Transplantation of Autologous Fat, Stromal Vascular Fraction (SVF) Cell and Platelet Rich Plasma (PRP) for Cell Therapy of Atrophic Acne Scars: Clinical Evaluation and Biometric Assessment

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Abstract

Background: Scarring is an unfortunate result of acne, because it causes psychological and cosmetic problems to patients. Unluckily no single treatment is suitable; using multiple methods may have better result. autologous fat and stromal vascular fraction (SVF) cells and their secretory factors can and enhance angiogenesis, collagen synthesis, and migration of fibroblasts therefore regenerate hurt tissues. Also, other treatments for acne scarring, like platelet rich plasma (PRP), induce the scare improvement. The aim of the study was to verify the effectiveness of transplantation of autologous fat, SVF cells and PRP as cell therapy technique on atrophic acne scars.

Methods: This study included 9 adult patients with atrophic acne scars on the face. All patients received transplantation of autologous fat, stromal vascular fraction (SVF) cells and PRP. The treatment outcome was measured by biometric assessment (Visioface 1000 D, Colorimeter, multi probe adapter Cutometer, Tewameter, Mexameter, and skin ultrasound imaging system), also patients' satisfaction was evaluated. The patients were followed 6 months after treatment.

Results: A significant improvement in the skin pores, spots, skin lightness and melanin content of the skin, skin elasticity and TEWL after 6 months of treatment. Also denser skin layers were observed both in the epidermis and dermis. Furthermore, 66.6 % of the patients showed well satisfied after treatment.

Conclusion: Briefly, transplantation of autologous fat, SVF cells and PRP is an effective cell therapy for atrophic acne scars.

Introduction

Numerous skin disorders like scars or aging signs such as wrinkles may adversely affect the appearance and beauty of the skin. Scarring occurs as a natural process after a wound healing. However, the appearance of wounds is influenced by several factors. keloids and hypertrophic scars can treat by topical or injection application of corticosteroids [1]. However, there are some side effects like hypopigmentation and irreversible subcutaneous atrophy [2]. Scars are frequently treated by fewer invasive silicone dressing, but positive effects of them presently absence scientific evidence [3]. Laser therapy of scars is other option that may improve the appearance, however, laser technology has some limitation like skin discoloration [4, 5]. Finally, surgery can be a choice for treat overly obvious scars like dermabrasion, excision, subcision and skin grafting [6]. Nevertheless, aggressive surgical procedures are related to higher complications, leading to even larger scars with persistent contraction, which may worsen the condition [7]. By doing so, current scar treatments usually use ablative mechanisms that may have irreversible side effects. So, emphasizing the need for substitute techniques. Autologous fat injections have become very common in tissue regeneration over the past decade. Its good properties in regeneration and skin disorders have been reported in some studies [8–10]. Fat transplantation for repairing soft tissue defects have been applied for many years [1, 2]. Also in many study fat transplantation was used for acne scare treatment. [11, 12]. Particularly, the study's results on restoring

fat, bone, cartilage, nerve tissue, and muscle by adipose tissue-derived stem cells (ADSCs) have been informed [3, 10]. It is reported that ADSCs can repair damaged tissue by their secretory factors that can induce angiogenesis, collagen synthesis and fibroblasts migration [11]. Also, recently, platelet rich plasma (PRP), alone or in combination with other techniques, is considered for acne scare treatment. A combination of PRP with other treatment options was performed in the treatment of many dermatological disorders such as acne scarring [13, 14]. The PRP work way depends on the presence of protein, that increases the synthesis of collagen and elastic fibers lead to improves scar tissue and skin appearance [15, 16]. The present study aimed to assess the efficacy and safety of transplantation of autologous fat, stromal vascular fraction (SVF) cells and PRP as cell therapy for atrophic acne scars treatment.

Methods

Patients

In this study, 9 patients with rolling acne scars were enrolled. Lesions were graded and classified by a board-certified dermatologist. Virus tests was done for all patients before treatment. Exclusion criteria were as follow: the existence of any active infectious diseases, patients who had received any procedure for acne scar treatment, patients with history of coagulopathy, skin cancer, oral steroid therapy, anticoagulant therapy, patients with systemic retinoid intake in the previous six months, patients who were pregnant or lactating were excluded from the study.

Procedures and treatment monitoring

Liposuction surgical technique

Taking into attention the individual characteristics of each patient, donor areas were selected mostly from hip, the lower abdomen, and thigh before preparing the appropriate design. On the day of surgery, lipoaspiration and injection of adipose was performed. In either general anesthesia or twilight anesthesia, anesthesia was induced by tumescent fluid (500 mL normal saline with 15 ml of 2% lidocaine [Pasteur institute of Iran] and 7 mL of bicarbonate and 1 mg of epinephrine). After that, fat tissue was gathered with a Luer Lock syringe by utilizing a 2.4 mm cannula (Figure 1). The volume of fat that was collected from each patient was about 100 ml. The aspirated fat tissue was divided into two aliquots (50 ml). 50 ml of lipoaspirated directly was grafted in the face and 50 ml was used for the SVF cells isolation.

SVF cells isolation

To remove most red blood cells and leukocytes, the tissue was washed with phosphate-buffered saline (PBS) (Miltenyi Biotech, Cologne, Germany), then digested with type I collagenase (Worthington Biochemical Corp., Lakewood, USA) at 37 ° C, 20 minutes under unbroken shaking. Solution of collagenase, final concentration of 0.2%, was made just before use by adding collagenase powder to the Hanks balanced salt solution (HBSS) (Invitrogen, Carlsbad, USA). Digestion was prevented by washing

with PBS (3 times). Floating and lysed adipocytes were waste and cells of the SVF were pelleted by 10 min centrifugation at 500 g. The pellet was suspended in the HBSS and an erythrocyte lysis buffer (Sigma-Aldrich Corp, St. Louis, USA) was added and incubated 10 minutes at 37°C. This cell suspension was centrifuged (500 g, 5 min), and cells were counted and viability of cells were evaluated using Automatic cell counter (TC20^{TM} Automatic Cell Counter, Bio-Rad). Some of the suspension was subjected to flow cytometry (Partec, Görlitz, Germany) for evaluating cell surface markers and cell viability.

Platelet-rich plasma preparation

A sterile tube containing 1.5 mL anticoagulant (ACDA1) was arranged. Then, 10 mL of whole blood was drawn from each patient and collected in the sterile tube including 1 mL anticoagulant. In the next step the tube was centrifuged. The centrifugation process separates components of blood through their diverse specific gravities as follow; RBCs is the heaviest, after that WBCs, whereas platelets and plasma are the lightest. Centrifugation was performed in two-step; first step was a low level centrifugation to distinct whole plasma from platelets and red cells (at 900 RPM, 10-12 minutes). Then, all the supernatant plasma was aspirated by sterile angiocatheter and transferred from the tube in a sterile pure tube. The second step was high level centrifugation (2400 RPM, 8 minutes) to separated platelet-poor plasma from platelet-rich pellet; about 2/3 of the supernatant platelet-poor plasma were wasted and the platelet-rich pellet was re-suspended in the remaining volume of plasma. The count of platelet in the developed PRP was expected to be 3 to 4-fold more than in the whole blood. The obtained PRP was aspirated, and in order to platelets activation, 0.1 mL of calcium chloride was added per 0.9 mL of resulting PRP. The PRP of each patient was used to re-suspend the pellet of SVF for transplantation.

Transplantation of aspirated fat tissueand SVF cells

A topical anesthetic cream (EMLA containing 2.5%lidocaine HCL and 2.5 % prilocaine) was used for 45 minutes and afterward the area was sterilized via alcohol 70% and washed through normal saline to get finally dry skin surface. The aspirated fat tissue was injected (cannula with an 18-gauge blunt needle) subcutaneously into the skin of the face. Immediately, after aspirated fat tissue injection, the prepared SVF cells was re-suspend in the PRP and injected (1 mL syringe with a 30-gauge blunt needle) intradermal at the dose of 2×10^7 total for whole face of each patient.

Outcome evaluation

SVF cells outcome

The SVF cells counted by automatic cell counter. Also The SVF cells viability was evaluated by automatic cell counter. SVF cells surface markers and cell viability were evaluated by flow cytometry.

Patients outcome

Biometric assessment

Before and 6 months after treatment, Visioface (D1000 ck, Cologne, Germany) photographs of each patient were taken by a high-resolution digital camera. Biometric characteristics of the patients was evaluated by Visioface 1000 D, Colorimeter, multi probe adapter Cutometer (L parameter), Tewameter, Mexameter, (all purchased from Courage + Khazaka Electronics, Cologne, Germany) and a skin ultrasound imaging system (TPM, Luneburg, Germany) to calculate the skin layers' thickness, the skin lightness, the skin elasticity by providing three parameters (R2, R5, R7), trans epidermal water loss (TEWL) and melanin content and the intensity of skin erythema before and after aspirated fat tissue and SVF cells transplantation, respectively. When the transplantation procedure was performed and the patients were followed up for 6 months.

Patients' satisfaction

The participants were requested to scale their subjective satisfaction of the treatment on a quartile grading scale (grade 1 = slightly satisfied, grade 2 = moderately satisfied, grade 3 = well satisfied).

Statistical analysis:

After testing for normal distribution of data by Kolmogorov-Smirnov test, the data were analyzed using paired-samples t-test through SPSS 14.0 (SPSS Inc, Chicago, Illinois, the United States). In all tests, P value < 0.05 was considered statistically significant.

Results

Automatic cell counter

The viability and count of SVF cells harvest from fat tissue

The nucleated cell harvest was counted by the automatic cell counter. Also the cell viability of the cell was assessed. The results were shown in the Table 1 for each patients. The results showed that the mean of yield cell was $22 \pm 1.5 \times 10^6$ cells/mL of aspirated fat tissue and the mean of viability was 94.1 ± 2.5 (Table 1).

Table 1
Count and viability of SVF after evaluation by the automatic cell counter.

Sample No.	SVF count	SVF viability (%)	Total volume (mL)
1	24×10^6	92	80
2	28×10^6	93	80
3	22×10^6	95	80
4	25×10^6	94	80
5	20×10^6	93	80
6	19×10^6	98	80
7	21×10^6	90	80
8	20×10^6	97	80
9	23×10^6	95	80

Svf Cells Flow Cytometric Analysis

The viability of nucleated SVF cells

The viability of nucleated SVF cells isolated from all patients was evaluated by flow cytometry (Fig. 2). According to the flow cytometry results the mean viability of cells was about 97 ± 1.2%.

The Surface Markers Of Nucleated Svf Cells

The properties of SVF cells were investigated by flow cytometry (Fig. 3). The examination of the fresh isolated SVF cells surface markers displayed the expression of endothelial markers included CD146, CD31, and CD34. Moreover, the expressions of the mesenchymal markers comprising CD44, CD73, CD90, and CD105 were determined. It should be noted that CD44 is a hyaluronic acid receptor which contributes in the dermal thickness and can be used for the molecular cues of skin rejuvenation assessment. Also, CD14, CD15, and CD45 as hematopoietic stem cell markers were found in the SVF isolated cell population. The CD56, natural killer cell marker, was expressed as well.

Biometric Characteristic

The biometric data of the patients are shown in the Table 2. Briefly, the size and number of skin pores and spots were reduced after treatment (Figs. 4 and 5). The Visioface results displayed that the transplantation can significantly decrease the number of skin pores and skin spots, and the percentages of change in the number of fine pores, large pores and spots were 43.01 ± 11.14, 47.37 ± 14.13 and 41.98 ± 10.19, respectively (P < 0.001; Table 2). The colorimeter results showed the skin lightness before and after treatment was 11.46 ± 2.64 and 15.94 ± 2.86 (Table 2). There was a significant change in skin lightness before and after treatment Fig. 6, P < 0.05 and the percentage of change in the skin lightness after treatment was 36.79 ± 10.80, (Table 2) P < 0.05. Similarly, the results of Cutometer showed the significantly increase in the elasticity of the skin and the R2, R5 and R7 percentage of changes were (33.12 ± 8.28), (25.41 ± 11.38) and (36.09 ± 13.16) before and after treatment (P < 0.001). Also the results showed the treatment cause decreased in TEWL. The significant changes in melanin content of the patients were seen and the changes in the melanin content before and after treatment were (295.85 ± 80.98) and (200.43 ± 40.45) respectively and the percentage of melanin changes was (32.21 ± 10.72). There were not significant changes in erythema intensity before and after treatment (Table 2). Also, the results of skin ultrasonography exhibited denser skin layers both in the epidermis and dermis (Fig. 6; Table 2). According to the Table 2, a significant increase was detected in the density and thickness of the epidermis and dermis before and after treatment and the percentage of change in the density and thickness of the epidermis and dermis was (56.01 ± 30.41), (48.58 ± 50.12) and (58.04 ± 20.39), (43.11 ± 29.50) respectively (P < 0.001).

Table 2
Comparing biometric characteristics of the patient's skin before and 6 months after the treatment.

	Measured values		Percent change	P Value
	Before	After		
Skin Ultrasonography	20.00 ± 6.13	32.13 ± 11.26	60.13 ± 20.05	< 0.001
Skin Density (µm)	1190.25 ± 204.5	1594.15 ± 216.97	34.12 ± 13.12	< 0.001
Skin Thickness (µm)	35.24 ± 30.916	54.83 ± 31.12	56.01 ± 30.41	< 0.001
Epidermis Density Epidermis Thickness	195.40 ± 161.17	288.19 ± 199.45	48.58 ± 50.12	< 0.001
Dermis Density	19.50 ± 3.19	30.28 ± 12.74	58.04 ± 20.39	< 0.001
Dermis Thickness	954.25 ± 201.27	1364.10 ± 136.52	43.11 ± 29.50	< 0.001
Visioface	11.13 ± 3.63	6.30 ± 2.60	43.01 ± 11.14	< 0.001
Fine pores	0.19 ± 0.19	0.10 ± 0.11	47.37 ± 14.13	< 0.001
Large pores	17.13 ± 29.06	10.14 ± 11.76	41.98 ± 10.19	< 0.001
Spots				< 0.001
Mexameter	295.85 ± 80.98	200.43 ± 40.45	32.21 ± 10.72	< 0.01
Melanin	387.18 ± 81.43	379.21 ± 60.16	2.01 ± 1.06	0.583
Erythema				
TEWL[a]	15.23 ± 7.21	12.23 ± 5.12	20.21 ± 8.71	< 0.01
Skin lightness[b]	11.46 ± 2.64	15.94 ± 2.86	36.79 ± 10.80	< 0.01
Elastisity[c]	0.60 ± 0.12	0.80 ± 0.05	33.12 ± 8.28	< 0.01
R2	0.55 ± 0.30	0.69 ± 0.12	25.41 ± 11.38	< 0.01
R5	0.45 ± 0.04	0.61 ± 0.05	36.09 ± 13.16	< 0.01
R7				

[a] Transepidermal water loss, measured by Tewameter.

[b] Skin lightness measured by Colorimeter.

[c] Elasticity of the skin measured by Cutometer (mm/time).

Patients' Satisfaction Results

The mean score of patients' satisfaction was shown in the Table 3. 22.3% of the patients showed moderately satisfied and 66.6% showed well satisfied after treatment.

Table 3
Patient satisfaction six months after treatment. The P < 0.05 was considered as statistically significant in all the tests

Valid	Frequency	Percent	P value
No satisfaction	0	0%	0.01
Slightly satisfied	1	11.1	
Moderately satisfied	2	22.3	
Well Satisfied	6	66.6	
Total	9	100	

Discussion

Acne is a common disorder that affects about 80% of young and 5% of adult's people [17]. One of the major mechanisms that is involved in the atrophic acne scars pathogenesis is collagen loss. So, stimulation of collagen production is the goal of several methods that have been proposed for the acne scar treatment [18]. Fat transplantation has been displayed to have beneficial effects on acne scars, which were primarily treated for volume loss. It seems, fat transplantation can repair collagen organization and reduce the fibrotic response to radiation and it is most likely induce improvement by many growth factors already present in lipoaspirate, which helps regenerating and remodeling of skin and scars. Also, studies indicate that tissue remodeling, the formation of fresh and new blood vessels, and inflammatory responses are possible causes of scars treatment in fat transplantation [11]. Because of biocompatible and not immunogenic properties of the adipose tissue, it is an ideal transplant for a patient with acne scar. In addition, it is easy to yield with minimal side effects in the donor site. The first autologous fat transfer for facial volume loss was reported in 1893, when fat was applied to fill subcutaneous defects [19]. In 1912, the correction in retracted scar after mastectomy was reported by fat injections [12]. However, in recent times, the method of fat harvesting and injection has been modified and significantly improved, so it takes better results. In some studies, the plasticity and elasticity of scar tissue was increased, which was also observed microscopically in scar sample after lipofilling treatment [20, 21]. In previous clinical study, regenerative effects of adipose tissue in the dermis and subcutaneous tissue was informed [22, 23]. Fat transplantation has been applied in a diversity of disorders relating volume loss like panfacial global subcutaneous atrophy secondary to intrinsic aging or trauma [24].

Furthermore, stem cells have many unique properties that make them theoretically have great potential in managing a large number of diseases [25]. Some of these features include unlimited proliferation

capability and plasticity [26]. It seemed recent research have shown interested to use of stem cell injection in acne scars treatment [27]. There is mutual agreement that autologous adipose tissue-derived stem cells (ADSCs) are multi- and pluripotent [28–30]. ADSCs are found in large amounts in the stromal vascular fraction (SVF) of adipose tissue [31]. ADSCs and their secretory factors can induce angiogenesis, collagen synthesis and fibroblasts migration therefore regenerate impaired tissues [11]. In the Zhang et al. study the effect of intralesionally injection of adipose tissue derived stem cells into rabbit ears are evaluated and reduction in the hypertrophic scarring formation was reported by enhancing collagen deposition [32]. In Abou Eitta study, it is shown that ADSCs is more effective than fractional carbon dioxide laser in the treatment of acne scars [11]. The efficacy of ASCs on scar appearance improvement has been studied in some studies. In the study of Lee et al. it is reported that SVF cells injections can enhance tissue regeneration via contributing stem cells and growth factors to improve the results in tissue grafts or scar revisions [33]. Lee and collogues evaluated the effect of combination of adipose tissue with SVF cells on the facial skin disorder and they declare Facial Soft Tissue significantly increase in the facial area grafted with adipose tissue in combination with SVF cells in compare to adipose tissue without SVF cells [34]. Also Recently, platelet-rich plasma (PRP) used alone or in combination with other therapy as an effective option for the atrophic acne scars treatment [14, 35]. The PRP work way depends on the presence of protein, that increases the synthesis of collagen and elastic fibers lead to improves scar tissue and skin appearance [15, 16]. So in recent study we used combination of transplantation of autologous fat, SVF cells and PRP for atrophic acne scars treatment. In the study of Gentill et al., the effect of SVF cells and PRP the face scars were evaluated and they reported that the patients showed 69% maintenance of contour restoring after fat grafting and PRP treatment [36]. In the Pradeep V Mahajan study. Regenerative Medicine Using Platelet Rich Plasma and Stem Cells in Atrophic Acne Scars: A Case Report [37]. Our results showed that transplantation of autologous fat and SVF cells and PRP is a good technique for treatment of atrophic acne scars with significantly increase in skin lightness and melanin content of the skin. Also the elasticity of the skin was increased. Oure results indicated that number of skin fine pores, large pores and spots were significantly decrease after treatment. Briefly transplantation of autologous fat, SVF cells and PRP is very promising strategy based on cell therapy for atrophic acne scars improvement with a minimal side effect.

Conclusion

transplantation of autologous fat, SVF cells and PRP is very promising strategy based on cell therapy for atrophic acne scars improvement by repair the collagen organization, increase elastic fibers and reduce the fibrotic response to radiation and it is most likely induce improvement by many growth factors, which helps regenerating and remodeling of skin and scars. Also, tissue remodeling, the formation of fresh and new blood vessels, and inflammatory responses are possible causes of scars treatment in this technique.

Declarations

Abbreviations

SVF
stromal vascular fraction
PRP
platelet rich plasma
PBS
phosphate-buffered saline
ADSCs
autologous adipose tissue-derived stem cells
HBSS
Hanks balanced salt solution
RBC
Red Blood Cells
WBC
Wight Blood Cells

Declarations

Ethical Approval and Consent to participate

The authors stat that the patients have given their informed consent for participate, the photos and details.

Consent for publication

The authors stat that the patients have given their informed consent for the photos, details and publication.

Availability of data and material

Data available on request from the authors

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Authors' contributions

Mohammad Ali Nilforoushzadeh: Supervisor, Maryam Heidari-Kharaji: Manuscript writing and data analysis, Shiva Alavi: clinical methods, Mona Mahmoudbeyk: Collecting data, Maryam Nouri: Biometric characteristics evaluation, Aisan Peyrovan: Collecting data, Sona Zare: PRP preparation and cell evaluation.

Competing interests

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Figures

Figure 1
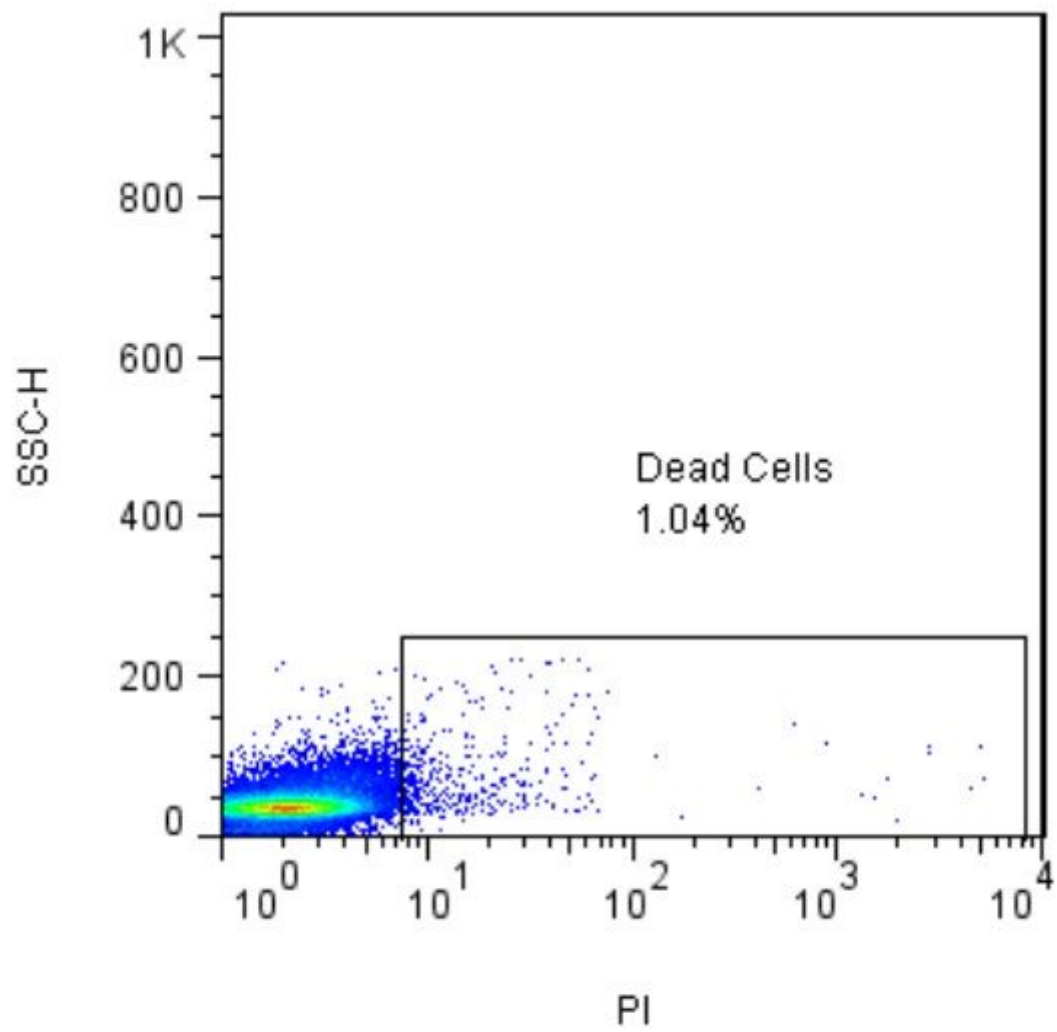
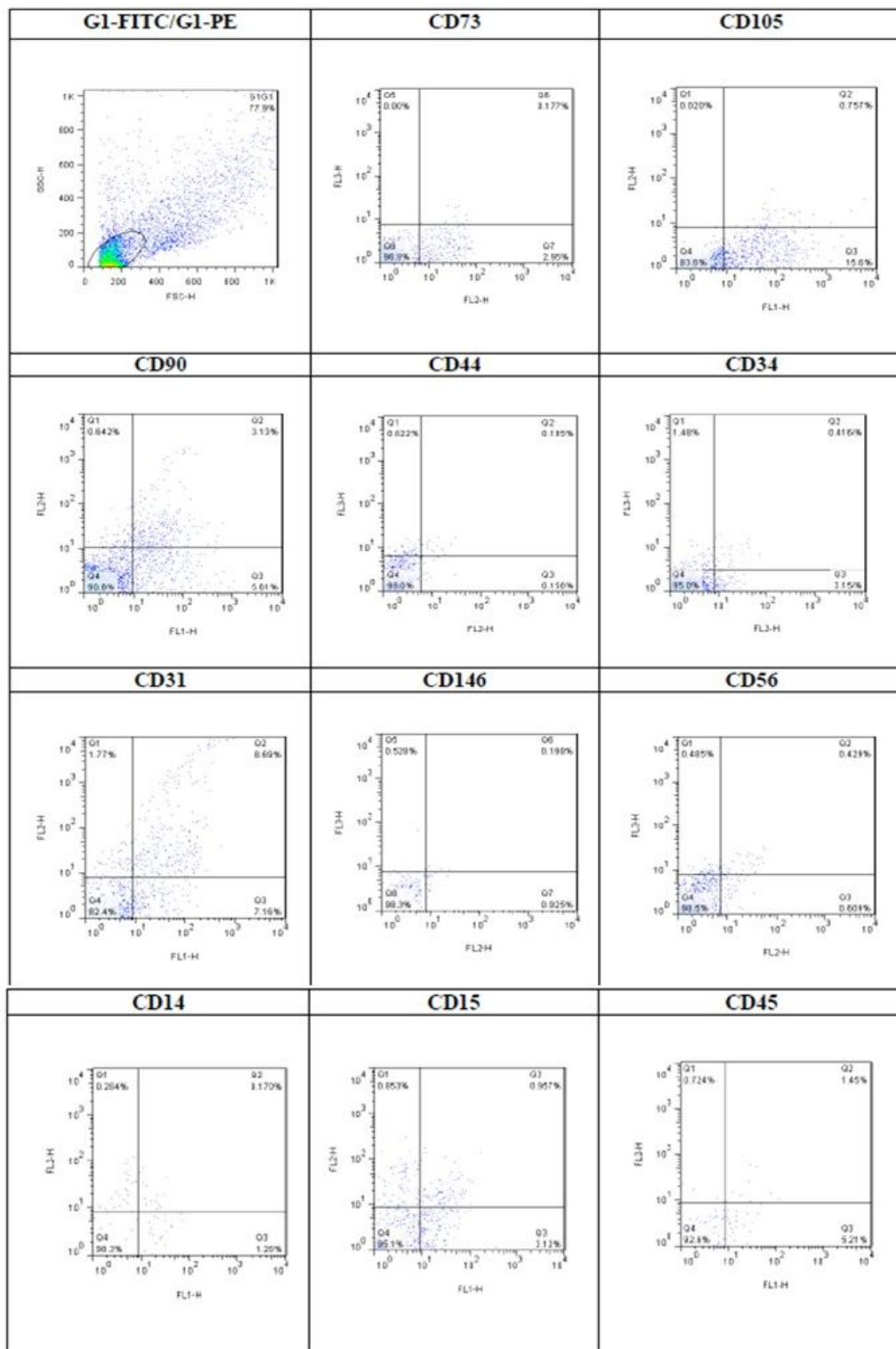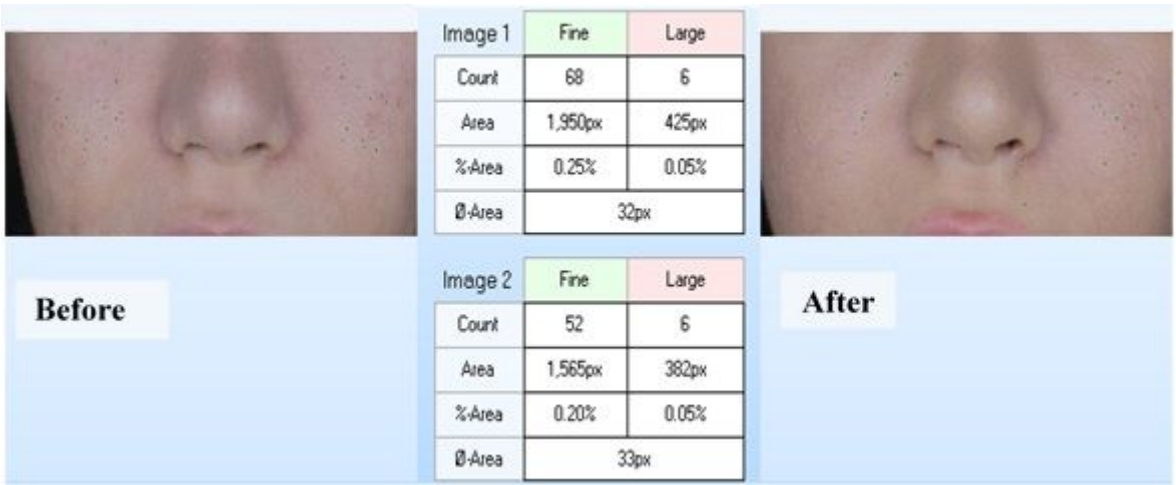SVF-T.060
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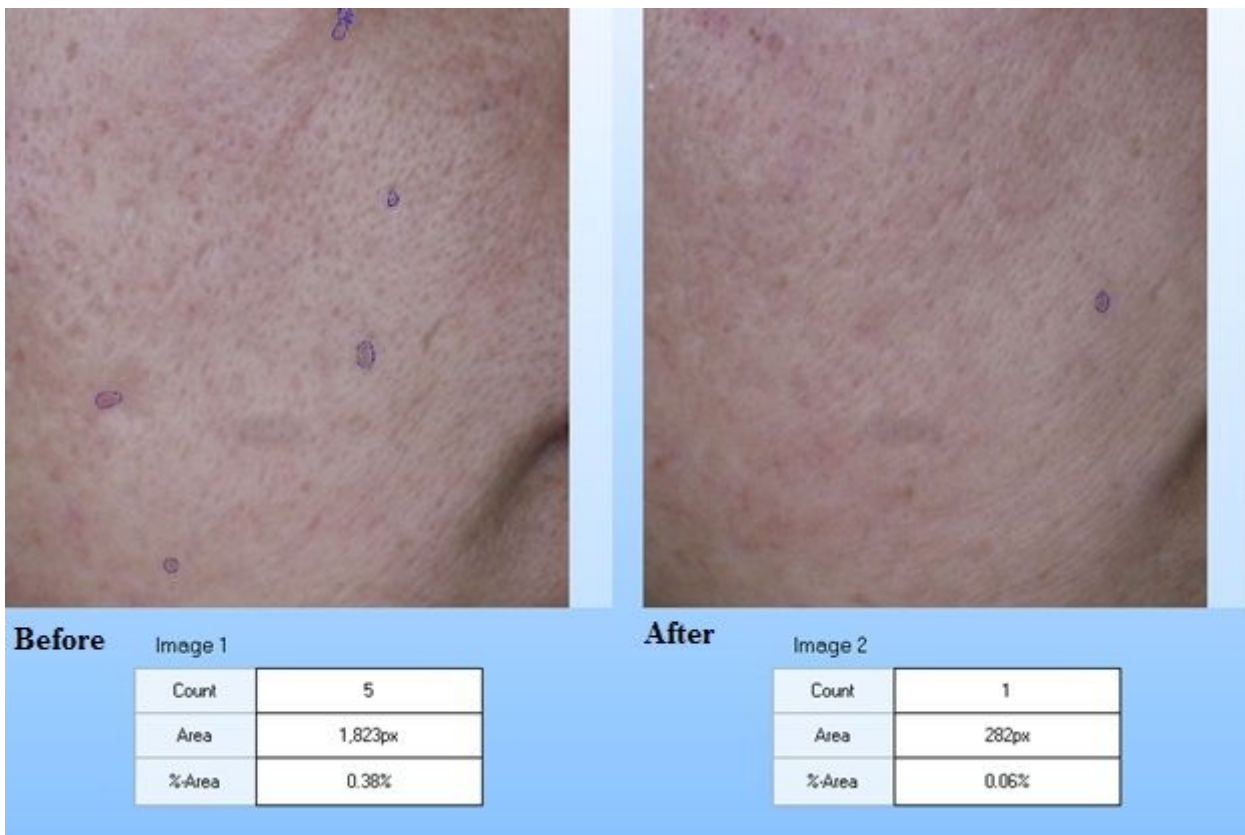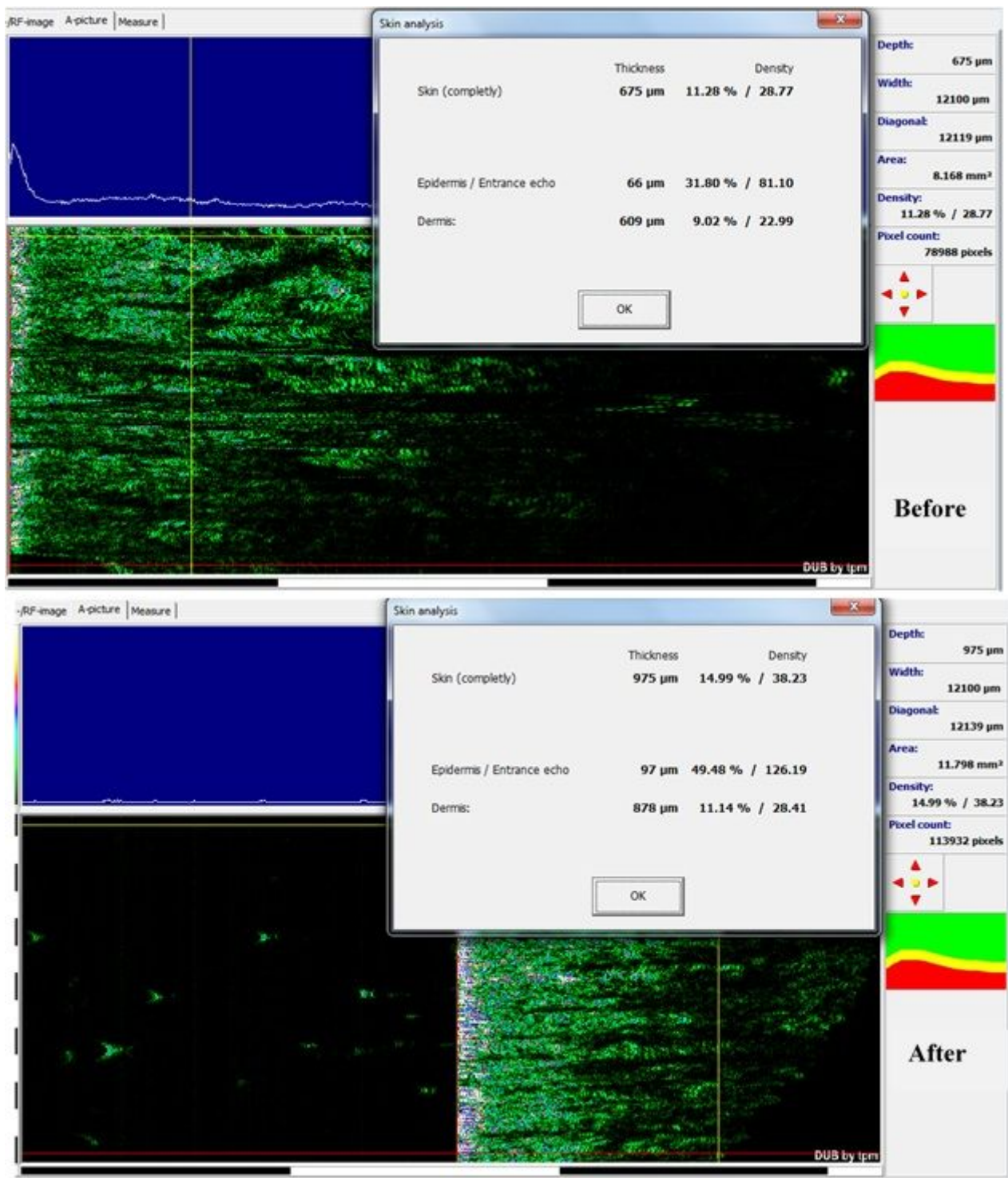42497

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6