Fractional versus ablative erbium:yttrium-aluminum-garnet laser resurfacing for facial rejuvenation: An objective evaluation

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Background: Laser is one of the main tools for skin resurfacing. Erbium:yttrium-aluminum-garnet (Er:YAG) was the second ablative laser, after carbon dioxide, emitting wavelength of 2940 nm. Fractional laser resurfacing has been developed to overcome the drawbacks of ablative lasers.

Objective: We aimed to objectively evaluate the histopathological and immunohistochemical effects of Er:YAG 2940-nm laser for facial rejuvenation (multiple sessions of fractional vs single session of ablative Er:YAG laser).

Methods: Facial resurfacing with single-session ablative Er:YAG laser was performed on 6 volunteers. Another 6 were resurfaced using fractional Er:YAG laser (4 sessions). Histopathological (hematoxylin-eosin, orcein, Masson trichrome, and picrosirius red stains) and immunohistochemical assessment for skin biopsy specimens were done before laser resurfacing and after 1 and 6 months. Histometry for epidermal thickness and quantitative assessment for neocollagen formation; collagen I, III, and VII; elastin; and tropoelastin were done for all skin biopsy specimens.

Results: Both lasers resulted in increased epidermal thickness. Dermal collagen showed increased neocollagen formation with increased concentration of collagen types I, III, and VII. Dermal elastic tissue studies revealed decreased elastin whereas tropoelastin concentration increased after laser resurfacing. Neither laser showed significant difference between their effects clinically and on dermal collagen. Changes in epidermal thickness, elastin, and tropoelastin were significantly more marked after ablative laser.

Limitations: The small number of patients is a limitation, yet the results show significant improvement.

Conclusion: Multiple sessions of fractional laser have comparable effects to a single session of ablative Er:YAG laser on dermal collagen but ablative laser has more effect on elastic tissue and epidermis. (J Am Acad Dermatol 2013;68:103-12.)

Key words: collagen; elastin; epidermal thickness; erbium:yttrium-aluminum-garnet; fractional; skin aging.

Ablative laser resurfacing remains the gold standard for rejuvenating severely photodamaged facial skin, but it is associated with long-term sequel-related patient downtime (delayed re-epithelialization and postlaser erythema which may lead to hyperpigmentation). Recently, fractional resurfacing has been introduced in the dermatologist's armamentarium as an alternative to ablative laser resurfacing, designed to decrease the photothermal side effects while still achieving good results, with faster healing and significant reduction in downtime.[1]

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Erbium:yttrium-aluminum-garnet (Er:YAG) laser emits a wavelength of 2940 nm that closely approximates absorption peak of water, therefore nearly all its energy is absorbed in the epidermis and papillary dermis, yielding superficial ablation.[2] Each pass of Er:YAG 2940-nm laser (250-350 microseconds) ablates approximately 20 to 25 μm at 5 J/cm^2 (4 μm of tissues per J/cm^2). Depth of thermal damage has been shown to be 30 to 50 μm beyond the ablation area.[3,4]

Fractional resurfacing creates microscopic treatment zones (MTZs) of controlled width, depth, and densities; these controlled zones of thermal heating and tissue damage are surrounded by spared areas of viable epidermis and dermis that allow for rapid repair of the MTZs.[5]

Although not equaling the results seen after conventional ablative resurfacing treatment, clinically notable improvements in facial rhytides, photodamage, and even in skin laxity have been reported with the new ablative fractional laser devices even after a single treatment.[6] However, fractional resurfacing with Er:YAG laser will usually require multiple sessions to enhance the condition of moderate to severely photoaged skin.[1]

The aim of this study was to objectively evaluate and compare the effects of multiple sessions of fractional laser versus a single session of ablative Er:YAG laser resurfacing both histopathologically and immunohistochemically after 1 month and 6 months of laser facial rejuvenation.

CAPSULE SUMMARY

- Ablative laser resurfacing remains the gold standard for rejuvenating severely photodamaged facial skin, but it is associated with long-term sequel-related patient downtime (delayed re-epithelialization and postlaser erythema which may lead to hyperpigmentation).
- Both multiple sessions of fractional erbium:yttrium-aluminum-garnet (Er:YAG) laser and a single session, with multiple passes, of ablative Er:YAG laser have comparable efficacy clinically and on dermal collagen.
- Multiple sessions of fractional Er:YAG laser resurfacing are effective with higher safety and shorter downtime.

METHODS

This study was conducted on 12 volunteers who desired facial rejuvenation to improve laxity and wrinkles. The subjects, ranging in age from 35 to 66 years, were recruited from the dermatology outpatient clinic of Al-Minya University Hospital, Egypt. The volunteers had Fitzpatrick skin types III to V, with class II to IV wrinkles based on Glogau scale.[7] The patients were not using any antiaging topical medications and did not perform any other cosmetic procedure. Treatment and study details were fully explained to subjects, and all gave informed consent for laser facial rejuvenation, study participation, and skin biopsy specimens. The volunteers were randomly selected and divided into 2 groups: 6 individuals (2 male and 4 female) were treated by a single session of short pulsed ablative Er:YAG laser, whereas the other 6 volunteers (3 male and 3 female) were treated by 4 sessions of fractional Er:YAG laser.

The clinical changes and improvement were rated and evaluated by the dermatologic surgeon and 2 independent observers before treatment and at 1 and 6 months after the start of treatment, based on a 5-point scale (none = 0%, poor = 1%-25%, fair = 26%-50%, good = 51%-75%, and very good = 76%-100%).

Devices and techniques

Ablative Er:YAG laser resurfacing. The device used for complete or full ablative (traditional) laser resurfacing was SkinPlus Er:YAG device, (Fotona medical laser, Ljabljana, Slovania) (code 51082; model M 220A).

Acyclovir tablets (400 mg/8 hours) were taken 1 day before laser resurfacing and for 5 days after the procedure. The face was covered with a thin layer of topical anesthesia (lidocaine 2.5% and prilocaine 2.5% cream) for 1 hour before the procedure in all patients. Eye protection goggles were applied for the patients. Two to 3 passes of short pulsed ablative Er:YAG laser were applied to ablate the epidermis (points of bleeding) at the forehead and the crow's feet areas with pulse width of 350 microseconds and spot size of 5 mm at a fluence of 3 to 5 J/cm^2 per pass.[4,8,9] Meanwhile, an additional 1 to 2 passes were only performed over the rhytides until they were effaced.

All patients received an oral broad-spectrum antibiotic for 1 week after the procedure. The treated area was covered with Fucidin Intertulle (fusidic acid—impregnated sterile gauze) as a postoperative dressing and covered by facial mask, which was changed every day for 1 week.

Fractional Er:YAG laser resurfacing. The fractional laser device was Fotona ablative fractional laser system Er:YAG 2940-nm model Dualis XS, "Ljabljana Slovania." The laser system has 5 levels, with MTZ (pixel) number ranging from 4 to 256 and MTZ size of 20 to 300 μm according to the selected level.

Acyclovir tablets (400 mg/8 hours) were given 1 day before the fractional laser sessions and for 3 days after resurfacing. No anesthesia was needed;

70% ethyl alcohol was used to clean the skin before and after it had been sterilized by povidone iodine. Patient eye-protection goggles were used. The fractional Er:YAG 2940-nm laser was used at a fluency of 1200 mJ/cm^2, with a pixel number of 30/cm^2, pixel size of 270 μm via the short-pulse mode (300 microseconds), and 10-mm spot size.

Volunteers were subjected to 2 months of treatment (4 sessions at 2-week intervals). Four complete laser passes per session were performed over the forehead and crow's feet areas. After treatment a thin layer of fusidic acid antibiotic ointment was applied and the patient was instructed to use it 2 to 3 times each day for 4 days.

After skin re-epithelialization, both groups were instructed to apply sunscreens, with sun-protection factor (SPF) value of 35 or more, every 2 hours during daytime.

Follow-up and assessment

Patients were seen daily for 1 week after the procedure in both groups, then weekly during the first month after resurfacing and monthly for 6 months after the last treatment session. Photographs and skin biopsy specimens (3 mm) from crow's feet area were obtained before treatment, and after 1 and 6 months of treatment. Skin biopsy specimens were processed and sectioned for histometry, and histopathological and immunohistochemical study.

Histologic staining and histometry

Skin biopsy specimens were stained with hematoxylin-eosin, orcein for elastin, and both Masson trichrome and picrosirius red (Direct Red 80, Sigma, St Louis, MO) for collagen. Epidermal thickness was estimated histometrically (mean distance between the outermost surface of the epidermis, excluding the stratum corneum, and the dermoepidermal junction). Five measurements for each skin biopsy specimen were taken by a computer-assisted program (analySIS Five, Olympus Soft Imaging Solutions GmbH, Münster, Germany). Picrosirius red was evaluated using a microscope (Nikon, Melville, NY) equipped with filters to provide circularly polarized illumination. Immunohistochemical and picrosirius red staining were quantified using software (Image-Pro Plus, Media Cybernetics Inc, Silver Spring, MD). Epidermal thickness and immunohistochemical evaluation was done by 2 independent blinded dermatopathologists. For each stain and each marker a single staining technique was used and all specimens were stained at a single session for each marker.

Immunohistochemical study

Immunoperoxidase technique was used for detection of total elastin (1:300; E4013, Sigma), type I collagen (1:400; sc-59772, Santa Cruz, CA), and type III collagen (1:600; ab6310, Abcam, MA).[10,11]

Indirect immunofluorescence was used to evaluate type VII collagen (1:600; sc-33710, Santa Cruz Biotechnology) and tropoelastin (tropoelastin GA317, 1:400; Elastin Products, Owensville, MO).[11,12]

Statistical analysis

The collected data were analyzed using software (SPSS for Windows, Version 16.0, IBM Corp, Armonk, NY). Data were summarized as mean ± SD. Statistical analysis was performed using Student t test, 1-way analysis of variance, and χ^2 tests. Correlation between results was studied using Pearson test to assess the correlation coefficient (r value). Statistical significance for all results was defined as P less than or equal to .05.

RESULTS

Clinical evaluation of study population

Both ablative (1 session) and fractional (4 sessions) Er:YAG laser groups showed comparable clinical improvement (Fig 1), with no statistically significant difference ($P > .05$). Clinical improvement after 6 months of ablative Er:YAG laser resurfacing was rated as: very good (3 patients; 50%), good (2 patients; 33.3%), and fair (1 patient; 16.7%). Complete re-epithelialization occurred within 2 weeks and mild erythema was encountered in 4 cases (66.7%) by the first month and resolved within 3 months.

On the other hand, clinical improvement after fractional Er:YAG laser resurfacing was rated as: very good (2 patients; 33.33%), good (2 patients; 33.33%), and fair (2 patients; 33.33%) with complete healing occurring within 2 to 4 days. By the time of the next session (second week) there was no erythema for any volunteer.

Histometric evaluation of epidermal thickness

Mean epidermal thickness increased significantly 1 month after ablative ($P < .001$) and fractional ($P = .001$) Er:YAG laser resurfacing and then decreased at 6 months ($P = .003$ and $P = .009$, respectively) but was still thicker than pretreatment level (Fig 2 and Table I). Ablative Er:YAG laser induced more significant ($P = .013$) epidermal thickness changes than the fractional type. However, the effects of both lasers on the epidermal thickness were significantly positively correlated ($r = +0.707$, $P = .001$).

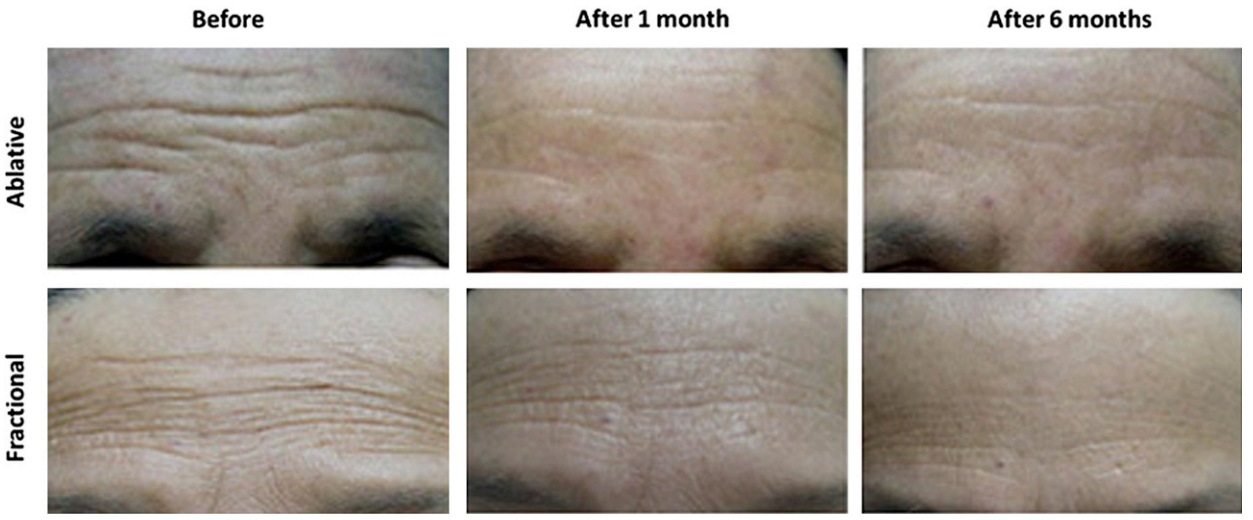

Fig 1. Clinical evaluation of volunteers. Representative photographs showing comparable improvement after ablative and fractional erbium:yttrium-aluminum-garnet 2940-nm laser resurfacing.

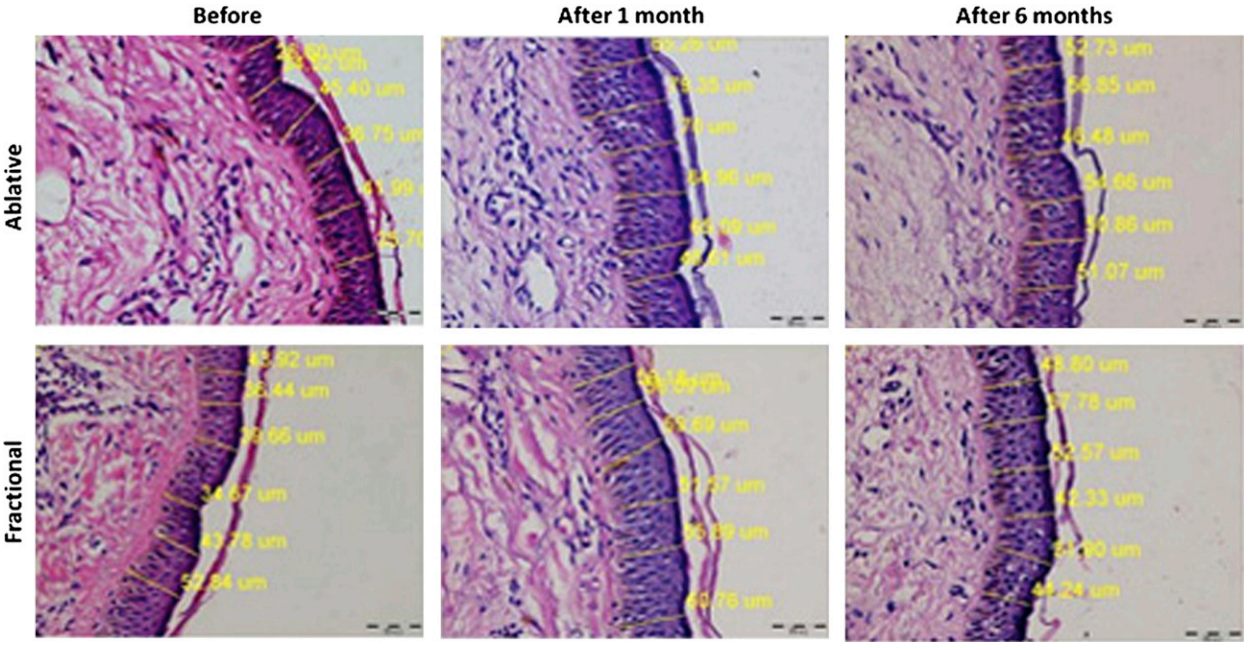

Fig 2. Epidermal histometry. Significant increase in epidermal thickness after 1 month with gradual decrease by 6 months, but still more than before laser resurfacing. (Hematoxylin-eosin stain; original magnifications: ×200.)

Evaluation of dermal collagen

Immunohistochemical quantitative evaluation of collagen type I (Fig 3, *A*) showed increased concentration in ablative and fractional Er:YAG laser groups after 1 month ($P < .001$ and $P = .002$, respectively) and 6 months ($P < .001$ and $P = .014$, respectively) with a statistically significant ($P < .05$) positive correlation in collagen type I content after 1 and 6 months of therapy in both groups. However, there was no significant difference between fractional and ablative Er:YAG laser ($P = .57$) (Table I).

Both lasers also increased collagen type III concentration (Fig 3, *B*) with significant positive correlation ($r = +0.589$, $P < .05$). Collagen type III significantly increased by ablative and fractional laser after 1 month ($P < .001$) and 6 months ($P < .001$). The effects of both laser modalities on collagen III were not significantly different ($P = .563$) (Table I).

Table I. Mean epidermal thickness and concentration of neocollagen; collagen I, III, and VII; elastin; and tropoelastin before, 1 month after, and 6 months after ablative and fractional erbium:yttrium-aluminum-garnet laser resurfacing

	Ablative			Fractional			Unpaired *t* test*
	Before	1 mo	6 mo	Before	1 mo	6 mo	
Epidermal thickness (μm)	37 ± 5.4 $P^{\dagger} < .001^{\ddagger}$	60.9 ± 7.6 $P^{\S} < .001^{\ddagger}$	51 ± 6.4 $P^{\P} = .003^{\ddagger}$	42.8 ± 4.9 $P^{\dagger} < .001^{\ddagger}$	54.1 ± 7.4 $P^{\S} = .001^{\ddagger}$	48 ± 5.5 $P^{\P} = .009^{\ddagger}$	$.013^{\ddagger}$
Neocollagen (Relative content, %)	19.2 ± 1.6 $P^{\dagger} < .001^{\ddagger}$	25.8 ± 1.4 $P^{\S} < .001^{\ddagger}$	33.1 ± 2.7 $P^{\P} < .001^{\ddagger}$	18.4 ± 1.2 $P^{\dagger} < .001^{\ddagger}$	23.7 ± 1.6 $P^{\S} < .001^{\ddagger}$	29.7 ± 0.6 $P^{\P} < .001^{\ddagger}$	.23
Collagen I (Relative content, %)	62 ± 2.4 $P^{\dagger} < .001^{\ddagger}$	66.2 ± 2.1 $P^{\S} < .001^{\ddagger}$	71.9 ± 4.8 $P^{\P} < .001^{\ddagger}$	60.5 ± 2.3 $P^{\dagger} < .001^{\ddagger}$	63.9 ± 2.7 $P^{\S} = .002^{\ddagger}$	71.6 ± 5.4 $P^{\P} = .002^{\ddagger}$	.57
Collagen III (Relative content, %)	55.7 ± 3.2 $P^{\dagger} < .001^{\ddagger}$	63.4 ± 4.7 $P^{\S} < .001^{\ddagger}$	68.3 ± 5 $P^{\P} < .001^{\ddagger}$	56.2 ± 3.7 $P^{\dagger} = .001^{\ddagger}$	58.5 ± 4 $P^{\S} < .001^{\ddagger}$	67.7 ± 5.1 $P^{\P} < .001^{\ddagger}$	.563
Collagen VII (Relative content, %)	10.5 ± 1.2 $P^{\dagger} < .001^{\ddagger}$	14 ± 0.9 $P^{\S} < .001^{\ddagger}$	18.9 ± 2.9 $P^{\P} < .001^{\ddagger}$	11.2 ± 1 $P^{\dagger} < .001^{\ddagger}$	13.8 ± 0.8 $P^{\S} < .001^{\ddagger}$	18.3 ± 1.6 $P^{\P} < .001^{\ddagger}$	.323
Elastin (Relative content, %)	51.6 ± 3.5 $P^{\dagger} < .001^{\ddagger}$	46.6 ± 5.9 $P^{\S} = .005^{\ddagger}$	35 ± 6.7 $P^{\P} < .001^{\ddagger}$	52.6 ± 2.5 $P^{\dagger} < .001^{\ddagger}$	48 ± 4 $P^{\S} = .004^{\ddagger}$	41.7 ± 4.3 $P^{\P} = .001^{\ddagger}$	$.04^{\ddagger}$
Tropoelastin (Relative content, %)	14.1 ± 2.6 $P^{\dagger} < .001^{\ddagger}$	18.5 ± 2.1 $P^{\S} < .001^{\ddagger}$	25.3 ± 2.4 $P^{\P} < .001^{\ddagger}$	14.1 ± 1.5 $P^{\dagger} < .001^{\ddagger}$	17.8 ± 1.9 $P^{\S} < .001^{\ddagger}$	21 ± 1.6 $P^{\P} < .001^{\ddagger}$	$.003^{\ddagger}$

*Ablative versus fractional erbium:yttrium-aluminum-garnet laser groups.
†Analysis of variance; compare before, after 1 month, and after 6 months in same group.
‡Significant: $P \leq .05$.
§Paired *t* test; compare before and after 1 month in same group.
¶Paired *t* test; compare before and after 6 months in same group.

Mature collagen fibers change color under polarized light (birefringence). Large collagen fibers stain red whereas the thinner ones, which represent the newly synthesized fibers, stain yellow to orange.[13,14] We measured the yellow to orange birefringence under a polarized microscope to estimate neocollagen formation by picrosirius red stain (Fig 4, *A*). Both groups showed significantly strong positive correlation in the induction of neocollagen formation ($r = +0.904$, $P < .001$). Both ablative and fractional Er:YAG resurfacing revealed a significant increase in neocollagen formation after 1 month ($P < .001$) and 6 months ($P < .001$) (Table I).

Type VII collagen is the main component of the anchoring fibrils mediating dermoepidermal adherence in human skin.[15] The effect of the aging process on collagen VII biosynthesis and degradation has been previously noted.[16-18] In both groups, collagen type VII has increased (Fig 4, *B*) with significantly positive correlation ($r = +0.947$, $P < .001$) (Table I).

Evaluation of dermal elastic tissue

Orcein stain revealed dense elastotic material in biopsy specimens before treatment, whereas after treatment it decreased in density with downward displacement (Fig 5, *A*). These changes were more evident with ablative laser. Elastin concentration was quantitatively decreased by laser facial resurfacing in both groups (Fig 5, *B*) with a significantly positive correlation ($r = +0.722$, $P = .001$). The elastin changes were significant after 1 and 6 months in both ablative ($P = .005$ and $P < .001$, respectively) and fractional ($P = .004$ and $P = .001$, respectively) Er:YAG lasers. The decreased elastin concentration was significantly greater after ablative Er:YAG laser resurfacing ($P = .04$) (Table I).

Ablative Er:YAG laser resurfacing had significantly ($P = .003$) increased tropoelastin concentration than the fractional one (Fig 5, *C*). The increase in tropoelastin was significant after 1 and 6 months in both groups ($P < .001$). Results in both groups showed significant positive correlation ($r = +0.87$, $P < .001$) (Table I).

New dermal changes in collagen, elastin, and tropoelastin were generally distributed in all specimens in both groups; no focal changes were encountered even in biopsy specimens after fractional Er:YAG laser resurfacing.

DISCUSSION

Laser resurfacing is a cornerstone in facial rejuvenation that may be ablative, nonablative, or fractional, which fills the gap between the ablative and nonablative modalities.[5]

The new concept of fractional photothermolysis was developed to overcome the high risk of side effects caused by ablative lasers, to shorten the downtime after laser treatment, and to give better results than nonablative procedures.[6] In the current study, prolonged healing time was observed after

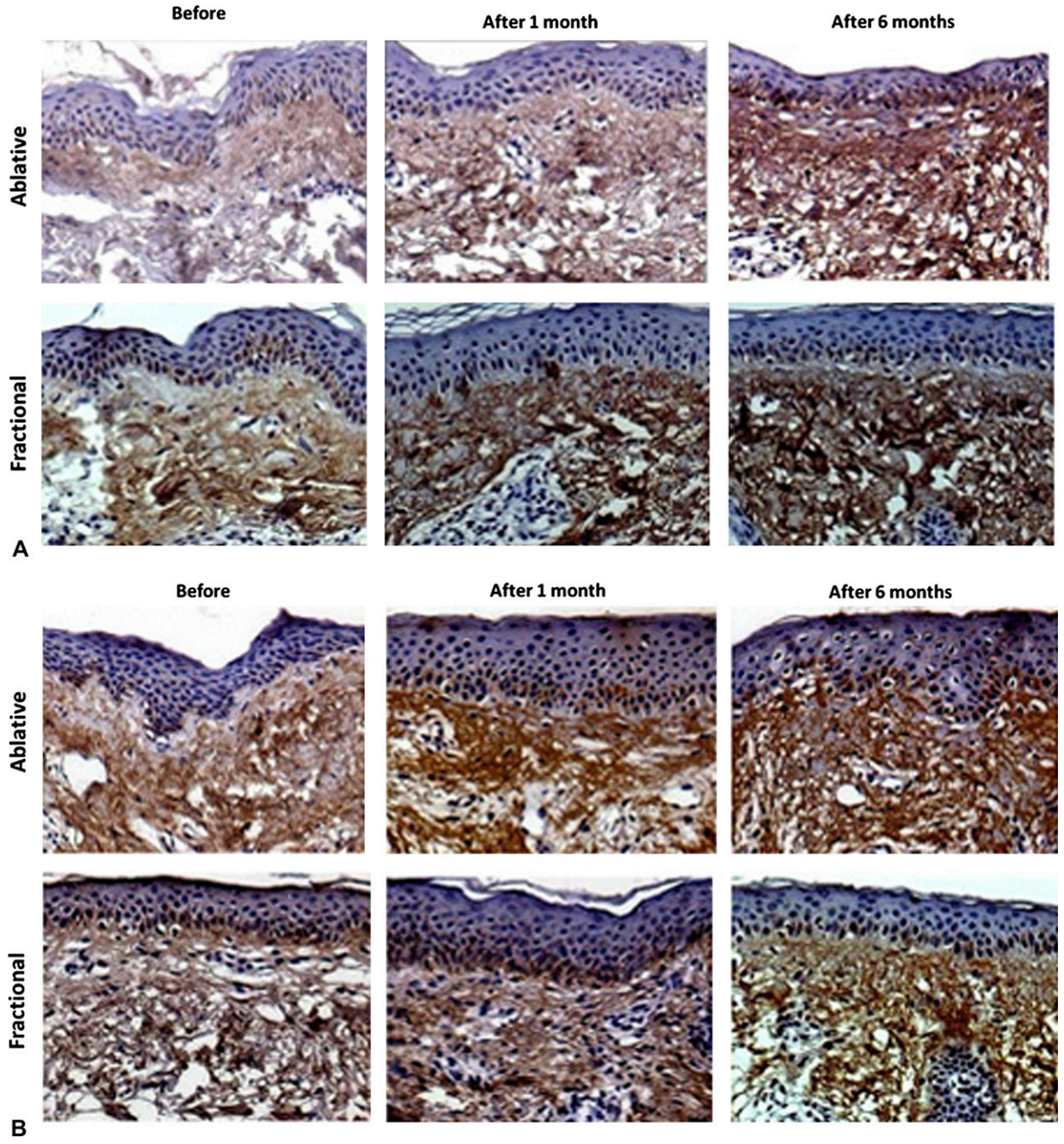

Fig 3. Increase in collagen I **(A)** and collagen III **(B)** concentration after laser resurfacing in both groups. (Immunohistochemistry; original magnifications: ×200.)

ablative Er:YAG resurfacing versus short downtime after fractional laser.

Photodocumentation has also been shown to be an insufficient way of representing the efficacy of treatment. The current work has been conducted to objectively study, evaluate, and compare the histopathological and immunohistochemical changes resulting from fractional (4 sessions) versus ablative (1 session) Er:YAG laser resurfacing for facial rejuvenation.

The dermal matrix in adult skin is composed of collagen in addition to glycosaminoglycans and elastic fibers.[19] Dermal collagen synthesized by fibroblasts is normally composed of 80% to 85% type I collagen and 10% to 15% type III collagen.[20] Reduction of fibrillar collagen is a characteristic feature of chronologically aged skin and is enhanced by photodamage. However, the histologic hallmark of photodamaged skin is accumulation of elastotic materials in papillary dermis, a process known as solar elastosis.[21,22]

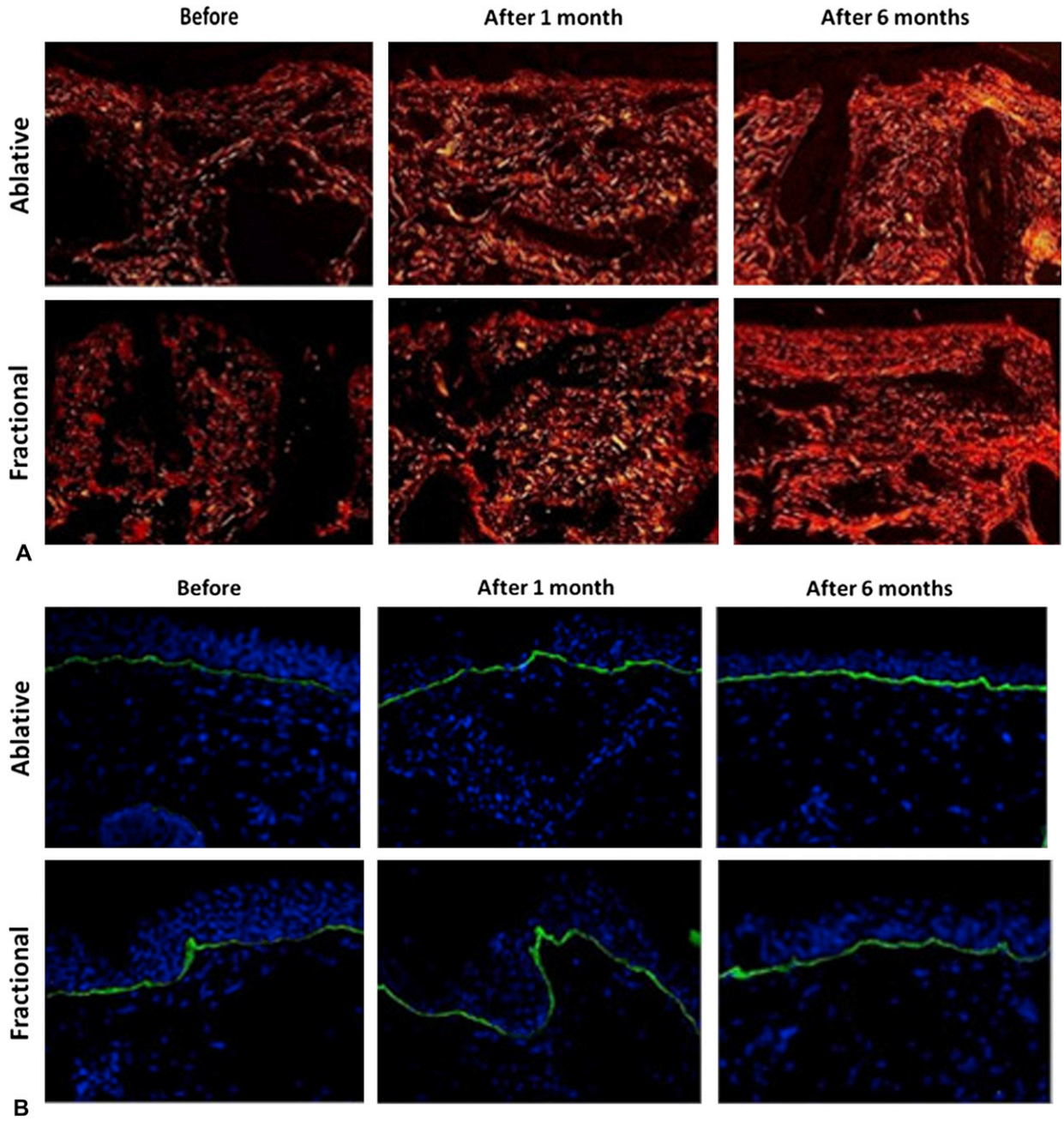

Fig 4. New collagen synthesis and collagen VII. **A**, Increased neocollagen formation after laser resurfacing (*yellow to orange*). **B**, Increased collagen VII fluorescence at dermoepidermal junction after laser resurfacing. (**A**, Picrosirius red stain under polarized light microscopy; **B**, immunofluorescence; **A** and **B**, original magnifications: ×200.)

Er:YAG laser resurfacing induces a significant zone of neocollagen formation, which replaces elastotic material of the connective tissue matrix in papillary dermis of photoaged skin.[23,24]

All previous reports about neocollagen formation were qualitative. In the current study a significant quantitative increase in neocollagen formation and concentration of collagen types I, III, and VII after ablative and fractional Er:YAG laser resurfacing was noticed, with no statistically significant difference between the 2 modalities. The results of the current study confirm those of Orringer et al,[25] who in 2010 reported that fractional photothermolysis—in vivo—increases collagen I and III gene expression and also increases procollagen I protein expression in photodamaged human skin.

After laser treatment, production of collagen, procollagen, and elastin is induced by the laser

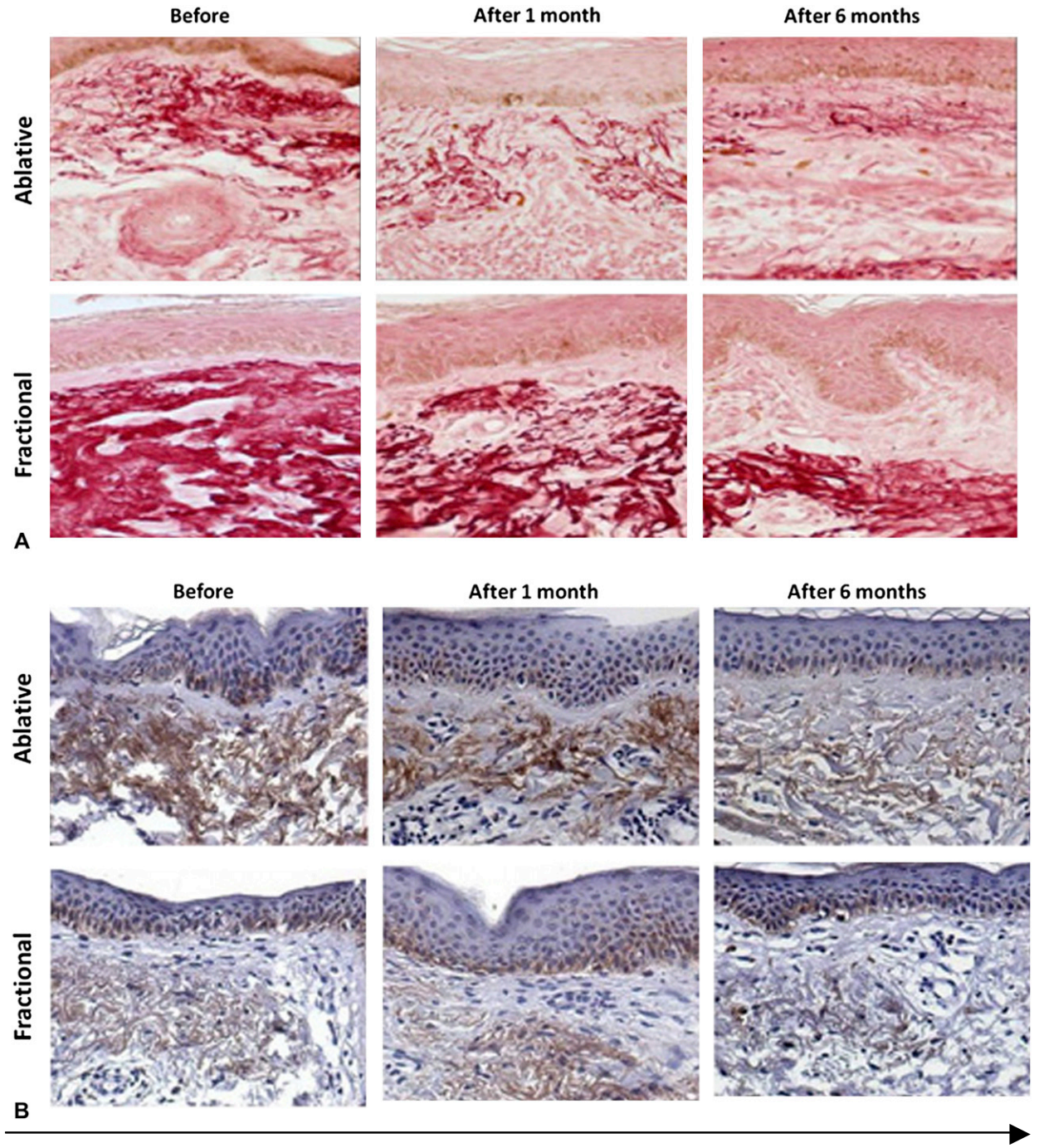

Fig 5. Elastic tissue. **A**, Elastotic material decreased and displaced downward after laser resurfacing. **B**, Further decrease in elastin is evident after ablative erbium:yttrium-aluminum-garnet laser. **C**, Increased tropoelastin level in both groups. This increase is more evident after ablative laser. (**A**, Orcein; **B**, immunohistochemistry; **C**, immunofluorescence; **A** to **C**, original magnifications: ×200.)

thermal effect.[26] Thermally damaged collagen inside the MTZs is completely replaced with neocollagen after 3 months and there is immunohistochemical evidence of increased collagen III production 7 days after fractional photothermolysis.[27] The current study has quantitatively evaluated collagen types I, III, and VII and found that both lasers increased the concentration of these collagen types with no significant difference between modalities.

Elastic fibers are composed mainly of elastin, a connective tissue protein that is initially synthesized as tropoelastin.[28] The current work demonstrated a

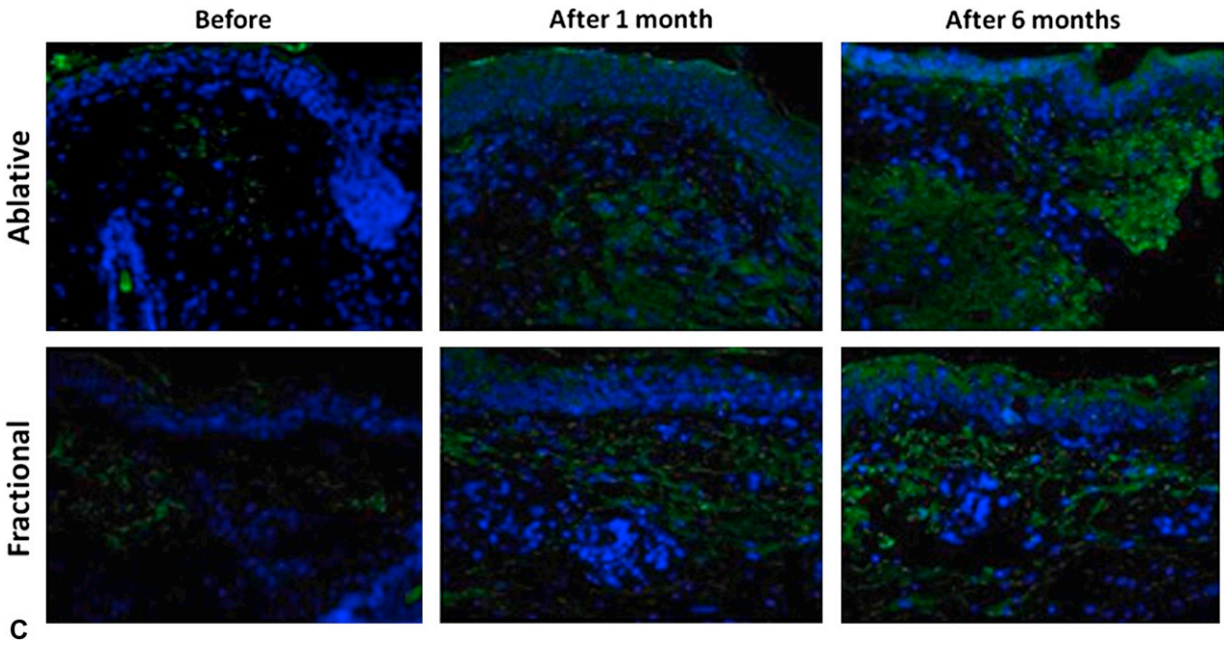

Fig 5. Continued.

quantitative decrease in elastin and increase in tropoelastin concentration after both ablative and fractional Er:YAG laser resurfacing with significantly stronger effects after ablative laser.

To our knowledge, no previous reports compared quantitatively the effects of ablative versus fractional Er:YAG laser resurfacing on epidermal thickness; neocollagen formation; collagen types I, III, and VII; elastin; and tropoelastin.

This study clarified that both laser modalities induced significantly positive correlated changes after resurfacing, which means that they have similar effects on the skin. Collagen changes showed no significant differences between the 2 laser modalities whereas epidermal and elastic tissue changes were more pronounced after ablative laser resurfacing.

The authors are aware that one of the limitations of this study is the relatively small number of volunteers. However, it provided a quantitative in-depth analysis of the histologic skin changes after laser resurfacing in both groups. Further studies on a larger group are needed to confirm and clarify such findings.

In conclusion, both ablative and fractional Er:YAG laser resurfacing showed significant effects on the epidermis and dermal collagen, elastin, and tropoelastin, but ablative Er:YAG laser resurfacing had more significant effects on epidermal thickness, elastin, and tropoelastin. Meanwhile, the effect of both lasers on collagen (neocollagen formation and collagen types I, III, VII) showed no significant difference. The current study suggests that multiple sessions of fractional Er:YAG laser are comparable in efficacy clinically and on dermal collagen to single session with multiple passes of ablative Er:YAG laser but with higher safety and shorter downtime.

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