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Effects of Nanofat and PRP on Type I Collagen Production in Striae Distensae: Preliminary Findings from a Prospective, Randomized Single-Blind Study

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Abstract

Introduction Striae distensae (SD) appear clinically as parallel striae, lying perpendicular to the tension lines of the skin. SD evolve into two clinical phases, an initial inflammatory phase in which they are called "striae rubrae" (SR) and a chronic phase in which they are called striae albae (SA). This study investigates the synergistic effect of nanofat and platelet-rich plasma (PRP) injections on collagen production in fibroblasts derived from SA (SAF).

Material and Methods A prospective, randomized single-blind study was conducted in fifty women presenting with SA in the abdominal region who had voluntarily sought a conventional abdominoplasty procedure and accepted to test an autologous treatment for their SDs. SA were treated using: PrP 10 ml; PrP 2ml (20%) + nanofat 8ml (80%); nanofat 10ml. Following the abdominal dermolipectomy, biopsies from treated and untreated SDs were taken and analyzed for type I collagen quantification. Results were processed through statistical analysis models using the Student's *t* test.

Results Collagen concentration in untreated SA biopsies was significantly lower than in healthy skin. Both PRP and nanofat treatments significantly increased collagen biosynthesis compared to controls, with the combined PRP-nanofat treatment showing the highest increase in collagen levels ($p < 0.0001$). A superior clinical improvement was observed in the areas that received the combined treatment of PRP and nanofat ($p = 0.001$).

Conclusion Our findings indicate that both PRP and nanofat treatments effectively enhance collagen production in SA, with the combined PRP-nanofat treatment showing a synergistic effect. This combined therapy holds promise for effectively treating SA, providing a new potential treatment avenue for SMs and similar skin conditions. Further studies are needed to validate these results and explore clinical applications.

Level of Evidence I This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Stretch marks · Striae distensae · Platelet-rich plasma · Nanofat · Fibroblast

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Introduction

Striae distensae (SD), commonly known as stretch marks (SMs), progress through two clinical phases: an initial inflammatory phase (striae rubrae, SR) and a chronic phase (striae albae, SA). SDs result from damage to the dermal connective tissue [1]. These lesions begin with an inflammatory response that eventually leads to scarring. The underlying cause of SD formation is a chronic alteration in the quantity and quality of dermal collagen, linked to specific metabolic abnormalities in fibroblasts [2]. Excessive skin stretching, which inflicts mechanical damage on dermal components, appears to be the trigger event. Early changes observed under electron microscopy include mast cell degranulation and macrophage activation, accompanied by moderate elastolysis of the dermis. These findings suggest that the production and release of elastases by mast cells are critical triggering events in the pathogenesis of SD [3–5]. As SDs become clinically apparent, collagen fibers exhibit structural changes, and fibroblast anomalies are evident. At this stage, mast cells disappear, and there is an increase in dermal edema with infiltrating lymphocytes [6]. The initial SR phase is marked by inflammatory lesions, while the SA phase is characterized by epidermal atrophy and collagen anomalies that microscopically resemble dermal scar tissue. Research into the etiology of SDs has yielded varied results, and no universally accepted definitive treatments for SA currently exist [3–6].

Among the two forms of SD, SA are certainly the most difficult to treat, whereas SR can be greatly improved through multiple techniques such as non-ablative fractioned laser resurfacing [6–43].

A promising and innovative approach involves the use of platelet-rich plasma (PRP) microneedling combined with sodium ascorbate [7–12]. In our previous in vitro study, we demonstrated that fibroblasts derived from SA (SAF) are quiescent and produce lower amounts of collagen compared to fibroblasts from normal skin (NSF) and SR (SRF) [12]. Furthermore, a synergistic effect of PRP and sodium ascorbate was observed on SA fibroblasts (SAF), significantly increasing type I collagen secretion [12]. However, after consulting with a multidisciplinary team of seven plastic surgeons and five dermatologists, it was decided to use nanofat (an autologous product) instead of sodium ascorbate in this in vivo study to avoid potential allergic reactions caused by some sodium ascorbate excipients, such as sodium metabisulfite [13]. Combined stimulation with PRP and nanofat has the potential to reactivate fibroblast metabolic activity, increasing the production of type I collagen in vivo. This study aims to investigate the synergistic effect of nanofat and platelet-rich plasma injections on collagen production in SAF. The findings could pave the way for new treatments for SMs.

Materials and Methods

A prospective, randomized single-blind study was conducted on fifty women aged between 37 and 50 years (43 ± 6.8) with no comorbidities and a mean BMI < 30 (29 ± 1.3), all presenting with striae albae (SA) in the abdominal region. These patients voluntarily sought treatment for their stretch marks and a conventional abdominoplasty, planned at least three months before the study commenced. Exclusion criteria included previous stretch mark treatments, ongoing corticosteroid treatments, and Cushing syndrome, as these conditions can alter normal dermal metabolism [7]. From October 2017 to October 2019, patients were informed about the study's purpose and characteristics. All procedures in this study adhere to the checklist provided by our local ethics committee and conform to the ethical standards of our institution, as well as to the 1964 Helsinki Declaration and its subsequent amendments. For randomization, 100 sealed envelopes were prepared by our medical secretary. Each envelope contained a note indicating whether the patient would be included in the study (50 envelopes) or not (50 envelopes). Patients selected a sealed envelope from a blind surgeon who was unaware of the contents. At the end of the randomization process, 30 patients were included in the study. All selected patients agreed to test a new procedure on the SAs in the area to be excised during abdominoplasty and to donate their excess abdominoplasty skin, which included the treated areas and would otherwise be discarded. Privacy was strictly ensured, and all patients signed an appropriate written consent form. The first author performed all operations.

The focus on treating SAs arises because SR can be significantly improved through various techniques, such as non-ablative fractioned laser resurfacing [11].

Given the in vitro study's statistically significant increase in collagen production when SAFs were treated with PRP [12, 13], it was decided to select for each patient four SAs divided into two equal parts for different treatments: PRP 10 ml; PRP 2 ml (20%) + nanofat 8 ml (80%); nanofat 10 ml; and no treatment (control area). The products were injected intradermally using a 10-cc syringe with a 30-gauge needle. To minimize inter-individual variations, four severe SAs (grade 4, according to our Objective Stretch Marks Photonumeric Assessment Scale, Table 1) [14] were selected on each patient. Three were treated (each treated on one half, leaving the other half untreated for control), and the fourth (normal skin without stretch marks from the same patient) was used as a control.

Table 1 The Objective Stretch Marks Photonumeric Assessment Scale: Each scale severity grade is defined to range between 0 (no striae distensae) and 4 (very intense or visible striae distensae)

Severity of SD for area	No SD	Slight intensity	Mild intensity	Moderate intensity	Severe intensity
Abdomen	0	1	2	3	4
Breasts	0	1	2	3	4
Hips	0	1	2	3	4
Gluteal area	0	1	2	3	4
Back area	0	1	2	3	4
Thighs	0	1	2	3	4
Calves	0	1	2	3	4
Arms	0	1	2	3	4

The results of each scale are combined to obtain a final score ranging from 0 to 32

The primary outcome was to determine which treatment was most effective in increasing type I collagen concentrations in the treated areas. The secondary outcome was to assess which treatment was better at clinically improving the appearance of stretch marks.

PRP and Nanofat Preparation Protocol

Three months before surgery (abdominoplasty), patients were treated in our hospital offices under local anesthesia. After infiltrating an adrenaline-saline solution and xylocaine 10 mg/ml (with adrenaline 0.005 mg/ml), a 10-cc lipoaspirate sample was obtained from the abdominal region of each patient using a 10-cc luer lock syringe and a 1-mm hole aspiration "tulip" cannula.

Nanofat was obtained from the autologous fat collection, filtered via a Tulip kit by passing the adipose graft through three reducers (2.4 mm, 1.4 mm, 1.2 mm) and a nanofilter to create an emulsion (Fig. 1) More precisely, the adipose tissue was passed 30 times through each reducer and only once through the nanofilter. PRP was obtained using the RegenKit®-BCT, collecting two 8-ml tubes of venous blood from each patient. The tubes were centrifuged at 1500 rpm for 5 minutes, yielding 4 ml of PRP. A small portion of each sample was allocated for hematological analysis. Platelet concentration was determined using an automated blood cell counter (XS-1000i; Sysmex Co.). Prior to conducting the tests, we measured the platelet concentration in the PRP.

For the SAs treated with a combination of nanofat and PRP, nanofat (80%) was mixed with PRP (20%) (Figs. 2 and 3) [40]. The SDs were located in the skin area to be removed by abdominal dermolipectomy, performed three months after treatment (Video 1).

Following the excision of the abdominal skin and adipose panniculus, two biopsies (2-mm punch) were taken from treated areas (nanofat, PRP, and nanofat + PRP), untreated areas, and healthy skin. The biopsies were placed in formalin and analyzed using the Biotechne ELISA Human Pro-Collagen I α1/COLIA1 kit to quantify type I collagen.

Fig. 1 Shown in this image are 2 of the 3 reducers (2.4 and 1.4 mm) and the nanofilter through which the adipose tissue is passed to obtain the nanofat

Fig. 2 For the SAs treated with a combination of nanofat and PRP, nanofat (80%) was mixed with PRP (20%)

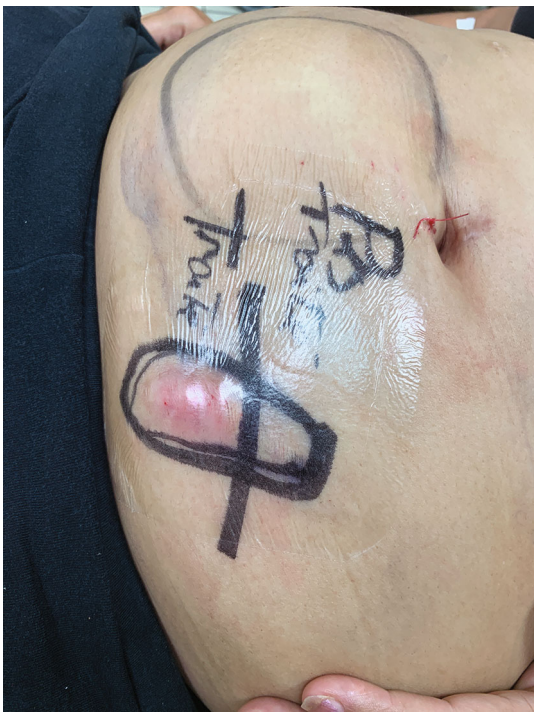

Fig. 3 Four-grade 4 SAs were selected on each patient. Three were treated (each on one half, leaving the other half untreated for control), while the fourth (normal skin without stretch marks from the same patient) was used as a control. Highlighted in this image is a stretch mark in a 60-year-old patient included in the study, half of whom had just been treated with nanofat+PRP

Protein Extraction and Pro-collagen Enzyme-Linked Immunosorbent Assay (ELISA)

Serial frozen sections of 7–200 µm thickness were prepared from OCT (optimal cutting temperature compound)-embedded skin biopsy specimens. The dermal areas of the 7-µm sections were measured using Image ProPlus software (Media Cybernetics, Bethesda, Maryland) to calculate the volume of the 200-µm samples. Soluble proteins were then extracted from the 200-µm samples using an ice–cold extraction buffer (50 mM tris hydrochloride, pH 7.4; 0.15 M sodium chloride; 1% Triton X-100; protease inhibitors [Complete Mini; Roche Diagnostics, Indianapolis, Indiana]). After centrifuging for 5 minutes at 10,000g at 4°C, the supernatants were collected and analyzed for pro-collagen I using a commercial ELISA kit (Human Pro-Collagen I α1/COLIA1, Biotechne—France). Pro-collagen I concentrations were normalized to the tissue volume used for each sample.

Preliminary Clinical Evaluation

High-resolution photographs were taken of each studied area before administering the treatments and on the day of the abdominoplasty procedure to obtain preliminary data on the clinical efficacy of the treatments for each area. The pre- and post-treatment images were evaluated using the Objective Stretch Marks Photonumeric Assessment Scale (Table 2) [14] developed by the authors. Since the focus was on the abdominal area, only the abdominal stretch mark scale was used, which ranges from a minimum score of 0 (no stretch marks) to a maximum score of 4 (severe stretch marks).

Each photograph was anonymized and assigned to an individual scorecard, which was then independently reviewed by three blinded assessors, including two plastic surgeons and a dermatologist. The assessors used the Objective Stretch Marks Photonumeric Assessment Scale to evaluate the photographs taken before treatment and three months after treatment, without knowing the patients' ages or the specific procedures performed. The assessors rated five items (0–4) to indicate the severity of striae distensae for each area studied.

The Patient and Observer Scar Assessment Scale (POSAS) was used to evaluate five parameters: vascularity, pigmentation, thickness, relief, and pliability, offering a subjective assessment of each patient's striae distensae (Table 3). Preoperative and 3-month postoperative scores were calculated, and statistical significance was determined by analyzing the *P* value. Each category was rated on a

Table 2 Mean scores obtained using the Objective Stretch Marks Photonumeric Assessment Scale (Abdomen Scale ranging from 0 to 4) before and 3 months after treatment

Administered treatment	Pre-treatment	After treatment	*P* value
Control	3.8 ±0.2	3.9 ±0.1	0.3
PRP	3.9 ±0.1	3.4 ±0.4	0.2
Nanofat	3.8 ±0.2	3.2 ±0.5	0.005
PRP+nanofat	3.8 ±0.2	2.9 ±0.2	0.001
Differences between treatments			
	PRP 3.4 ±0.4	Nanofat 3.2 ±0.5	0.4
	PRP 3.4 ±0.4	PRP+nanofat 2.9 ±0.2	0.001
	Nanofat 3.2 ±0.5	PRP+nanofat 2.9 ±0.2	0.03

Additionally, the scores obtained 3 months after the treatment were compared to see whether any differences were observed between the various treatments.

scale from 1 to 10, with a score of 1 indicating a near-normal skin appearance, and a score of 10 representing the most severe SA [44].

Mean scores from pre-treatment and three months post-treatment were compared using a matched T test. Data were statistically analyzed using PRISM software (GraphPad, USA). Differences in the results were evaluated using the *T* test, with statistical significance set at $p < 0.05$. All authors had full access to the database and took full responsibility for its integrity.

Results

The average platelet concentration (X $10^4/\mu L$) was 23.2 ± 3.99 in whole blood before centrifugation and 71.21 ± 13.4 in the PRP.

Protein Extraction and Pro-collagen Enzyme-Linked Immunosorbent Assay (ELISA)

The mean concentration of type I collagen obtained from the COLIA1 assay for healthy skin biopsies (normal skin, NS) was 15,850 ± 390 pg/mL, while for untreated striae albae skin biopsies (SA–NT), the mean concentration was significantly lower at 3,950 ± 239 pg/mL. As illustrated in Fig. 4, both PRP and nanofat treatments significantly increased collagen biosynthesis compared to the control (SA–NT). Specifically, the mean collagen concentration for SA treated with PRP alone was significantly higher than that of the control group, demonstrating the effectiveness of PRP in enhancing collagen production. Similarly, nanofat treatment also resulted in a significant increase in collagen levels compared to the control.

The most pronounced effect, however, was observed in the group treated with the combined PRP-nanofat treatment. This combination therapy resulted in a mean collagen concentration that was higher than both the PRP and nanofat treatments alone. Statistical analysis confirmed that the increase in collagen biosynthesis in the PRP-nanofat group was highly significant compared to the control ($p < 0.0001$).

Regarding the comparison between the treatments, we observed that:

The mean concentration of type I collagen obtained from the COLIA1 assay for the area treated with PRP alone was 9011 ± 97 pg/mL, while for the area treated with nanofat alone, it was 9710 ± 187 pg/mL. No statistically significant differences were observed between the PRP-alone and nanofat-alone treatments ($p = 0.3$). However, the mean concentration of type I collagen for the area treated with the combined PRP+nanofat treatment was 12,350 ± 173 pg/mL. This difference in collagen concentration for the areas treated with the combined PRP+-nanofat treatment was statistically significant compared to both PRP alone ($p = 0.0045$) and nanofat alone ($p = 0.0031$).

Preliminary Clinical Evaluation

The mean scores of the Objective Stretch Marks Photonumeric Assessment Scale after 3 months of treatment improved in all cases (except for the control areas) (Table 2). In particular, the difference between the pre-treatment and 3-month post-treatment scores assessed by three blinded evaluators was statistically significant only for the stretch mark areas treated with nanofat alone and the combination of nanofat + PRP. A superior clinical improvement was observed in the areas that received the combined treatment of PRP and nanofat (Figs. 5 and 6). Additionally, the comparison of the scores obtained 3 months after the treatment showed statistically significant differences between PRP and the combined treatment, as well as between nanofat and the combined treatment, with a lower and thus better score for the areas treated with nanofat+PRP (Table 2).

The subjective assessment using the POSAS scale also showed encouraging results (Table 3). In fact, the

Table 3 Patient and Observer Scar Assessment Scale (POSAS) pre- and 3-month post-treatment scores

Treatment	Vascularity		Pigmentation		Thickness		Relief		Pliability		Total score	
	preop	postop	preop	postop	preop	postop	preop	postop	preop	postop	preop	postop
Control	6 ± 0.2	6 ± 1.2	7 ± 1.3	7 ± 0.7	7 ± 0.7	7 ± 0.9	7 ± 0.6	7 ± 0.5	6 ± 0.8	6 ± 05	41 ± 3.4	41 ± 3.2
p	*p* = 0.1		p = 0.2		*p* = 0.1		*p* = 0.1		*p* = 0.1		p = 0.1	
PRP	6 ± 0.2	5 ± 1.2	7 ± 1.3	5 ± 0.7	7 ± 0.7	5 ± 0.9	7 ± 0.6	5 ± 1.1	6 ± 0.8	5 ± 05	41 ± 3.4	17 ± 4.6
p	*p* = 0.5		*p* = 0.002		*p* = 0.002		*p* = 0.001		*p* = 0.003		*p* = 0.004	
Nanofat	6 ± 0.2	6 ± 1.1	7 ± 1.3	4 ± 0.5	7 ± 0.7	4 ± 1.9	7 ± 0.6	5 ± 1.4	6 ± 0.8	4 ± 0.1	41 ± 3.4	16 ± 3.4
p	*p* = 0.7		*p* = 0.001		*p* = 0.001		*p* = 0.004		*p* = 0.004		*p* = 0.004	
PRP+nanofat	6 ± 0.2	6 ± 1.2	7 ± 1.3	3 ± 0.7	7 ± 0.7	4 ± 0.1	7 ± 0.6	5 ± 0.8	6 ± 0.8	4 ± 05	41 ± 3.4	14 ± 2.2
p	*p* = 0.5		*p* = 0.001		*p* = 0.004		*p* = 0.002		*p* = 0.003		*p* = 0.004	

Five parameters were evaluated: vascularity, pigmentation, thickness, relief, and pliability, providing a subjective assessment of the patient's striae distensae.

parameters of pigmentation, thickness, relief, and pliability in the areas treated with PRP, nanofat, and the combination of PRP and nanofat improved. However, a superior improvement was observed in the areas that received the combined treatment of PRP and nanofat. Regarding the comparison of total POSAS scores across the various treatments, we obtained a score of 17 ± 4.6 for the areas treated with PRP alone, 16 ± 3.4 for the areas treated with nanofat alone, and 14 ± 2.2 for the areas treated with PRP+nanofat. The total score for the areas treated with nanofat alone was better than those treated with PRP alone ($p = 0.0045$), and the total score for the areas treated with PRP + nanofat was superior to both the areas treated with nanofat alone ($p = 0.002$) and those treated with PRP alone ($p = 0.001$).

Discussion

The primary goal of this study was to determine the most effective treatment for enhancing collagen production and improving the appearance of striae albae. Based on our findings, the combined treatment of PRP and nanofat emerges as the superior option for treating this condition.

Our results show that both PRP and nanofat treatments independently led to significant improvements in collagen biosynthesis compared to untreated SA skin, as well as clinical improvements in the appearance of the stretch marks. Specifically, PRP alone increased the concentration of type I collagen to 9011 ± 97 pg/mL, and nanofat alone led to a similar increase, with a concentration of 9710 ± 187 pg/mL. However, no statistically significant differences were found between the PRP-alone and nanofat-alone treatments ($p = 0.3$).

The most remarkable outcome was observed with the combined PRP and nanofat treatment, which resulted in a significantly higher collagen concentration (12,350 ± 173 pg/mL) compared to both PRP alone ($p = 0.0045$) and nanofat alone ($p = 0.0031$). This combination therapy not only promoted collagen biosynthesis more effectively, but also produced superior clinical results, as demonstrated by both objective and subjective assessments. Nanofat, which is emulsified and filtered fat, contains a high concentration of adipose stem cells. Numerous mesenchymal stem cells (MSCs) present in nanofat are referred to as nanofat-derived stem cells (NFSCs) [42]. NFSCs are a subset of adipose-derived stem cells (ASCs), which are known to participate in tissue repair [15]. The multiple differentiation and paracrine functions of ASCs contribute to their tissue-repairing properties, which are further enhanced by PRP stimulation [42]. Combined stimulation with PRP and nanofat appears to reinitiate cellular metabolic activity, leading to increased

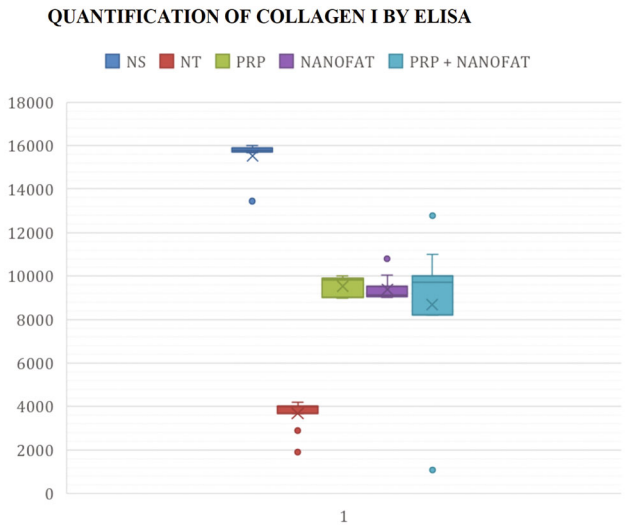

Fig. 4 Quantification of type I collagen obtained using enzyme-linked immunosorbent assay (ELISA) for Human Pro-Collagen I α1/COLIA1. NS: normal skin without stretch marks; NT: control, untreated stretch mark area (SA–NT). Amount of pro-collagen type I; Y = concentration pg / ml. In the image the small star (*) indicates that the observed differences were statistically significant compared to the control

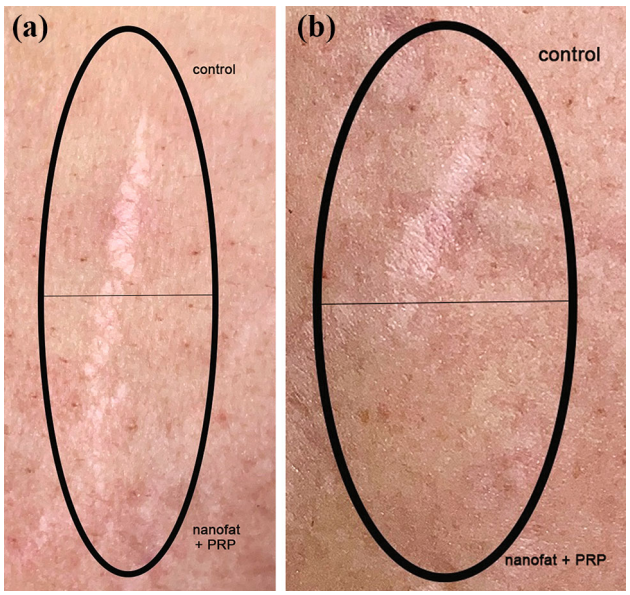

Fig. 5 This image shows a stretch mark divided into two parts on the abdominal region of a 43-year-old patient before the administration of the treatment. The upper half is the control area, and the lower half was treated with nanofat+PRP **a**. Three months after treatment, a clinical improvement is visible in the area that received the combined treatment **b**

production of type I collagen. In our study, nanofat treatment also resulted in a significant increase in collagen levels compared to the control. This increase supports the therapeutic potential of nanofat in treating striae albae, a condition considered pathological due to the underlying

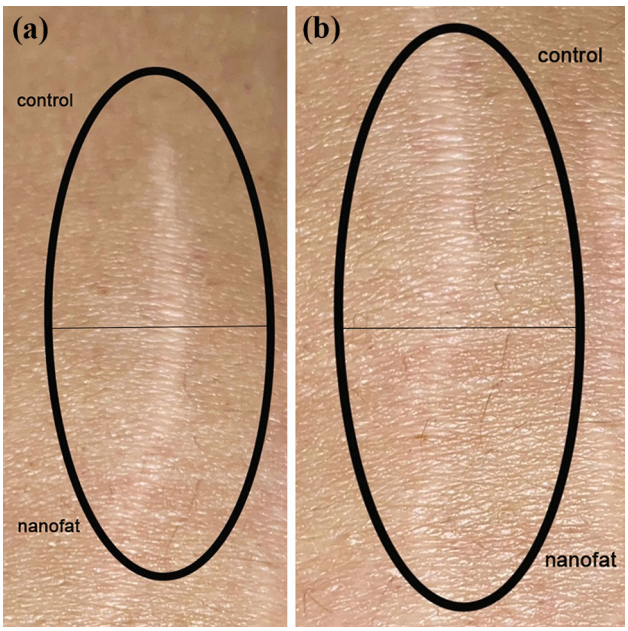

Fig. 6 This photograph shows a stretch mark divided into two parts on the abdominal region of a 38-year-old patient before the administration of the treatment. The upper half represents the control area that did not receive any treatment, while the lower half was treated with nanofat **a**. Three months after treatment, a slight clinical improvement is visible in the treated area **b**

tissue damage. In our study, the combined treatment of PRP and nanofat offered the best results for treating SA. While PRP and nanofat alone provided benefits, the combination of the two treatments produced a synergistic effect, leading to significantly better outcomes both histologically and clinically. This combination therapy could lead to improved clinical outcomes for patients with striae albae, providing a new avenue for treatment that harnesses the regenerative capabilities of both PRP and nanofat.

The primary limitation of this study is the absence of a control group treated with 0.9% saline alone. The effect of microneedling on scarring cannot be excluded, as it is known to promote collagen synthesis. To address this, future studies will take this factor into account, as it may introduce bias in the current research. Another limitation is the small sample size. However, since the treatments were applied to striae distensae with similar characteristics and each patient served as their own control, the results can be considered reliable. This approach effectively eliminates inter-individual variability that could arise from using different patients.

A further limitation may be the exclusive use of the ELISA method to quantify type I collagen. However, this technique is highly sensitive and specific, and has been widely validated in numerous studies [12] for its accuracy in detecting and measuring small amounts of proteins. Given resource constraints and the need for consistency in

our measurements, ELISA was the most practical and reliable choice for this study. Lastly, the timing of the clinical evaluation could also be considered a limitation. A 3-month post-treatment assessment may not provide a fully reliable measure, and a longer-term evaluation at one year would likely yield more consistent results. However, the primary objective of this study was to investigate type I collagen concentration in the treated areas.

To date, no studies have examined the effects of combined PRP and nanofat stimulation on SDs. [13–24]. The results of our study are very encouraging, offering a new potential effective treatment for stretch marks and other skin conditions where fibroblasts are in a quiescent state and need to be stimulated to reactivate their metabolism to produce type I collagen. The rationale behind the use of PRP and nanofat lies in the fact that they are autologous products, which therefore do not cause allergic reactions and both have significant regenerative potential [42]. The treatment is quick, can be performed on an outpatient basis, and is low cost.

Further analysis should be conducted on the count of stem cells actually present in the nanofat obtained using the described method to further validate its regenerative power. Additional multicentric randomized studies with a larger number of patients could be crucial to confirm our results, especially considering the clinical improvement of stretch marks after treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00266-024-04560-7.

Acknowledgements All the authors meet the criteria for authorship.

Declarations

Conflicts of interest The authors declare that they have no conflicts of interest to disclose.

Ethical Approval All procedures in the study involving human participants have been performed in accordance with the ethical standards of institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent All patients signed a written informed consent for enrollment in the study.

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