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ORIGINAL ARTICLE

The effect of succinylated atelocollagen and ablative fractional resurfacing laser on striae distensae

JUNG U SHIN[1], MI RYUNG ROH[1], DONG KYUN RAH[2], NAM KYOUNG AE[1], HWAL SUH[3,4] & KEE YANG CHUNG[1,4]

[1]*Department of Dermatology and Cutaneous Biology Research Institute,* [2]*Department of Plastic Surgery,* [3]*Department of Medical Engineering, Yonsei University College of Medicine, Seoul, Korea and* [4]*BK 21 Research Team of Nanobiomaterials for the Cell-based Implants*

Abstract

Striae distensae are dermal atrophic scars with epidermal thinning and decreased collagen and elastic fiber. There is no 'gold standard' treatment modality in the treatment of striae distensae. Collagen is a major extracellular matrix component and is important in wound healing. The ablative CO_2 fractional laser is effective in various cutaneous scars and this study was attempted to evaluate the effect of succinylated atelocollagen and ablative CO_2 fractional laser in the treatment of striae distensae. Participants were divided into two groups and received three laser treatments at a 4-week interval. Clinical improvement was evaluated by participants and two blinded physicians by observing the comparative photographs. Skin biopsies were randomly taken from six participants. The ablative fractional resurfacing laser was effective in the clinical improvement of striae distensae. Statistically significant differences were partly observed between the collagen and placebo groups. Clinical improvement scored by doctors showed more improvement in the collagen group. However, scoring by participants did not show significant differences between the collagen and placebo groups. In conclusion, the ablative fractional resurfacing laser is effective in the treatment of striae distensae and succinylated atelocollagen may also be effective for striae distensae treatment. However, to prove the effect of succinylated atelocollagen, further research with a larger group of participants is needed.

Key words: *ablative fractional laser, collagen, striae distensae*

Introduction

Striae distensae (SD) are dermal scars with linear atrophic depression. SD are common and do not cause a significant medical problem but may cause emotional stress in cosmetic aspects. They are usually located on the buttocks, thighs, knees, calves, and lumbosacral areas (1,2). Clinically, SD start as linear pink lesions which evolve to longer and wider red lesions and then become white atrophic scars. Histologically, in the early stage, there are dermal edema and perivascular lymphocytic cuffing (3) and, in the later stage, there are epidermal atrophy and loss of rete ridges (4).

Although several treatment modalities have been tried to improve SD, they are associated with suboptimal outcomes. Weight gain can induce SD but weight loss does not ameliorate them (5,6). Topical tretinoin (0.1%) improves SD and the improvement may persist for almost a year after discontinuation of therapy (7). Various laser treatments have been used to treat SD. The 585-nm pulsed dye laser (PDL) has a moderately beneficial effect in the treatment of striae rubra (8). The 308-nm excimer laser was effective in the repigmentation of striae alba (9). Intense pulsed light was also effective, and had minimal side effects (10). Recently, Kim *et al.* (11) introduced a fractional photothermolysis as a useful treatment modality for

Correspondence: Kee Yang Chung, Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, 134 Shinchon-Dong, Seodaemoon-Gu, Seoul, 120-752, Korea. Fax: 82 2 393 9157. E-mail: kychung@yuhs.ac/derma@yuhs.ac

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the improvement of SD in both clinical and histological aspects. Other treatment modalities include the 1320-nm Nd-YAG laser, the 1450-nm diode laser, radiofrequency, and the 585-nm PDL, but none of these laser therapies is sufficiently effective.

The ablative fractional resurfacing laser is a novel approach for the treatment of scars, such as acne and surgical scars, as well as wrinkles (12). According to the concept of fractional photothermolysis, these lasers deliver energy in a novel beam pattern and ablate only a fraction of the epidermis and dermis in the treatment area. An array of microscopic thermal zones is created; adjacent to these areas, the epidermis and dermis are spared. Thereby, unlike the conventional CO_2 resurfacing laser technique, the fractional CO_2 laser is safer, healing is more rapid, and recovery time is dramatically reduced. It has been proved to be effective for photoaging, periorbital wrinkling, acne scarring, melasma, and pigmented lesions (13–15).

Collagen is a major component of extracellular matrix in dermis and is important in the wound-healing process (16). Succinylated atelocollagen is a non-immunogenic hydrophilic molecule modified to enhance skin penetration. We hypothesized that if we can deliver collagen through the microthermal treatment zone, SD may be treated more effectively. To confirm the effectiveness of the ablative fractional resurfacing laser and succinylated atelocollagen, we performed a double-blind, randomized, controlled study on Korean participants with SD.

Participants and methods

Participants

Fourteen female participants (Fitzpatrick skin types III–IV) with moderate to severe atrophic striae alba were recruited. Exclusion criteria were history of keloid scarring, isotretinoin use, non-ablative laser procedures within 1 year of study initiation, ablative resurfacing procedures within 3 years of the study initiation, pregnancy, use of immunosuppressive drugs, and any other diseases which can affect the wound-healing process. The protocol and informed consent were approved by the Severance Hospital Institutional Review Board. All participants were female.

Treatment

The participants were divided into two groups. One group applied succinylated atelocollagen (L-lysin, sodium hyaluronate, succinylated atelocollagen) and the other group applied placebo (L-lysin, sodium hyaluronate) (Table I). Each patient had three treatment sites: the left site for only laser treatment; the middle site for laser treatment and collagen or placebo application; and the right site for only collagen or placebo application (Figure 1). The size of the treated site was 4×4 cm.

Prior to ablative fractional resurfacing laser treatment, a topical anesthetic cream (EMLA®, lidocaine and prilocaine; AstraZeneca, Wilmington, DE, USA) was applied under an occlusive dressing for 1 hour and subsequently washed off. SD on the left and middle sites were treated with an ablative fractional resurfacing laser (eCO2™; Lutronic, Seoul, Korea) at a pulse energy of 50 mJ, spot density of 200 spots/cm^2, using a scan area of 12 mm $\times$ 12 mm in a static mode. After laser treatment, the areas were cooled down with ice packs for 10 minutes to protect spared epidermis. Participants were educated to apply collagen or placebo twice a day on the middle and right sites and not to apply any other moisturizers on the treated sites. Each patient received three laser treatments at 4-week intervals and was followed-up 4 weeks after the final treatment. In six participants, skin biopsies for histologic analysis were completed before treatment and 4 weeks after the final treatments.

Assessment of clinical effect

Therapeutic outcomes were assessed by digital photography and measurements of the erythema index (EI) and melanin index (MI) at every visit. Digital photographs were obtained under identical camera settings (Canon 400D; Japan) and lighting conditions at every visit. The EI and MI of SD were measured by narrow-band reflectance spectrophotometry (DermaSpectrometer II®; Cortex Technology, Hadsund, Denmark) using 568-nm and 655-nm probe wavelengths. Clinical improvement was evaluated by participants and two blinded physicians by observing the comparative photographs and rated using a 4-point score system (0 = no, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100% improvement)

Table I. Ingredients of succinylated atelocollagen and placebo solution.

Ingredients (g/30 ml)	Placebo	Collagen
Sodium hyaluronate	0.12	0.12
L-lysine	0.00006	0.00006
Succinylated atelocollagen	–	0.12

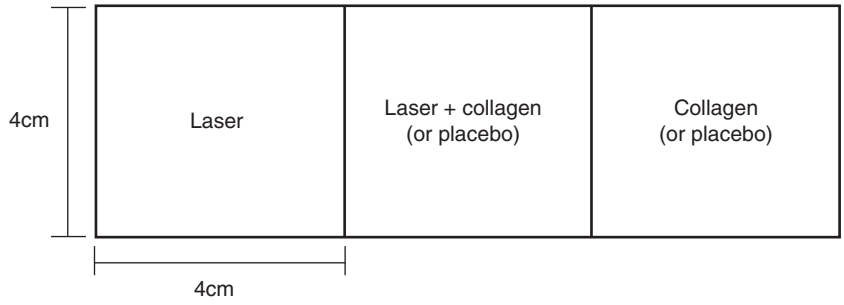

Figure 1. Laser treatment area (left: laser only; middle: laser + succinylated atelocollagen (or placebo); right: succinylated atelocollagen (or placebo) only).

at the time of the last visit. Complications were recorded at each visit.

Assessment of histologic change

Skin biopsies were performed in six participants before treatment and 4 weeks after the final treatment using a 2-mm biopsy punch. At the first visit, normal skin and untreated striae were obtained. The biopsy after treatment was performed right next to the previous biopsy site. Biopsy specimens ($n = 4$ per participant at the initial, $n = 3$ per participants at the final) were fixed in 10% formalin and embedded in paraffin. Each section was stained with hematoxylin and eosin (H&E), Masson trichrome (for collagen analysis), and Verhoeff Van Gieson (for elastic fiber analysis). Images of each section were taken at a magnification $\times 200$ with a 12.5 megapixel digital camera (DP70; Olympus Optical Co., Tokyo, Japan) connected to a light microscope (BX40; Olympus Optical Co.). The images were analyzed by MetaMorph (Molecular Devices, Sunnyvale, CA, USA).

Statistical analysis

Statistical analysis was performed using the Wilcoxon signed rank test and Kruskal Wallis test for evaluation of EI, MI, and histological change. The GENMOD procedure was performed to evaluate clinical improvement scoring by two doctors. The Wilcoxon rank sum test was used to evaluate clinical improvement by the participants.

Results

Twelve of 14 participants completed the 12-week study. One patient withdrew because of development of psoriasis on the laser-irradiated sites, and another patient dropped out due to an unsatisfactory residual scar at the initial skin biopsy site.

Degree of clinical improvement

The clinical improvement scores evaluated by two doctors were analyzed by the GENMOD procedure. There was a significant difference between succinylated atelocollagen and placebo applied sites after laser irradiation ($p = 0.03$), and also between succinylated atelocollagen only and placebo only applied sites ($p = 0.03$). However, evaluation by participants showed no significant difference between laser and succinylated atelocollagen treated sites and laser and placebo treated sites, and between succinylated atelocollagen only treated and placebo only treated sites ($p = 0.57$, $p = 0.78$). A photograph of a representative subject who showed excellent response can be seen in Figure 2.

Spectrophotometric analysis

Spectrophotometric analysis was carried out by measuring the EI and MI before and after treatment. Both EI and MI were increased in laser irradiated sites and laser plus collagen or placebo treated sites (Figures 3 and 4). However, there was no significant difference between laser plus collagen treated sites and laser plus placebo treated sites (EI: $p = 0.40$; MI: $p = 0.59$)

Histologic changes

Prior to treatment, the epidermal thickness, collagen and elastic fiber of untreated SD differed significantly from those of normal skin (Figure 5).

H&E stain showed epidermal thinning in untreated SD, with flattening of the rete ridges.

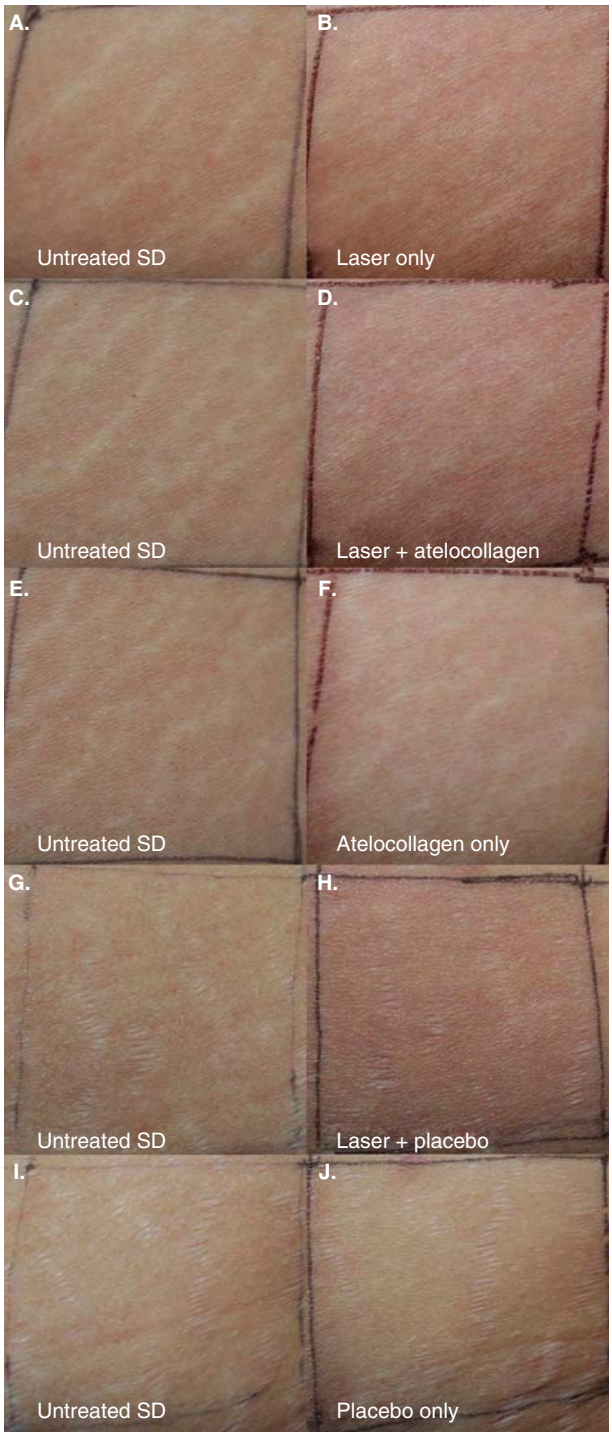

Figure 2. Clinical improvement of SD. Before treatment (A, C, E, G, I) and 1 month after treatment (B, D, F, H, J) using laser only (B), laser plus succinylated atelocollagen (D), succinylated atelocollagen only (F), laser plus placebo (H), and placebo only (J).

Four weeks after the final treatment, laser-irradiated striae and laser and succinylated atelocollagen treated striae exhibited thickening of the epidermis (Figure 6). Quantitative image analyses of pre- and post-treatment biopsies revealed that at 4 weeks following treatment, the epidermal thickness of each group had increased significantly compared with baseline ($p = < 0.002$; Bonferroni correction adjusted p-value), but there was no difference between succinylated atelocollagen and placebo only treated sites, and between succinylated atelocollagen and placebo applied after laser irradiation sites ($p > 0.002$).

The quantities of collagen fibers in the untreated SD were reduced compared with the normal control at baseline, but increased 4 weeks after the final treatment in all groups ($p = < 0.002$; Bonferroni correction adjusted p-value). However, there was no difference between succinylated atelocollagen and placebo only treated sites, and between succinylated atelocollagen and placebo applied after laser irradiation sites ($p > 0.002$) (Figure 7).

The quantities of elastic fibers in the untreated SD were reduced compared with the normal control at baseline, but increased 4 weeks after the final treatment in all groups ($p = < 0.002$; Bonferroni correction adjusted p-value). There were significant statistical differences between succinylated atelocollagen and placebo only treated sites, and between laser with succinylated atelocollagen and laser with placebo treated sites ($p = < 0.002$). Succinylated atelocollagen was better than placebo (Figure 8).

Complications

The treatments were well tolerated and most complications were limited and transient. Post-treatment erythema was observed in all participants and generally resolved within 2–3 days after treatment. Pruritus and post-inflammatory hyperpigmentation occurred in nine (75%) participants. One patient developed psoriasis due to a Koebner phenomenon.

Discussion

Striae distensae are considered as dermal scars associated with many physical conditions, including pregnancy, adrenocortical excess, and weight gain. It is very common and does not cause a medical problem but may cause emotional stress in a cosmetic perspective. Although numerous attempts have been made to improve SD, there is no ‘gold standard’ treatment modality. Tretinoin is an effective topical medication but has to be used in the active stage, before the scarring process is complete (7). PDL is one of the most widely used laser therapies but it is effective only for the immature element of striae and is not effective in darker skin.

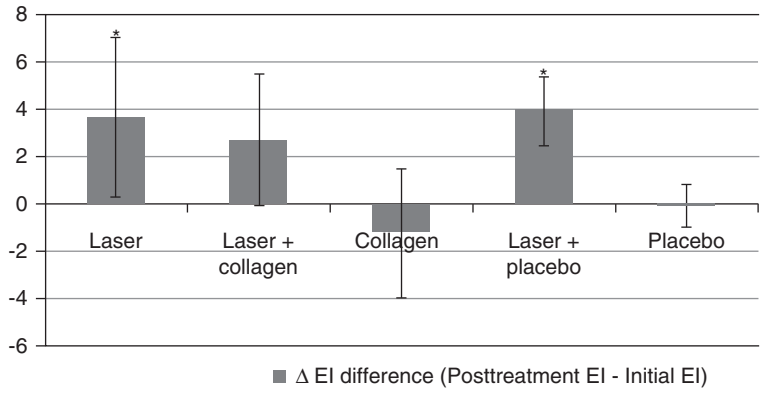

Figure 3. Average of the erythema index (EI) difference in each site. $*p < 0.05$.

The ablative fractional CO_2 laser is a new modality which is more effective and has a reduced side-effect profile compared with other ablative laser devices. It delivers microscopic columns of energy which vaporize tiny holes covering only a small percentage of the skin surface. The majority of the epidermis is left intact, allowing rapid healing and limited complications. There are a few published studies on SD and non-ablative fractional photothermolysis. Geronemus (15) reported evidence of new collagen formation and demonstrated an overall increase in the density of collagen after fractional photothermolysis. Recently, Kim *et al.* (11) demonstrated an increase in collagen and elastic fiber deposition and clinical improvement in SD after fractional photothermolysis using a 1550-nm erbium-doped FP laser. The fractional CO_2 laser has a similar laser irradiation system but in an ablative mode. Therefore, it is supposed to have an effect on SD.

Succinylated atelocollagen solution is composed of sodium hyaluronate, L-lysine, succinylated atelocollagen and purified water. Collagen is a major component of extracellular matrix in the dermis and accelerates wound healing (16). Hyaluronic acid is another major component of extracellular matrix and regulates cell behavior during embryonic development, healing processes, inflammation and tumor development (17,18). Using collagen with hyaluronic acid is supposed to have a synergistic effect in that they accelerate the differentiation of fibroblasts and increase cell migration and proliferation (19). The size of the succinylated atelocollagen molecule in this study is 300 nm $\times$ 2.4 nm. Removing telopeptides from collagen molecules reduces the size and immunogenicity, and succinylation enhances the skin penetration of the molecules. It is thought to be small enough to penetrate stratum corneum based on the evidence that solid particles smaller than 3 μm can penetrate stratum corneum and hair follicles (20). Therefore, in theory, succinylated atelocollagen molecules can penetrate skin and may improve SD, which is characterized by decreased collagen. Like other techniques that aid penetration of particles, such as microneedles, iontophoresis and needleless jet injectors, it was assumed that the ablative fractional laser could increase the penetration of collagen molecules.

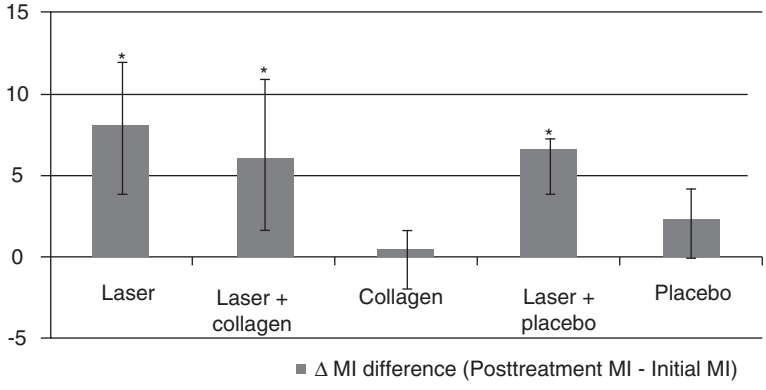

Figure 4. Average of the melanin index (MI) difference in each site. $*p < 0.05$.

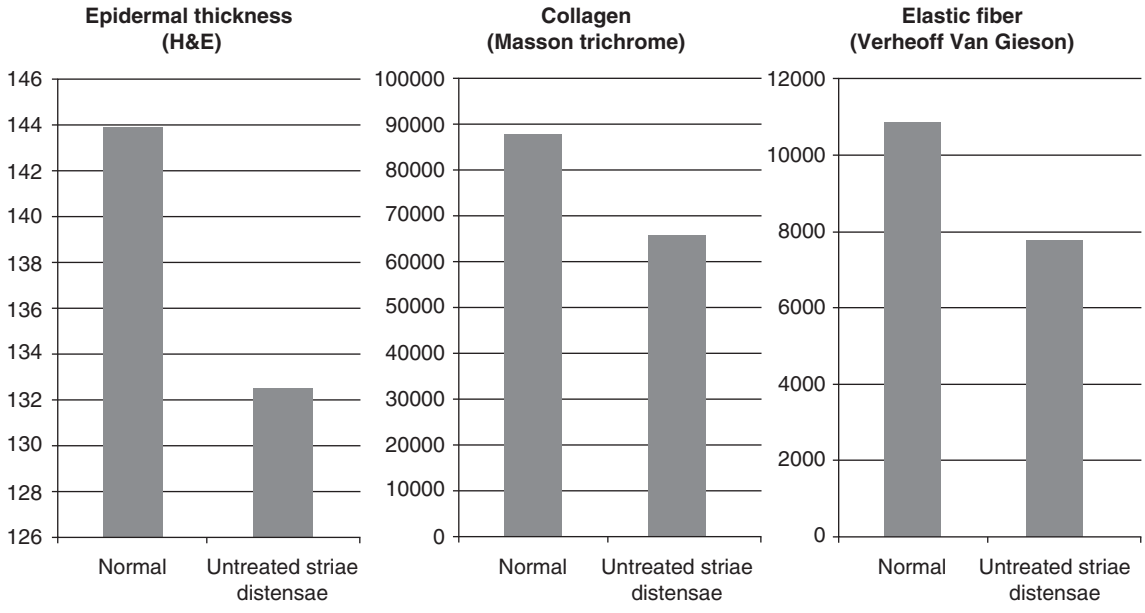

Figure 5. Average of epidermal thickness, collagen and elastic fiber amount in normal and untreated SD.

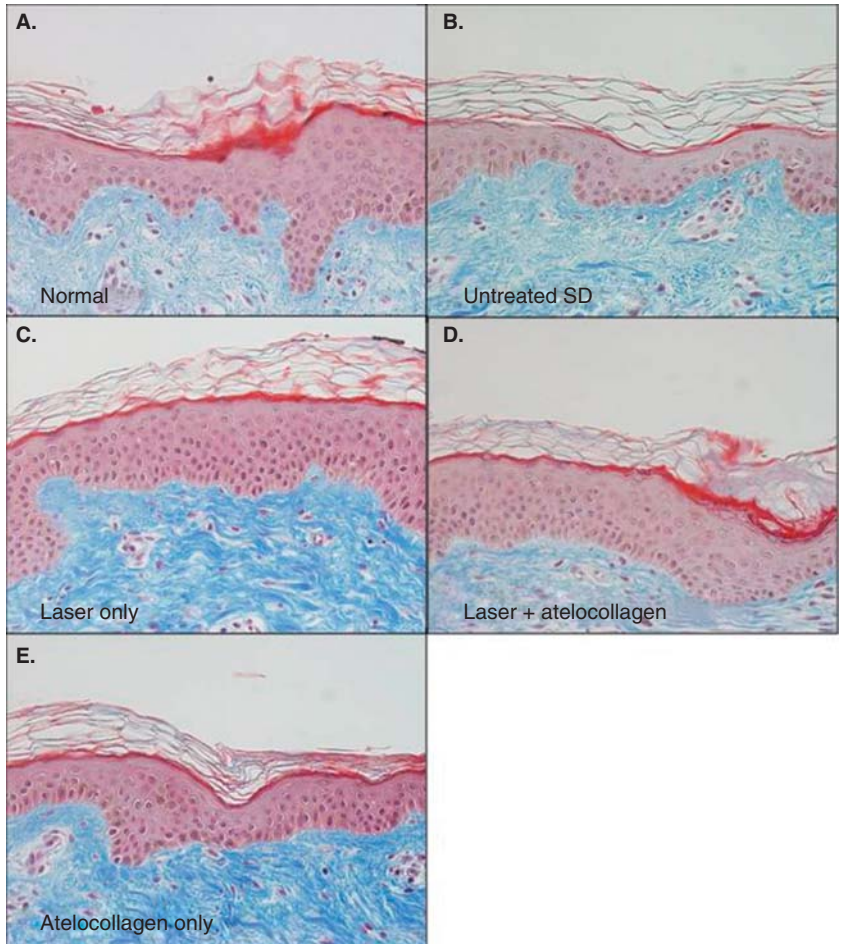

Figure 6. H&E stain (×200). Normal (A), untreated SD (B), laser only (C), laser + succinylated atelocollagen (D), and succinylated atelocollagen only (E).

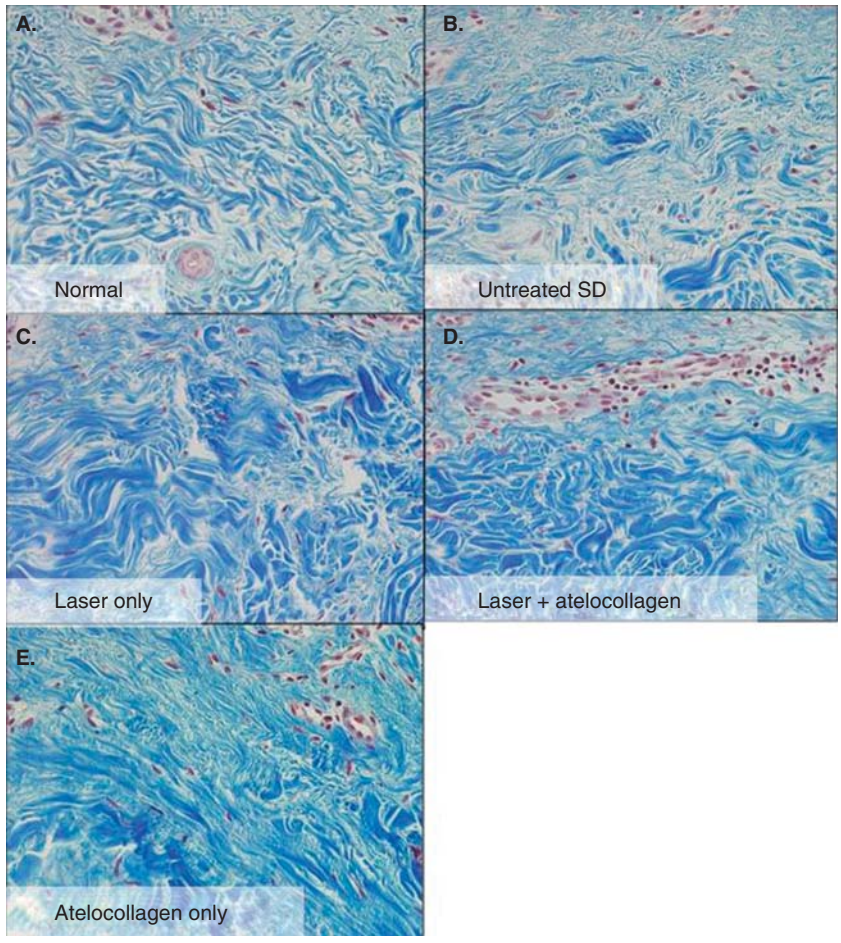

Figure 7. Masson trichrome stain (×200). Normal (A), untreated SD (B), laser only (C), laser + succinylated atelocollagen (D), and succinylated atelocollagen only (E).

This study was intended to investigate the efficacy of the ablative fractional laser and succinylated atelocollagen in the treatment of SD. The results showed that the ablative fractional resurfacing laser was effective in the treatment in SD. The EI and MI were increased after laser irradiation and histologic analysis showed epidermal thickening and increased collagen and elastic fibers. Increased erythema and pigmentation after treatment of striae alba may result from upregulated angiogenic activity or activation of melanocytes by a variety of growth factors induced during the wound-healing process (21). Because striae alba presents with decreased erythema and pigmentation, an increase of EI and MI can improve the clinical appearance of SD.

Succinylated atelocollagen or placebo applied sites also showed epidermal thickening and increased collagen and elastic fibers. There was a significant difference between two sites in EI, MI, and quantities of elastic fiber. However, no significant difference was seen in epidermal thickness and quantities of collagen fiber. In some participants, succinylated atelocollagen treated sites showed a more significant epidermal thickening and increase in the amount of collagen, but the small number of subjects (each group, $n = 3$) may be a reason for the lack of difference between the two sites. There was an increase in collagen in all treated sites, including the placebo sites, compared with the pretreatment status. Mast *et al.* (22) showed that collagen synthesis by fetal rabbit fibroblasts was stimulated upon addition of hyaluronic acid in vitro. Therefore, hyaluronic acid in placebo solution may have induced the collagen synthesis in placebo only treated sites. This can also explain the difference in the amount of elastic and collagen fibers between succinylated collagen treated sites and placebo treated sites. Analysis of the clinical improvement score measured by two blinded physicians showed more improvement in the succinylated atelocollagen treated sites than in placebo treated sites. We also tried to compare the clinical effect by subjective evaluations by the participants but there was no significant

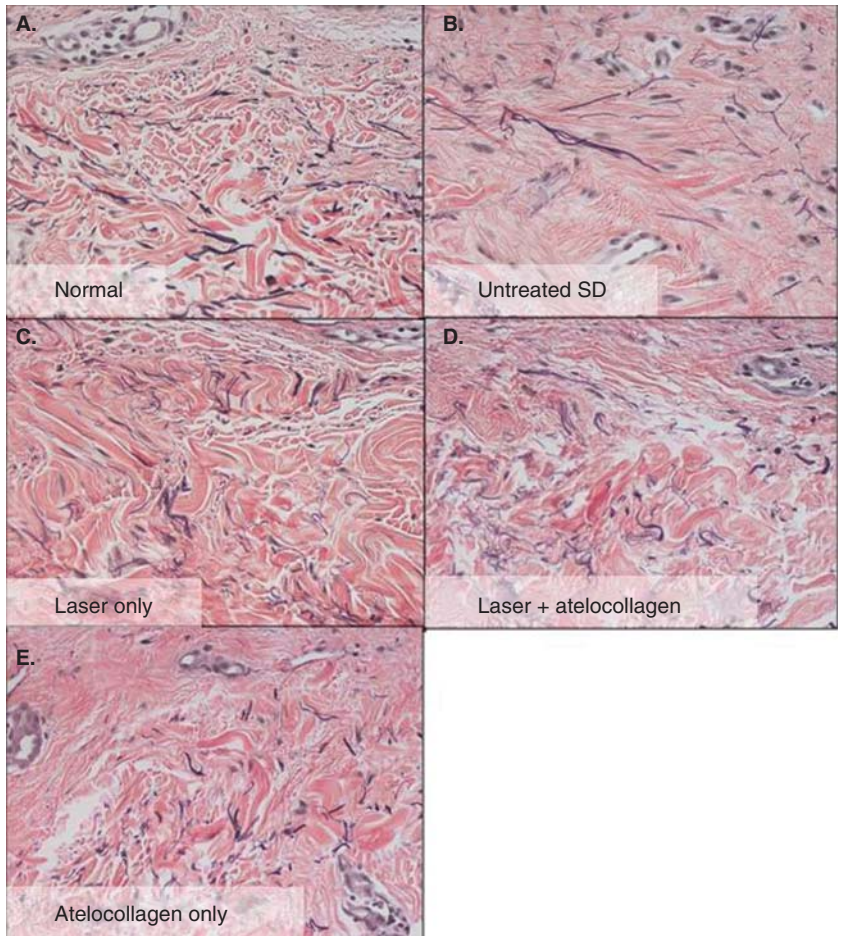

Figure 8. Verhoeff Van Gieson stain (×200). Normal (A), untreated SD (B), laser only (C), laser + succinylated atelocollagen (D), and succinylated atelocollagen only (E).

difference between the two sites. It is likely that subtle and gradual changes cannot be noticed by the individuals.

Ablative fractional resurfacing laser therapy is safer than other ablative laser modalities, but it may result in transient erythema, edema and persistent scarring. One patient developed psoriasis at the laser irradiated sites and nine participants experienced pruritus and post-inflammatory hyperpigmentation. The psoriasis lesion probably developed due to a Koebner phenomenon in a volunteer without any previous history. Therefore, it is critical to be aware of and to recognize the possible complications, and careful history taking of past medical history is mandatory.

In conclusion, the ablative fractional resurfacing laser is effective in the clinical improvement of SD. Statistically significant differences were partially observed between succinylated atelocollagen treated sites and placebo treated sites. Clinical evaluation by doctors showed more improvement in succinylated atelocollagen treated sites. Our study shows that the ablative fractional laser is an effective, non-invasive treatment for SD and succinylated atelocollagen may also improve SD, but a larger blinded study is needed to confirm the result of this pilot study.

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Declaration of interest: The authors declare there are no conflicts of interest.

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