal women who had either urgency incontinence, urinated 8 or more times during daytime and one or more times during night-time, had one or more episodes of urinary urgency incontinence, and experienced a feeling of urgency per 24 hours. The following factors would rule out the participation: unwillingness to participate in the study, use of other OAB therapies (drug, pelvic floor muscle training, Botox injection) within the 3 months prior to the commencement of the study, prolapse

staged III and IV, recent treatment with isotretinoin, presence of vaginal wound, an abnormal Pap smear, diabetes, body mass index (BMI) > 30 kg/m<sup>2</sup>. These patients were selected from women referred to the Pelvic Floor Disorders Clinic, Imam Khomeini Hospital, Tehran, Iran.

After being sure that the procedure was explained to the participants in full, they were asked questions based on the PISQ-12, ICIQ-OAB, and UDI-6 by an investigator blinded to the type of interventions. All patients underwent urodynamic testing (UDS). Thereafter, they were treated with three laser applications using the intravaginal fractional microablative CO<sub>2</sub> laser (SmartXide 2 V 2 LR, Monalisa Touch, DEKA, Florence, Italy) with the following setting: dot power 40-watt, dwell time 1000 μs, dot spacing 1000 μm, and the smart stack parameter from 1 to 3. A vaginal probe was employed to gradually insert up to the top of the vaginal canal. Thereafter, it was withdrawn and rotated to entirely treat the vaginal wall with the laser beam. The dot power reduced to 24 watts at the level of the vaginal introitus. The treatment was carried out in an outpatient clinic with no particular preparation, such as analgesia or anaesthesia. Strong recommendations were made to the subjects to avoid coital sexual activity for at least 3 days following these three laser applications due to a mild inflammation which is more likely to continue up to 48 h.

The treatment sessions were at one-month interval (Months 1, 2 and 3) without any post-treatment follow-ups. The PISQ-12, ICIQ-OAB, and UDI-6 were filled out at baseline and every month thereafter up to the end of the laser treatment sessions. In addition to the mean scores of the PISQ-12, ICIQ-OAB, and UDI-6, four symptoms of leakage, nocturia, frequency, and urgency were also considered as the study outcome measures, examined by obtaining a frequency volume chart for 2 days.

OAB symptoms were measured by employing two validated questionnaires: International Consultation on Incontinence Overactive Bladder (ICIQ-OAB)<sup>(16)</sup> and Urogenital Distress Inventory Short Form (UDI-6).<sup>(17)</sup> Briefly, the former consists of two questions about patient's age and gender, four questions about symptom bother scored 0-4, and another four questions about their impact on quality of life scored 0-10. The ICIQ-OAB is a widely used tool for screening the symptoms of OAB with good validity and reliability in Iranian population.<sup>(18)</sup> The UDI-6 is a six-item questionnaire that examines urinary distress on a Likert scale from 0-4.

The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) as the short version of the PISQ-31 measure assesses sexual function in heterosexual women affected with urinary incontinence and/or pelvic organ prolapse.<sup>(19)</sup> This self-administered questionnaire is composed of three domains: behavioral-emotive (items 1-4), physical (items 5-9), and partner-related (Items 10-12). The items are rated on a five-point Likert scale from 0 (always) to 4 (never). The first four items are reversely scored; thus the maximum score is 48.<sup>(20)</sup> Its Persian version showed that the Cronbach's alpha coefficient was 0.84 for PISQ-12.<sup>(21)</sup>

## Statistical Analysis

In this non-blinded study, demographic characteristics, such as menopausal status, type of delivery, previous history of other diseases (i.e. hypothyroidism and diabetes mellitus), previous surgery (i.e. TL, cesarean section, HX, TOT, TVT,

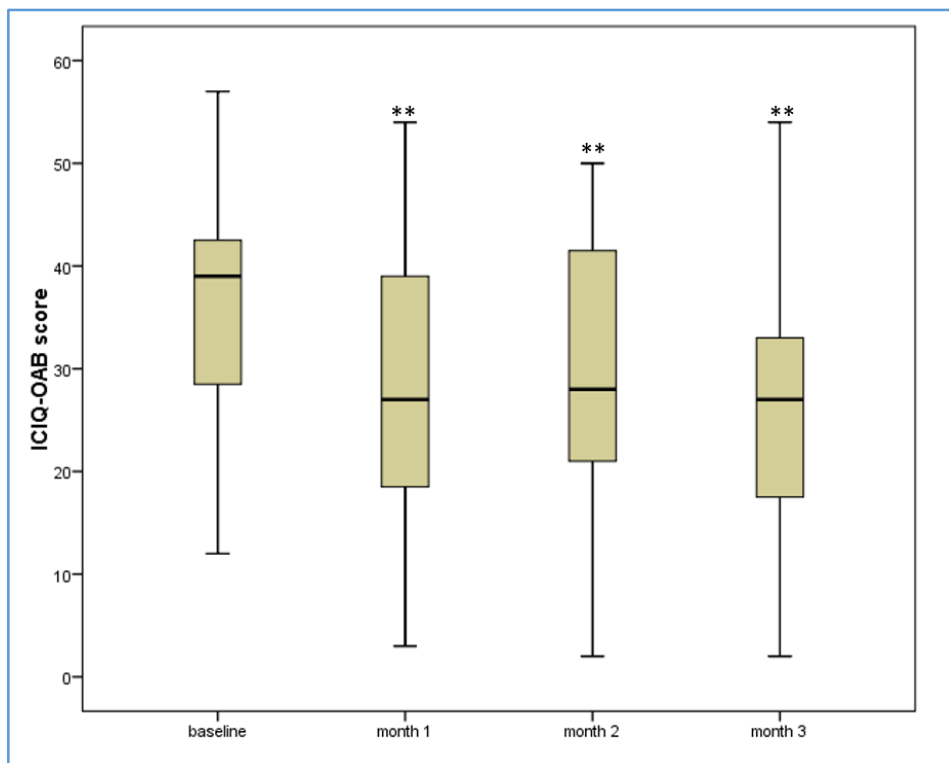
Sling, Burch, APR and surgery for endometrial cancer), and previous treatment (i.e. drug therapy, Botox® injections and pelvic floor muscle training) were collected and described as frequencies (Percentages). The continuous variables at baseline were age, BMI, menopause time, leakage, nocturia, urgency, frequency, PISQ-12, ICIQ-OAB, and UDI-6 reported as mean and standard deviation. Only parity (The number of previous pregnancies lasting more than 22 weeks' gestation) was presented as median value and range. The normal distribution of the outcome measures was investigated using Kolmogorov-Smirnov test. To compare between post-treatment and baseline data, paired samples t-test or non-parametric Wilcoxon rank test was performed. A p-value < 0.05 was considered statistically significant.

**RESULTS**

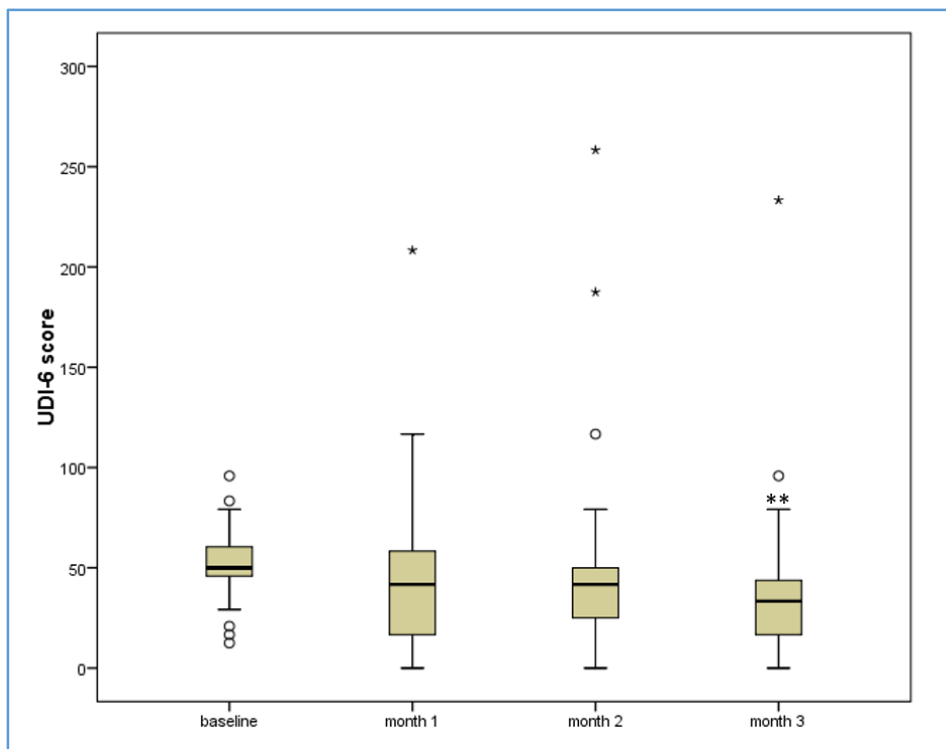
This study consisted of 31 women with established OABS. Their demographic characteristics were summarized in Table 1. The mean age, mean BMI, and mean menopause time were 63.5 ± 9.5 years, 25.5 ± 4.9 kg/m<sup>2</sup>, and 13.9 ± 9.7 years, respectively. Sexual activity status was stratified as active (n=14) versus inactive (n=17). A total of 6 cases (19.6%) were found to have drug therapy before the CO<sub>2</sub> laser therapy. There was no case with a history of Botox® injections and pelvic floor muscle training. Moreover, some patients reported previous surgery: caesarean section (3.2%), HX (38.7%), TOT (3.2%), and APR (22.6%). All patients who were recruited in the present study completed the three sessions.

Mean Age (SD), in years	63.5 (9.5)
Mean BMI (SD), kg/m <sup>2</sup>	28.5 (4.9)
Mean Menopause Time (SD), in years	13.9 (9.7)
Married, n (%)	
Parity, Median (Range)	5 (1-22)
Type of Delivery, n (%)	
Caesarean Section	1 (3.2)
Normal Vaginal Delivery	30 (96.8)
Hypothyroidism, n (%)	6 (19.4)
Diabetes Mellitus, n (%)	6 (19.4)
<b>Table 1. Demographic Characteristics of the Study Participants</b>	

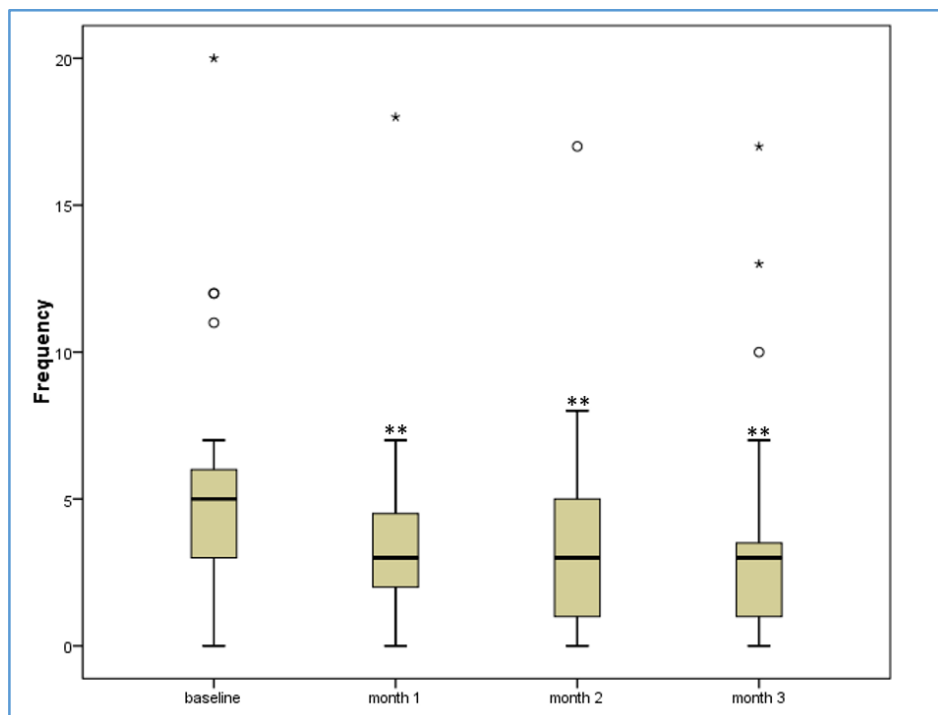
Figure 1 shows the changes of ICIQ-OAB scores prior to and following the CO<sub>2</sub> laser therapy. At the first laser session (month 1), the mean score of ICIQ-OAB significantly decrease from 35.0 ± 10.8 to 26.3 ± 13.6 (p = 0.003), which was followed by a slight increase at month 2 (27.5 ± 13.4), however, still notably lower than the mean scores at baseline (p = 0.031). Further amelioration in the ICIQ-OAB score was observed at the third treatment session (24.7 ± 13.1) (p = 0.001). As can be seen in Figure 2, upon administration of laser treatment, the mean score of UDI-6 declined to 44.3 ± 40.5 at months 1 (p = 0.355) and 42.5 ± 36.3 at month 2 (p = 0.390) when compared to the baseline (51.0 ± 17.5), although it was not statistically significant. At the last laser session, a marked reduction (37.6 ± 42.6) occurred in the mean score of UDI-6 (p = 0.001). The number of urgencies significantly reduced from 5.8 ± 4.3 at baseline to 3.4 ± 3.4 at month 1 (p < 0.001), 3.4 ± 3.5 at month 2 (p = 0.001), and 3.3 ± 4.1 month 3 (p < 0.001) (Figure 3).



**Figure 1. ICIQ-OAB Scores are Demonstrated by Box Plots (Medians, 1<sup>st</sup> and 3<sup>rd</sup> Quartiles, Minimum and Maximum Values, and Outliers). Statistical Analysis was Performed using Paired Samples t-test; \*\* indicates p<0.05.**



**Figure 2. UDI-6 Scores are Demonstrated by Box Plots (Medians, 1<sup>st</sup> and 3<sup>rd</sup> Quartiles, Minimum and Maximum Values, and Outliers). Statistical Analysis was Performed using Paired Samples t-test for Months 1 and 2, and Wilcoxon Signed Ranks Test for Month 3; \*\* indicates p<0.05.**



**Figure 3. Frequency of Urgency is Demonstrated by Box Plots (Medians, 1<sup>st</sup> and 3<sup>rd</sup> Quartiles, Minimum and Maximum Values, and Outliers). Statistical Analysis was Performed using Paired Samples t-Test for the Months 1 and 2, and Wilcoxon Signed Ranks Test for the Month 3; \*\* indicates p<0.05.**

Table 2 summarized the changes in other OABS symptoms (i.e., frequency, leakage, and nocturia) and sexual function using PIISQ-12. No marked improvement occurred in the number of frequencies, leakage, and nocturia during treatment visits when compared to the baseline ( $p > 0.05$ ). The PIISQ-12 was only used for sexually active persons. It was found that laser treatment did not affect sexual function ( $p > 0.05$ ).

Variable	Baseline	Month 1		Month 2		Month 3	
	Mean $\pm$ SD	Mean $\pm$ SD	Baseline to Month-1 p-Value	Mean $\pm$ SD	Baseline to Month-2 p-Value	Mean $\pm$ SD	Baseline to Month-3 p-Value
Frequency	8.4 $\pm$ 4.2	8.6 $\pm$ 3.7	0.653	7.9 $\pm$ 3.0	0.868	7.9 $\pm$ 2.9	0.905
Nocturia	2.1 $\pm$ 1.8	1.6 $\pm$ 1.3	0.233	1.5 $\pm$ 1.1	0.296*	1.3 $\pm$ 0.9	0.050
Leakage	2.9 $\pm$ 3.2	1.9 $\pm$ 2.2	0.645*	1.5 $\pm$ 1.9	0.397*	1.6 $\pm$ 1.8	0.833*
PISQ Score	12.4 $\pm$ 3.5	12.9 $\pm$ 4.6	0.577	11.6 $\pm$ 5.4	0.601	13.7 $\pm$ 6.4	0.418

*Table 2. Assessment of Change in Outcome Measures*

\* Wilcoxon signed ranks test.

## DISCUSSION

Overactive bladder syndrome is a wide-spread medical condition that may induce considerable disability, decreased quality of life, damaged social relationship, and deteriorated sexual function.<sup>(1,5)</sup> As documented, OABS treatment requires life-long adherence to overcome symptoms and promote quality of life while displaying an appropriate balance between efficacy and adverse effects.<sup>(2)</sup> On the whole, the first therapeutic option to OABS includes conservative measures, namely diet modification, fluid management and pelvic floor rehabilitation, but the outcomes are not satisfactory enough to for many patients. Despite clinical evidence supporting the effectiveness of antimuscarinic agents as the major pharmacological treatment for OABS patients,<sup>(22)</sup> most common side effects experienced are dry mouth, constipation, and blurred vision that culminate in rational discontinuation of such therapy. Furthermore, patients may be apt to avoid the treatment due to lack of sufficient symptom control.<sup>(23)</sup> More recently, mirabegron, known as the first  $\beta_3$ -adrenoceptor agonist, has been proposed that results in bladder relaxation throughout the storage phase of the micturition cycle, with no inhibitory effects on bladder voiding.<sup>(24)</sup> Nonetheless, randomized prospective trials of mirabegron are still limited.<sup>(24)</sup> In the similar fashion, another alternative for the management of OABS is intravesical botulinum toxin that clinical evidence from long-term controlled trial studies is clearly lacking.<sup>(25)</sup> Although, some undesirable complications upon Botox injections have been reported that arise from the drug (local swelling, constipation, transitory asthenia and dry mouth) or the protocol (pain and haematuria).<sup>(25)</sup> When it comes to neuromodulation therapy, the efficacy in reducing symptoms has been revealed among OABS patients, especially those with implanted sacral nerve stimulator.<sup>(26)</sup> The application of such technique fails to reach clinical practice because of invasiveness, costs, and declining function as well as frailty in the elderly and those affected with many medical comorbidities.<sup>(27)</sup> For the first time, this pilot study investigated the efficacy of fractional CO<sub>2</sub> laser for the treatment of OABS in women. The findings revealed that a three-month treatment cycle of laser applications was associated with significant decreases in the ICIQ-OAB score and urgency during a three-month treatment visit. Nocturia, frequency, leakage, and sexual function as additional finding did not improve upon laser administration. Only significant ameliorations were recorded in UDI-6 score at month 3 versus baseline. Consistent with our findings, Perino et al. indicated that vaginal fractional CO<sub>2</sub> laser treatment in postmenopausal women with OABS could cause notable improvements in vulvovaginal atrophy symptoms, micturition diary, number of urge episodes, development of

OABS assessed by Overactive Bladder Questionnaire Short Form, and vaginal health index at T1 (30 days post-treatment).<sup>(15)</sup>

The existing studies have showed the amelioration of sexual function upon laser treatment. Sokol et al. observed improved Female Sexual Function Index scores during follow-ups, which were indicative of enhanced sexual health after treating vulvovaginal atrophy symptoms with fractional laser in patients with genitourinary syndrome of menopause.<sup>(28)</sup> Moreover, Salvatore et al. reported the positive impact of the fractional microablative CO<sub>2</sub> laser on sexual function and overall satisfaction with sexual life in postmenopausal women with vulvovaginal atrophy at 12-week follow-up.<sup>(29)</sup> Their further study has substantiated this finding that following exposure to CO<sub>2</sub> laser, the patient's perception of overall sexual function demonstrated a statistically marked amelioration against genitourinary syndrome of menopause.<sup>(30)</sup> More recently, the rise in sexual gratification and satisfaction with fractional CO<sub>2</sub> laser treatment have been also reported in either peri- or postmenopausal women.<sup>(31)</sup> Despite differences in the study design and targeted patients, our results revealed that no improvement occurred in sexual activity of these female patients which can be attributed to the fewer number of sexually active patients in our study.

The main influences of OABS, such as urinary urgency, frequency, and nocturia, can be justified by changes in the anatomical features of the urogenital tissue, which highly depends on the effects of oestrogen; it has been documented that oestrogen receptors have appeared in the urethra and bladder trigone, besides in the round ligaments and levator ani muscles.<sup>(32)</sup> Akin to what found in vaginal tissue, the promotive reduction in oestrogens during the climacteric leads to atrophy of the urethral and bladder mucosa, thereby OAB symptoms, denoting that muscle atrophy along with diminished collagen content could account for urinary incontinence.<sup>(33)</sup> Interestingly, it has been reported that laser irradiation can impact deeper layers of the vaginal wall and, in the long run, stimulate components of the extracellular matrix, particularly collagen production.<sup>(14)</sup> Such positive effects could be carried over to the lower urinary tract (Urethra and bladder), which, in turn, bring about a substantial improvement of urogenital aging symptoms. In so doing, use of laser treatment with these regenerative characteristics can outweigh use of oestrogens or other local therapies that only involve the epithelium. With this mechanism in mind if larger studies can approve the effects of laser treatment, it is more likely to utilize it for menopausal patients who are unresponsive to maintenance therapies or intolerant to drug administration, or have prohibition of oestrogen therapy. This study had some limitation, including

the lack of randomization, patient blinding or a control group. Moreover, a larger sample size is required to assure statistical differences. Another significant issue associated with the potentialities of this approach regards the difficulty in following patients over long periods of time.

### CONCLUSION

In this pilot study, it was found that fractional CO<sub>2</sub> laser could be effective in the amelioration of some OABS symptoms in menopausal women. Further investigations with a larger sample size and long-term follow-ups are required to substantiate these preliminary findings.

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