

Fractional carbon dioxide laser for the treatment of facial atrophic acne scars: prospective clinical trial with short and long-term evaluation

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Received: 12 April 2017 / Accepted: 5 September 2017 / Published online: 11 September 2017
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Abstract The aim of this study was to evaluate the efficacy and safety of fractional carbon dioxide laser for the treatment of acne scars. Thirty-one participants, 15 female and 16 male, whose mean age was 34.84 ± 10.94 years, were included in this prospective study. The study took place between 2012 and 2016. Participants were evaluated with the “ECCA Grading Scale” before the first session, 3 months (short-term evaluation) and 3 years after the last session (long-term evaluation). Participants received two or three treatment sessions at 4-week intervals, with a 10,600 nm fractional carbon dioxide laser with pulse energies ranging between 100 and 160 mJ, 120 spot type, 75–100 spot/cm² density, and 30 W power. Self-assessments by the participants were done 3 months and 3 years after the last session. The mean ECCA score was 107.90 ± 39.38 before the first session, and 82.17 ± 36.23 at the time of short-term evaluation ($p = 0.000$). The grade of improvement at the short-term evaluation was as follows: no improvement, mild, moderate, and significant improvement for 7 (22.6%), 11 (35.5%), 9 (29%), and 4 (12.9%) of the participants, respectively. Regarding self-assessments, 80.6 and 61.3% of the participants rated themselves as having at least mild improvement at the short-term and the long-term follow-up periods, respectively. The results of this study suggest that fractional carbon dioxide laser is an efficient treatment option for acne scars. Furthermore, self-

assessment results show that more than half of the participants still experience at least mild improvement at the end of 3 years.

Keywords Laser therapy · Laser resurfacing · Fractional laser · Ablative laser · Acne scar · Acne vulgaris

Introduction

Acne is one of the most frequent chronic inflammatory dermatoses. It has a prevalence of over 80% among adolescents and persists into adulthood in up to 50% of cases [1–3]. It can negatively affect quality of life, self-esteem, and mood in adolescents, and is associated with an increased risk of anxiety, depression, and suicidal ideation [4]. Unfortunately, permanent scars may occur during the healing of active acne lesions. Acne scarring can be broadly divided into two major categories: atrophic and hypertrophic. The wound-healing process can result in either loss of collagen underlying the lesion as seen in the atrophic scars or overproduction of collagen as seen in the hypertrophic scars [5].

While the most important point is to prevent scar formation through effective treatment of acne, a variety of modalities have been used to treat acne scars including punch techniques, subcision, dermabrasion, needling, chemical peels, fillers, and laser skin resurfacing [6]. Laser skin resurfacing with ablative, nonablative, and fractional laser technologies are also in the use for the treatment of acne scars [7–9]. Although the conventional ablative laser is an effective treatment for skin resurfacing, prolonged downtime and complications such as bleeding, edema, infection, scarring, dyspigmentation, line of demarcation limit its widespread use. The absence of epidermal damage with nonablative resurfacing significantly decreases the side-effect profile; however, it is a well-known fact

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that the nonablative lasers produce less effective results than the conventional ablative lasers [10–12]. Most recently, fractional ablative technologies have overcome the higher side-effect profile of the ablative lasers and shortened the downtime while still achieving significant clinical outcomes comparable with the conventional ablative lasers [13, 14].

Fractional ablative lasers create microscopic columns of thermal injury, namely, microscopic thermal zones (MTZs) in the epidermis and dermis and stimulate the wound-healing response [14–16]. MTZs are surrounded by untreated normal tissue, which help in rapid reepithelialization of the skin with reduced downtime and reduced adverse reactions compared to the treatment with conventional ablative lasers. We see in the literature that these columns comprise approximately 15 to 82% of the skin surface area per treatment session; however, depending on the preferred laser parameters and the number of passes, the percentage of the thermally ablated tissue may be substantially widened [11, 15–18]. Although numerous papers have recently been published on ablative fractional resurfacing for acne scars, lack of information on the long-term results persist [19]. The aim of the present study was to evaluate the short-term and the long-term efficacy and safety of the fractional carbon dioxide laser in treating facial atrophic acne scars.

Materials and methods

Participants

This study took place in the Cosmetology and Laser Unit of the Department of Dermatology, Hacettepe University Faculty of Medicine between 2012 and 2016. Among those participants who were admitted to the outpatient clinics between May 1, 2012 and September 30, 2012, individuals who met the inclusion criteria were enrolled in the study. During October 1, 2012 and April 30, 2013, applications were done and the short-term follow-up was completed. The long-term follow-up was completed in 2016.

Participants with atrophic facial acne scars who were 18 years and older, with a skin phototype I, II, or III were recruited for the study. Exclusion criteria were pregnancy, lactation, history of hypertrophic scars or keloid formation, having skin phototype IV or above, active dermatitis, infection or malignancy over the treatment area, having received light source, radiofrequency, or laser skin resurfacing treatments 6 months before the study, active acne lesions, and systemic retinoid intake in the previous 6 months. Informed written consent was obtained from all participants.

Before the procedure

Starting 2 days before the procedure, participants received herpes infection prophylaxis, with oral antiviral tablet containing Valacyclovir, 500 mg, twice a day, for 5 days. None of the participants received oral and/or topical antibacterial drugs for prophylaxis. A topical anesthetic cream (mixture of 2.5% lidocaine and 2.5% prilocaine) was applied topically to the entire face under occlusion for 45 min prior to laser therapy after which the face was cleansed with normal saline solution and then dried. Right before the procedure an oral analgesic containing paracetamol was given orally and corticosteroid (40 mg/mL) was applied intramuscularly.

Pre-procedure assessment

Photographs were taken at baseline; before every application; and 1, 2, and 3 months and 3 years after the final application. Acne scars were graded by using ECCA (échelle d'évaluation clinique des cicatrices d'acné) grading scale [20]. With this grading scale, the total score can vary from 0 to 540. The overall score was determined as the "acne scar score". All assessments were done by two independent physicians and the mean value of the two assessments was calculated.

Level of improvement

A 25% or less decrease in the acne scar score was defined as "mild improvement," 26–50% decrease as "moderate improvement," 51–75% decrease as "significant improvement," and over 75% as "near total improvement". Lack of decrease in the acne scar score was defined as "no change" and an increase in the score was defined as "worsening".

Self-assessments by the participants were done 3 months after the last session and was scored as follows: – 1 as "worsening", 0 as "no change", 1 as "mild improvement", 2 as "moderate improvement", 3 as "significant improvement," and 4 as "near total improvement". For the long-term self-assessment participants were called by telephone and asked to do the same self-assessment 3 years after the last session.

Procedure

After removing the topical anesthetic cream and assuring that the face is completely dry, fractional carbon dioxide laser (Lutronic, eCO₂, Seoul, South Korea) was applied with a 120 μm spot size, 75–100 spot/cm² density, 30 W power, and pulse energies varying between 100 and 160 mJ, depending on the severity of the scars. Patients with deeper scars were treated using higher parameters, whereas patients with mild to moderate scars were irradiated with lower parameters. At the first pass, only the atrophic scars were treated using 4 mm square

pattern, 120–160 mJ pulse energy, and 100 spot/cm² density in the static operating mode with a percent coverage between 9.3 and 10.5%. At the second pass, the whole face was treated using 12 mm square pattern, 100 mJ pulse energy, and 75–100 spot/cm² density in the static operating mode with a percent coverage between 6.4 and 8.6%. In order to prevent a demarcation line formation, the untreated skin between the treated squares were additionally treated with the dynamic operating mode with 10 mJ pulse energy and a pulse rate of 50 Hz. The device produces 1.2 mm ablation depth when used with a setting of 100 mJ pulse energy and 100 spots/cm² density [21].

Right after the procedure, participants' faces were cooled by ice bags, wet dressings were applied with cooled tap water, and cold application was continued for approximately 30 min until the burning sensation eased off, and a thin layer of dexpanthenol cream was applied. During the procedure, a visual analog scale (VAS) was used to determine the amount of pain felt by the participants. No pain was scored as 0, and intolerable pain was scored as 10 in this scale. Pain at the 10th minute of the laser application was rated.

After the procedure

Participants were first assessed on the postoperative third and then on the seventh days for the presence of erythema, edema, pinpoint bleeding, herpes infection, bacterial infections, acne, milium cyst, dyspigmentation, and ectropion.

Short-term results were assessed 3 months after the last session, and long-term results were assessed 3 years after the last session.

Statistical analysis

Statistical analyses performed by IBM SPSS for Windows Version 21.0 statistical package. Continuous variables presented as mean \pm standard deviation and median [minimum–maximum]. Categorical variables summarized as frequencies and percentages. Wilcoxon sign-rank test was used to show the differences between dependent groups. For ordinal categorical variables with more than two categories, marginal homogeneity test was used. A *p* value less than 0.05 described as significant.

Results

Participants

A total of 31 participants, 15 (48.4%) female and 16 (51.6%) male who met the inclusion criteria, were recruited to the

study. Mean age was 34.84 ± 10.94 years, median 34 years, ranging from 18 to 59 years. Twenty-one (67.8%) participants had skin phototype III and 10 (32.2%) had skin phototype II. None of the participants had a history of photosensitivity. Ten participants were smokers, 1 was a regular alcohol drinker, 2 had history of frequent herpes infection, and 5 had herpes infection in the past 3 months. Twenty-nine of the 31 (93.5%) participants received three sessions, whereas 2 (6.5%) participants received two sessions of fractional carbon dioxide laser applications at 4-week intervals. Three participants (9.7%) were lost to follow-up after three sessions of application. Twenty-eight (90.3%) patients had 3 months of follow-up after the last application, and 3 years after the last application, 6 (19.3%) patients were still under follow-up. All of the 31 participants were reachable by telephone at the end of the third year.

Short-term results

The mean baseline acne scar score was 107.90 ± 39.38 , (median 105, range 40–210); whereas 3 months after the last session, it was 82.17 ± 36.23 (median 77.50, range 25–162). The acne scar score at baseline and at the end of the short-term follow-up period was statistically significantly different ($p = 0$). The level of improvement was found as “no change” in 7 (22.6%), “mild improvement” in 11 (35.5%), “moderate improvement” in 9 (29%) and significant improvement in 4 (12.9%) participants. None of the participants had either near total improvement or worsening. The level of improvement observed at the end of short-term follow-up period is shown in Fig. 1. The level of improvement between smokers and non-smokers was not statistically significantly different ($p = 0.2$).

Level of improvement assessed by the participants

Participants' self-assessment scores 3 months after the last session showed that 6 (19.4%), 11 (35.5%), 7 (22.5%), and 1 (3.2%) of participants rated themselves as having mild, moderate, significant, and near total improvement, respectively. Two participants (6.4%) reported worsening and 4 participants (12.9%) reported no change. There was no statistically significant difference between the level of improvement assessed by the physicians and the level of improvement assessed by the participants ($p = 0.1$).

Participants' self-assessment scores 3 years after the last session showed that 7 (22.5%), 8 (25.8%), and 4 (12.9%) of the participants rated themselves as having mild, moderate, and significant improvement, respectively. One participant (3.2%) reported worsening and 9 participants (29%) reported no change. Fifteen participants (48.3%) rated themselves as having the same improvement score and 3 (9.7%) participants rated themselves even better. The ages of these 3 participants

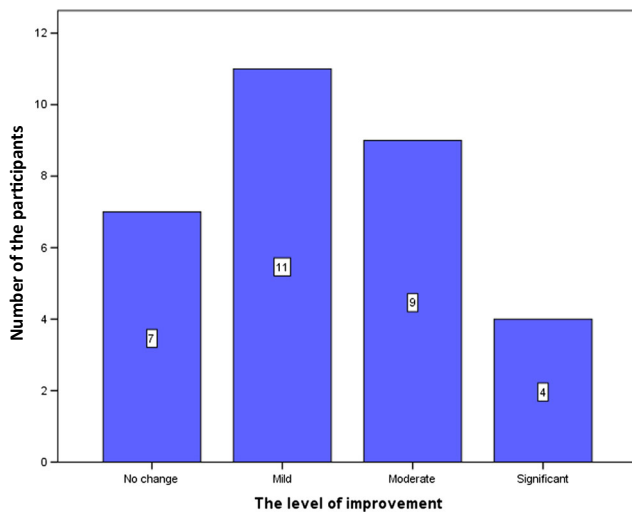


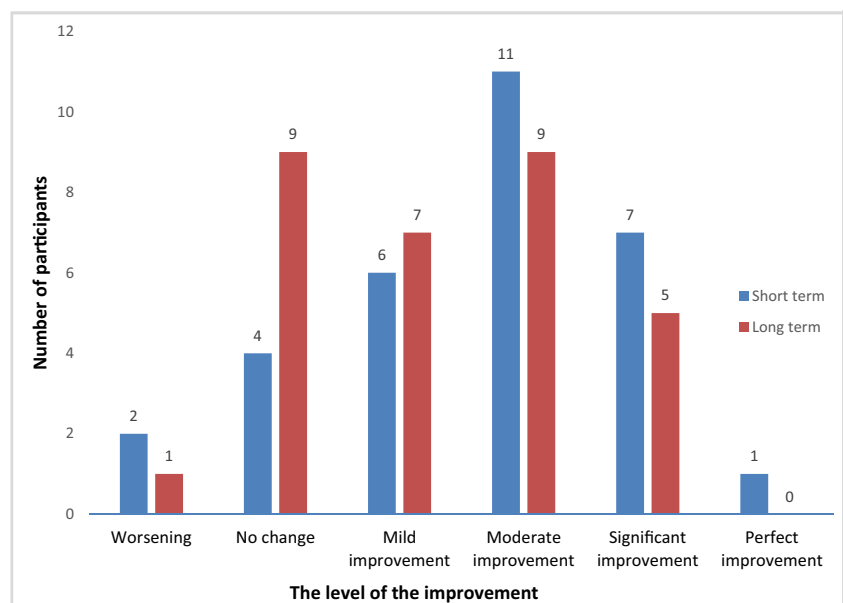
Fig. 1 Short-term results of the level of improvement observed by the physicians

were 30, 42, 49, and none of them were smoking. Participants' self-assessment scores at the end of the short-term and the long-term follow-up period did not change significantly ($p = 0.052$). Comparison of the level of improvement assessed by the participants at the end of the short-term and the long-term follow-up period are observed in Fig. 2.

Long-term results

Three years after the last session, all patient were called and reached by telephone. Six out of 31 patients accepted to be re-evaluated and re-photographed. All patients agreed to re-do the self-assessment. For those 6 patients who were followed

Fig. 2 The level of improvement assessed by the participants at the end of the short-term and the long-term follow-up period



up 3 years after the last session, the mean baseline acne scar score was 100.8 ± 18.2 (range 70–120). At the end of the long-term follow-up period, the mean acne score was 55 ± 18.6 (range 35–80). The acne scar score at baseline and at the end of the long-term follow-up period was statistically significantly different ($p = 0.01$). Clinical pictures of some participants before and after the applications are seen in Figs. 3–4.

Side effects

The mean pain level evaluated by VAS during the procedure was 5.32 ± 2.62 (median 5, range 1–10). Twenty-six participants (83.9%) had erythema on the third day, this number was 19 (61.3%) on the seventh day. Four participants (12.9%) had edema on the third day, with only 1 (3.2%) having edema on the seventh day. On the third day, 17 (54.8%) participants had pinpoint bleeding, whereas on the seventh day, this was reduced to 1 (3.2%) participant. Hyperpigmentation longer than 1 month duration which necessitated treatment was observed in 6 (19.4%) participants. Herpes infection, bacterial infections, and milium cyst did not occur in any participants. Four (12.9%) participants had acne exacerbation and required treatment. Five female participants (16.1%) had hypertrichosis, which required epilation.

Discussion

Acne vulgaris is one of the most prevalent skin condition for adolescents and young adults [22]. Scarring is a common result of acne, which often occurs in highly visible areas such as the face.

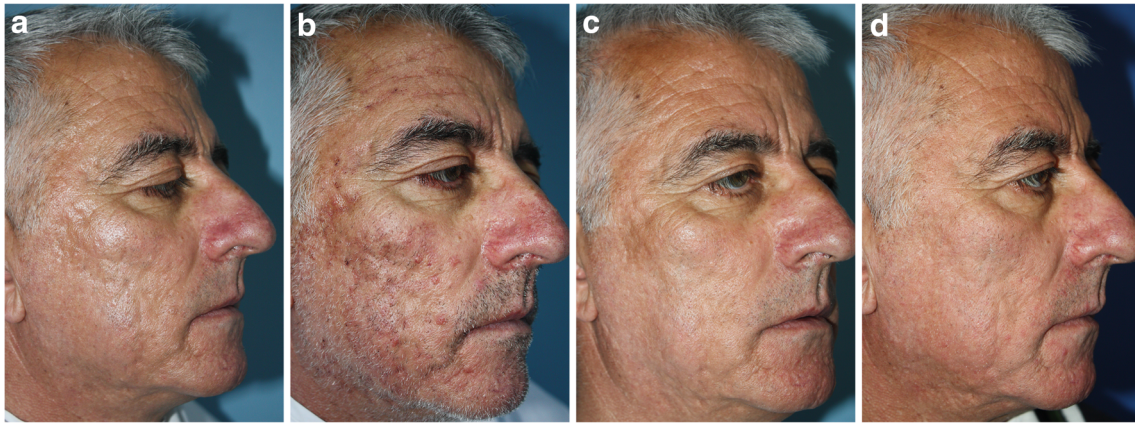


Fig. 3 Photos of the patient number 20 at baseline (a), 3 days after the session (b), 3 months (c), and 3 years (d) after the last session

Several classifications and scales have been proposed for facial acne scarring [20, 23–25]. In order to provide objective comparisons among studies, it is important to assess outcomes with standardized, validated scoring tools. In the current study, we used ECCA grading scale. The potential advantages of this scale include independent accounting of specific scar types, thereby providing separate atrophic and hypertrophic subscores in addition to total scores. Also scars that are more visibly disfiguring are weighted more heavily with this scale.

Comparing different treatment methods for the treatment of acne scars is rather difficult. A systematic review comparing the ablative and nonablative fractional photothermolysis (FP) for acne scars found that the ablative FP had an improvement range of 26–83%, whereas nonablative FP had an improvement range of 26–50% [9]. In a split-face study which included 8 patients, Cho et al. reported that there was no statistically significant difference for the improvement of the acne scars when a single treatment of ablative FP and nonablative FP was compared [26].

A split-face RCT of fractional carbon dioxide laser showed that a laser setting of high fluence, low density (a fluence of 70 mJ and a density of 150 spots/cm²) achieved better results than a setting of low fluence, high density (a fluence of 30 mJ

and a density of 250 spots/cm²). The mean grade of clinical improvement was reported 2.4 ± 0.5 for low-fluence, high-density settings and 3.3 ± 0.8 for high-fluence, low-density settings ($p = .02$) [27]. In the current study, we used 100–160 mJ fluences and 75–100 spot/cm² density. We applied higher energies on the top of the atrophic scars with a small pattern of 4 mm size at the first pass, and lower energies for the full face using larger patterns of 12 or 16 mm size at the second pass.

Manuskiatti et al. found that 6 months after one session of fractional carbon dioxide laser application 85% of the subjects had at least 25 to 50% improvement of the atrophic acne scars [28]. All of the 13 Asian subjects included in that study rated themselves as having at least 25 to 50% improvement and 62% of them rated themselves as having at least 50% improvement. Chapas et al. reported at least 26 to 50% improvement in texture, atrophy, and overall improvement after two or three treatments with a fractional carbon dioxide laser device. Furthermore, a 3-dimensional optical profiling system demonstrated that 100% of the patients had objective improvement in the depths of acneiform scars with an overall mean improvement of 66.8% [29]. In accordance with the literature in the current study, we found that 77% of the participants



Fig. 4 Photos of the patient number 30 at baseline (a), 3 days after the session (b), 3 months (c), and 3 years (d) after the last session

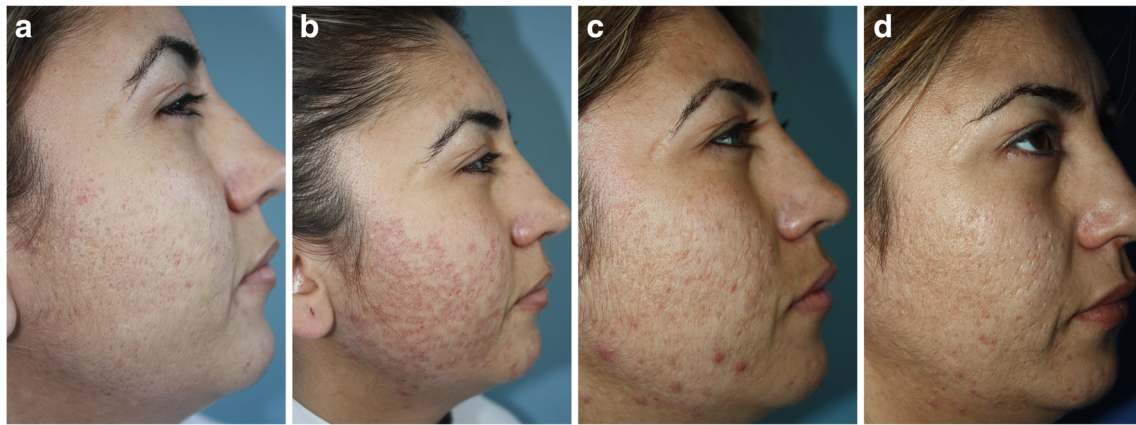


Fig. 5 Photos of patient number 4, who had hypertrichosis, at baseline (a), 3 days after the session (b), 3 months (c), and 3 years (d) after the last session

were having at least mild improvement. As far as we know, the long-term effect of fractional ablative laser on acne scars is rarely reported [19]. In this study, we were able to re-evaluate one fifth of the participants 3 years after the last session, and interestingly, we have found that some of these patients experienced further improvement of the acne scars without any further treatment. We believe this clinical finding reflects and is in accordance with the histopathological studies regarding fractional ablative resurfacing, which point out that the collagen remodeling is still present 3 months after treatment. Histopathological studies frequently report changes within 2–6 months after the treatment [14, 30–33] and relatively few studies report changes after 1 year [34]. We all know that transforming growth factor-beta (TGF- β) is considered to play an important role in the wound-healing process including inflammation, angiogenesis, reepithelialization, and connective tissue reconstruction [35–37]. It would be interesting to investigate the factors that trigger rejuvenation at the cellular level, even 3 years after fractional carbon dioxide laser ablation.

Regarding self-assessments, 80.6 and 61.3% of the participants rated themselves as having at least mild improvement at the short-term and the long-term periods, respectively. When long term self-assessments were taken into consideration, 15 participants rated themselves as having the same improvement score and 3 participants rated themselves even better compared to the short-term results. Although one third of the participants were smoker in the study, it was remarkable that none of these 3 participants were smoking. We wish to understand the reason why for those 3 participants the good effect of fractional carbon dioxide laser was durable, despite the common use of same machine, same laser parameters, and same operators.

Interestingly, 5 female participants (16.1%) had hypertrichosis, which required epilation (Fig. 5). The effect of lasers and light sources on hair growth has been discussed for many years. Paradoxical hair growth after laser hair removal is considered as an example of photoinduced hair

growth [38–42]. Stimulation of the hair follicle after wounding is another well-observed issue [43–45]. Moreover, promising results with fractional lasers have been reported not only for female and male patterns of hair loss, but also for alopecia areata [46–48]. In another study, we found an increase in the mean hair count in 7 of 32 (22%) alopecia areata patients on the scalp with lasers [49]. Similar to the hypertrichosis seen in our study, Neiner et al. and Beachkofsky et al. have also reported denovo hair formation after treatment of scars with fractional carbon dioxide laser [50, 51]. The paradoxical hair growth after laser hair removal tends to happen in darker skin phototypes (III–VI) [42, 52]; it is not clear yet whether same trend is valid for fractional ablative lasers. Additional studies are needed to define the risk factors for ablative laser-induced hypertrichosis, such as skin type, sex, and body site, to provide better clinical outcomes for patients. All other side effects observed in this study were in accordance with the current literature and all were reversible.

The results of this prospective study support the idea that fractional carbon dioxide laser application is an effective and safe treatment option for acne scars. Furthermore, self-assessment results show that more than half of the participants still experience at least mild improvement at the end of 3 years.

Compliance with ethical standards

Ethical approval This study was approved by the Hacettepe University Ethics Committee of Clinical Studies, with the code of KA-12-0043. This study was also approved by the Turkish Ministry of Health Turkish Medicines and Medical Devices Agency with the code of 0089075. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A written informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Conflict of interest The laser device used in this study was delivered to Hacettepe University according to the “Contract of Donation for Scientific Studies” by Cosmoplus Company. The authors have no conflict of interest.

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