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Contents

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All articles in their final version - completed with name, surname, affiliation, address, phone number and e-mail address of the author (s) - must be sent in word format to the Editorial Committee at the following e-mail address: aemj@aestheticmedicinejournal.org. Manuscripts must be written in English, and authors are urged to aim for clarity, brevity, and accuracy of information and language. All manuscripts must include a structured abstract. Authors whose first language is not English should have their manuscripts checked for grammar and stylistic accuracy by a native English speaker.

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· The authors must disclose any commercial interest that they may have in the subject of study and the source of any financial or material support

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The length of the abstract should be no more than 250 words and should include the following headings: Background, Aim, Methods, Results, Conclusions

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· Results
· Discussion and Conclusions
· Acknowledgments
· Conflict of interest
· Reference list
· Legends (max 10)

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· Use tab stops or other commands for indents, not the space bar
· Use the table function, not spreadsheets, to make tables

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The authors declare that they have no conflict of interest.
If potential conflicts of interest do exist, the authors should provide details (see below) for each affected author in a note in a separate DISCLOSURE section of the manuscript document text, before the list of references.

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Journal article - online* *if there is no DOI, provide the URL for the specific article	Coppinger T, Jeanes YM, Hardwick J, Reeves S. Body mass, frequency of eating and breakfast consumption in 9-13- year-olds. *J Hum Nutr Diet.* 2012; 25(1): 43-49. **doi: 10.1111/j.1365-277X.2011.01184.x**
Journal article - online from a library database* *there is no specific way to cite articles found in library databases according to the AMA so double check with your professor	Calhoun D, Trimarco T, Meek R, Locasto D. Distinguishing diabetes: Differentiate between type 1 & type 2 DM. *JEMS* **[serial online].** November 2011; 36(11):32-48. **Available from: CINAHL Plus with Full Text, Ipswich, MA. Accessed February 2, 2012.**
Newspaper article - in print* *if the city name is not part of the newspaper name, it may be added to the official name for clarity * if an article jumps from one page to a later page write the page numbers like D1, D5	Wolf W. State's mail-order drug plan launched. *Minneapolis Star Tribune.* May 14, 2004:1B.
Newspaper article - online	Pollack A. FDA approves new cystic fibrosis drug. *New York Times.* January 31, 2012. http://www.nytimes.com/2012/02/01/business/fda-approves-cystic-fibrosis-drug.html?ref=health Accessed February 1, 2012.
Websites	Outbreak notice: Cholera in Haiti. Centers for Disease Control and Prevention Web site. https://www.cdc.gov Published October 22, 2010. Updated January 9, 2012. Accessed February 1, 2012.
Entire book - in print	Modlin J, Jenkins P. *Decision Analysis in Planning for a Polio Outbreak in the United States.* San Francisco, CA: Pediatric Academic Societies; 2004.
Book chapter - in print	Solensky R. Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. In: Lockey P, ed. *Allergens and Allergen Immunotherapy.* 3rd ed. New York, NY: Marcel Dekker; 2004:585-606.

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Example Article

1. Zoellner J, Krzeski E, Harden S, Cook E, Allen K, Estabrooks PA. Qualitative application of the theory of planned behavior to understand beverage consumption behaviors among adults. J Acad Nutr Diet. 2012;112(11):1774-1784. doi: 10.1016/j.jand.2012.06.368.

In-Text Citation Example

LARGE INCREASES IN AMERICANS' CONSUMPTION OF sugar-sweetened beverages (SSB) have been a topic of concern. Between 1977 and 2002, the intake of "caloric" beverages doubled in the United States, with most recent data showing that children and adults in the United States consume about 172 and 175 kcal daily, respectively, from SSB,[1] it is estimated that SSB account for about 10% of total energy intake in adults[2,3]. High intake of SSB has....

References Section Example

References

1. Duffey KJ. Popkin BM. Shifts in patterns and consumptions of beverages between 1965 and 2002. *Obesity.* 2007:15(11):2739-2747.
2. Nielsen SJ. Popkin BM. Changes in beverage intake between 1977 and 2001. *Am J Prev Med.* 2004;27(3):205-210.
3. Drewnowski A. Bellisle F. Liquid calories, sugar, and body weight. *Am J Clin Nutr.* 2007;85(3):651-661.

Use commas to separate multiple citation numbers in text, like you see between references 2 and 3. Unpublished works and personal communications should be cited in the text (and not on the reference list).1 Superscript numbers are placed outside periods and commas, and inside colons and semicolons. When citing the same source more than once, give the number of the original reference, then include the page number (in parentheses) where the information was found. See pages 41-44 of the AMA Manual of Style for more information.

References

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aesthetic medicine

Original Article

Dermocosmetology and breast cancer patients: effectiveness on physical and mental wellbeing

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Abstract
Background: breast cancer (BC) treatments could be the cause of side effects affecting the skin which reduce compliance to therapy and negatively impact on the patients' perception of Body Image, on their well-being and quality of life (QoL).
Aim: the goal of this study is to evaluate if a specific dermatological treatment could reduce skin related side effects and consequently improve the patient's well-being.
Methods: sixty-one women with BC were recruited. They were divided into two groups based on the treatments they were to undergo (radiotherapy or chemotherapy) and, in turn, each group was randomized in Experimental (EG) and Control Group (CG). For 28 days, EG use a specific dermatological treatment, while CG use a non-specific treatment. Participants were asked to perform 3 self-report instruments (Skindex-16, Body Image Scale, WHOQoL-Brief) at three points: at baseline (T0), after 7 days (T1) and after 28 days (T2).
Results: after 28 days both EG showed statistical significative improvement in their symptomatology accompanied by a better perception of their Body Image. Data revealed that QoL in patients of both EG enhanced after 28 days of treatments regarding physical and psychological health, social relationship and environment. On the contrary patients belonging to both CG didn't show the same level of improvement over time.
Conclusions: our results show that the use of specific dermatological products designed for the treatment of skin related side effects of cancer helps to reduce the negative impact of skin-related symptoms on HRQoL. Consequently, it leads women in terms of QoL.

Keywords
Dermocosmetological treatments, breast cancer, skin, body image

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Introduction

In Italy, in 2019 almost 175.000 women were diagnosed with malignancy. Breast cancer is the most common form of cancer in adult women, diagnosed both in the age group ranging from 0-49 (40%) and from 50-69 (35%) years old[1]. In attempt to cure breast cancer, a mastectomy or conserving surgery combined with radiotherapy or other cancer treatments, such as chemotherapy[2] can be prescribed. Oncological treatments may cause temporary or permanent consequences on the patient's physical features due to their side effects which include skin toxicity and skin-related disorders.
External beam radiation therapy is usually prescribed for breast cancer. The most unpleasant events of this treatment are linked to tactile and nociceptive effects, such as pain, and changes in skin colour and texture[3]. Radiotherapy can induce acute skin reactions (radiation dermatitis) that may range from a mild erythematous rash to severe ulceration. Approximately 85% of patients treated with radiotherapy will experience a moderate-to-severe skin reaction[4-5]. Skin toxicity caused by chemotherapy agents is often multifactorial since other factors (such as chronic diseases or the simultaneous intake of multiple drugs) may play a role other than the drug itself. Chemotherapy causes several adverse events acting against the skin, mucosa and adnexa[5]. Cytotoxic agents like cyclophosphamide, chlorambucil, busulfan and procarbazine can cause adverse events affecting hair and nails (alopecia, paronychia, melanonychia and other abnormalities), skin (erythematousrash, dryness, hyperpigmentation) and mucosa (mucositis, Steven-Johnson syndrome and toxic epidermic necrolysis)[6-8]. Dry skin is often associated with pruritus, pigmentation alterations, nail changes, mucositis, photoreactions, radiodermatitis and alopecia, which are common findings of this type of treatment[9]. Adverse events due to chemotherapy and radiotherapy can reduce the patient's compliance to the therapy and also negatively impact on the women's well-being perception and quality of life (QoL)[3,6]. Distortion in the patient's perception of their body image is commonly experienced during cancer treatments by the majority of women diagnosed with breast cancer[10-17]. Body Image represents a multidimensional structure which includes cognitive, behavioural and affective aspects related to physical appearance[18]. Women who are treated for breast cancer are exposed to marked changes in their physical appearance, such as resection or disfigurement of one or both breasts, surgical scars and skin adverse events related to treatments[19]. Alterations of Body Image can be accompanied with shame, low self-esteem or social avoidance[20,21] and psychological distress in the forms of depression and anxiety[22,23]. Hopwood et al.[24] identified three areas that characterize the complex concept of Body Image in breast cancer patients: affective (feeling feminine, feeling attractive), behavioural (avoiding people because of appearance), and cognitive aspects (satisfaction with appearance, or with scar). In some patients, the negative conception of their own Body Image can persist for a long period after their treatment[19,25] and can negatively impact on the patient's QoL[10]. Therefore, Body Image is acknowledged as an important aspect of Health-Related Quality of Life (HRQOL) in cancer patients[10,26,27]. It is important to mention how to manage the skin related side effects secondary to the treatments, which could require a resolution time that goes beyond the end of oncological therapies. Moreover, it is important to monitor the changes in QoL in order to identify the benefits resulting from supportive care. The aim of this study is to evaluate the impact of skin side-effects of oncological treatments on HRQoL and on Body Image perception in breast cancer patients. In particular, we hypothesized that specific cosmetic treatments could significantly improve the women's wellbeing, decreasing the negative impact of iatrogenic side effects and enhancing Body Image perception and the QoL during antitumoral treatments.

Materials and Methods

We performed a monocentric observational study including 61 women with breast cancer who were enrolled at the Oncology Unit of ASST Bergamo Est, Italy. The inclusion criteria were women of age greater than 30 years old, who had received a diagnosis of breast cancer and were undergoing traditional chemotherapy or radiotherapy treatment. Patients were excluded from the study if they had previously skin related diseases and if they had psychiatric or neurological conditions.
Participants were randomized using a double-blind procedure in two groups: Experimental Group (EG) and Control Group (CG). In turn, each group was divided in two subgroups: women treated with chemotherapy and women treated with radiotherapy. All participants were asked to use a dermatological cosmetic: EG used a specific product for secondary side effects of oncological treatments, while CG used a non-specific product. The specific product is a lotion based on Almond Oil, Rice Oil, Vitamin E and shea butter, enriched with a hydration factor which guarantees the respect for the Natural Moisturizing Factor (NMF). For each woman of either experimental and control groups, sociodemographic (age, civil status, education, working profession, residency) and medical history (age at diagnosis, type of current or previous treatments, genetic mutation) data were registered. QoL-related questionnaires (Skindex-16, Body Image Scale, WHOQOL-Brief) were performed at three time points: at baseline during the recruitment (T0), after 1 week (T1) and after 28 days (T2) from when they enrolled. Women received the topical treatment at T0, when they started cancer treatment, in order to use it every day for the entire duration of the study. At the end of the dermatological treatment, the oncologists conducted a final evaluation on the skin's reaction to chemotherapy and radiotherapy. Skindex-16 is a self-report instrument that measures the effects of skin disease on HRQoL[28,19]. It is composed of 16 items rated on a 7 point Likert Scale, ranging from 0 (*never bothered*) to 6 (*always bothered*). It is divided into three subscales: Symptomatology, Social functioning and Emotive statement. Each categorical question asks the level of concern or discomfort related to the patient's skin condition. Scale of Skindex-16 had a high degree of internal consistency (Cronbach's α = .86, α = .93, α

= .92 for the Symptomatology, Emotive statement and Functioning scale respectively)[29].

The Body Image Scale (BIS)[24,30] is a self-report questionnaire which measures affective, behavioural and cognitive aspects linked to body image. It is composed of 10 items rated on a 5 point Likert Scale as follows: 0 (*never*), 1 (*a little*), 2 (*mildly*), 3 (*a lot*), 4 (*I don't know*). Five of ten items deal with general Body Image issue (i.e., feeling self-conscious, dissatisfied with body), the other five items are related to Body Image in relation to the cancer diagnosis (i.e., less feminine, body less whole). The BIS final score ranges from 0 to 30. A high score stays if there is a discomfort in the patient's perception of their Body Image. The Italian validation of BIS was done by Cheli et al.[30] showing a strong internal consistency (α = .91). WHOQOL-BREF[31,32] is a self-report questionnaire composed of 26 items assessing how individuals perceive each aspect of their life through 4 different aspects: *physical health, psychological health, social relationships and environment*. This tool has shown good psychometric properties in previous studies, in particular the WHOQOL-BREF items proved to have good internal consistency in the Italian context, ranging from 0.65 for the social relationship aspect to 0.80 for the physical aspect. In this study, the global internal consistency was 0.83. Cronbach's alpha of single subscales ranges from 0.68 (social relationship) to 0.80 (physical health).

Statistical analysis

Statistical analyses were performed using the Jamovi Software (Version 1.6.3.0, The Jamovi Project 2019, retrieved from https://www.jamovi.org). Groups were first explored using descriptive and frequency analyses to describe the whole sample and to investigate the possible presence of missing data. A second analysis, one-way analysis of variance (ANOVA) was conducted to investigate statistically significant difference between the four groups at the baseline, based on the questionnaires' results. Furthermore, an ANOVA for repeated measures and a Bonferroni post hoc test were performed to evaluate the trend of the variables across the three time points (at baseline - T0, 7 days after - T1 and 28 days after - T2).

Results

The study involved 61 women, 30 randomized to the EG (15 treated with chemotherapy and 15 treated with radiotherapy) and 31 to the CG (16 treated with chemotherapy and 15 treated with radiotherapy). *Table 1* reports information about patients' sociodemographic and clinical characteristics. The four groups were investigated on the following points:

- Skin disease: at T0, there wasn't any statistical difference between the four groups in terms of impact of skin lesions on their HRQoL. Patients of the EG treated with radiotherapy demonstrated strong improvement in their symptoms ($p < 0.05$), emotions ($p < 0.05$) and functioning ($p < 0.05$) already after 7 days of treatment. After 28 days of treatment, EG patients treated with chemotherapy and radiotherapy, showed a statistically significant improvement in their symptoms ($p < 0.001$, $p < 0.001$, respectively; *Figure 1A*), emotions ($p < 0.001$, $p < 0.001$, respectively; *Figure 1B*) and functioning ($p < 0.001$, $p < 0.001$, respectively; *Figure 1C*). Patients treated with chemotherapy and radiotherapy belonging to the CG did not exhibit any improvement during the study period.

- Body Image: at T0, there was no statistical difference between the four groups in terms of affective, behavioural and cognitive aspects related to Body Image perception. Patients of the EG treated with radiotherapy showed a statistical improvement already after 7 days of treatment ($p < 0.01$).
  After 28 days of treatment, the mean score of EG patients, treated with radiotherapy and chemotherapy, was significantly lower than at the baseline ($p < 0.001$, $p < 0.001$, respectively; *Figure 1D*). Women treated with chemotherapy and radiotherapy belonging to the CG did not show any improvement during the study period.

- Quality of life: at baseline, patients belonging to the EG and treated with chemotherapy showed higher scores in physical health than patients of the same group treated with radiotherapy ($p < 0.05$). Considering the psychological health item, patients of the EG treated with chemotherapy exhibited higher scores than patients treated with radiotherapy, both in the EG and CG ($p < 0.05$, $p < 0.01$, respectively).
  Furthermore, patients of the EG treated with chemotherapy showed higher scores in the environmental item than women treated with radiotherapy, both in EG and CG ($p < 0.001$). Considering the same domain, patients of the CG treated with chemotherapy showed higher scores than those treated with radiotherapy, both in EG and CG ($p < 0.01$, $p < 0.001$, respectively).

For the physical health domain (*Figure 2A*), patients of the EG treated with chemotherapy and radiotherapy showed significant improvement both after 7 days ($p < 0.01$, $p < 0.001$) and after 28 days ($p < 0.001$, $p < 0.001$) of treatment. In terms of psychological health (*Figure 2B*), significant improvement was observed after 28 days of treatment for EG patients, treated with chemotherapy and radiotherapy ($p < 0.001$, $p < 0.001$, respectively). In addition, patients of EG treated with radiotherapy showed statistical improvement already after 7 days of treatment ($p < 0.05$). For social relationships domain (*Figure 2C*), a significant improvement was reported after 28 days of treatment, but not after 7 days, for EG patients, treated with chemotherapy and radiotherapy ($p < 0.05$, $p < 0.05$, respectively). Considering the environmental domain (*Figure 2D*), after 28 days of treatment EG patients, showed a statistically significant improvement ($p < 0.05$, $p < 0.001$, respectively). Patients treated with radiotherapy showed a significant improvement already after 7 days of treatment ($p < 0.001$). In all four domains, patients treated with chemotherapy and radiotherapy belonging to the CG did not exhibit any improvement during the study period. Skindex-16, Body Image and WHOQOL-Bref scores are reported in *Table 2*.

Sociodemographic variables			Clinical variables		
	Frequencies (%)			Frequencies (%)	
Age, years (mean) Education	**54.4 (range: 41-75)**		**Type of cancer**		
< High school diploma	17	27.9	Breast cancer	59	96.7
HS diploma	27	44.3	Metastatic breast cancer	2	3.3
> HS diploma	7	27.9			
			Diagnostic age, years (mean) Treatments	**53.5 (range: 40-75)**	
Marital status					
Married	56	91.8			
Not married	5	8.2	Chemotherapy	34	55.7
			Radiotherapy	30	49.2
Employment			Surgery	60	98.4
Employed	9	14.8	Hormone treatment	21	34.4
Precarious	33	54.1	Enantone	12	19.7
Housewife	19	31.1	Vaccine	20	31.8

Table 1 *- Characteristics of the study sample (N=61).*

Questionnaire	Subscales	Groups	T0 enrollment Mean (SD)	T1 after 7 days Mean (SD)	T2 after 28 days Mean (SD)	Interaction between time and aesthetic treatment *p* value
Skindex-16	Symptoms	EG Chemotherapy	3.32 (0.486)	2.62 (0.886)	1.57 (0.770)	$p < 0.001$
		EG Radiotherapy	3.35 (1.295)	2.37 (0.865)	1.98 (1.195)	
		CG Chemotherapy	3.06 (1.039)	2.70 (0.833)	2.84 (0.970)	
		CG Radiotherapy	3.15 (0.986)	3.30 (0.851)	3.17 (0.816)	
	Emotions	EG Chemotherapy	3.30 (0.541)	2.50 (0.862)	1.72 (0.880)	$p < 0.001$
		EG Radiotherapy	3.22 (1.213)	2.26 (1.069)	1.97 (1.142)	
		CG Chemotherapy	3.20 (0.917)	2.85 (0.504)	2.90 (0.657)	
		CG Radiotherapy	3.27 (0.889)	3.36 (0.806)	3.30 (0.886)	
	Functioning	EG Chemotherapy	3.05 (0.840)	2.56 (0.989)	1.61 (0.686)	$p < 0.001$
		EG Radiotherapy	3.35 (1.065)	2.39 (1.115)	2.07 (1.202)	
		CG Chemotherapy	3.10 (1.065)	2.77 (0.505)	2.80 (0.793)	
		CG Radiotherapy	3.23 (0.965)	3.41 (1.076)	3.36 (0.936)	
Body Image Scale	Total Score	EG Chemotherapy	19.5 (5.71)	16.9 (3.36)	12.4 (5.87)	$p < 0.001$
		EG Radiotherapy	22.5 (2.29)	16.8 (3.80)	13.9 (4.03)	
		CG Chemotherapy	20.9 (3.32)	19.1 (3.75)	19.1 (4.30)	
		CG Radiotherapy	21.7 (4.61)	22.3 (4.10)	22.9 (2.94)	
WHOQOL-Bref	Physical health	EG Chemotherapy	3.30 (0.201)	3.62 (0.313)	3.90 (0.372)	$p < 0.001$
		EG Radiotherapy	3.16 (0.241)	3.57 (0.382)	3.76 (0.536)	
		CG Chemotherapy	3.19 (0.207)	3.21 (0.244)	3.23 (0.285)	
		CG Radiotherapy	3.07 (0.178)	3.04 (0.250)	3.03 (0.316)	
	Psychological health	EG Chemotherapy	3.01 (0.213)	3.17 (0.351)	3.53 (0.338)	$p < 0.001$
		EG Radiotherapy	2.74 (0.288)	3.01 (0.447)	3.26 (0.573)	
		CG Chemotherapy	2.80 (0.299)	2.77 (0.321)	2.77 (0.333)	
		CG Radiotherapy	2.69 (0.251)	2.57 (0.294)	2.52 (0.314)	
	Social relationships	EG Chemotherapy	3.02 (0.527)	3.02 (0.495)	3.40 (0.361)	$p < 0.01$
		EG Radiotherapy	2.84 (0.452)	3.18 (0.547)	3.20 (0.532)	
		CG Chemotherapy	2.92 (0.333)	2.96 (0.319)	2.94 (0.327)	
		CG Radiotherapy	2.69 (0.344)	2.64 (0.320)	2.67 (0.282)	
	Environment	EG Chemotherapy	3.74 (0.266)	3.94 (0.320)	4.06 (0.246)	$p < 0.001$
		EG Radiotherapy	3.12 (0.500)	3.60 (0.604)	3.98 (0.458)	
		CG Chemotherapy	3.64 (0.261)	3.60 (0.214)	3.60 (0.282)	
		CG Radiotherapy	3.10 (0.406)	3.07 (0.393)	3.10 (0.340)	

EG = Exerimental Group, CG = Control GroupWHOQOL-Bref = World Health Organization Quality Of Life – Shorter version

Table 2 *- Skindex-16 subscales, Body Image Scale and WHOQOL-Bref subscales mean scores in the experimental and control groups, at T0, T1 and T2.*

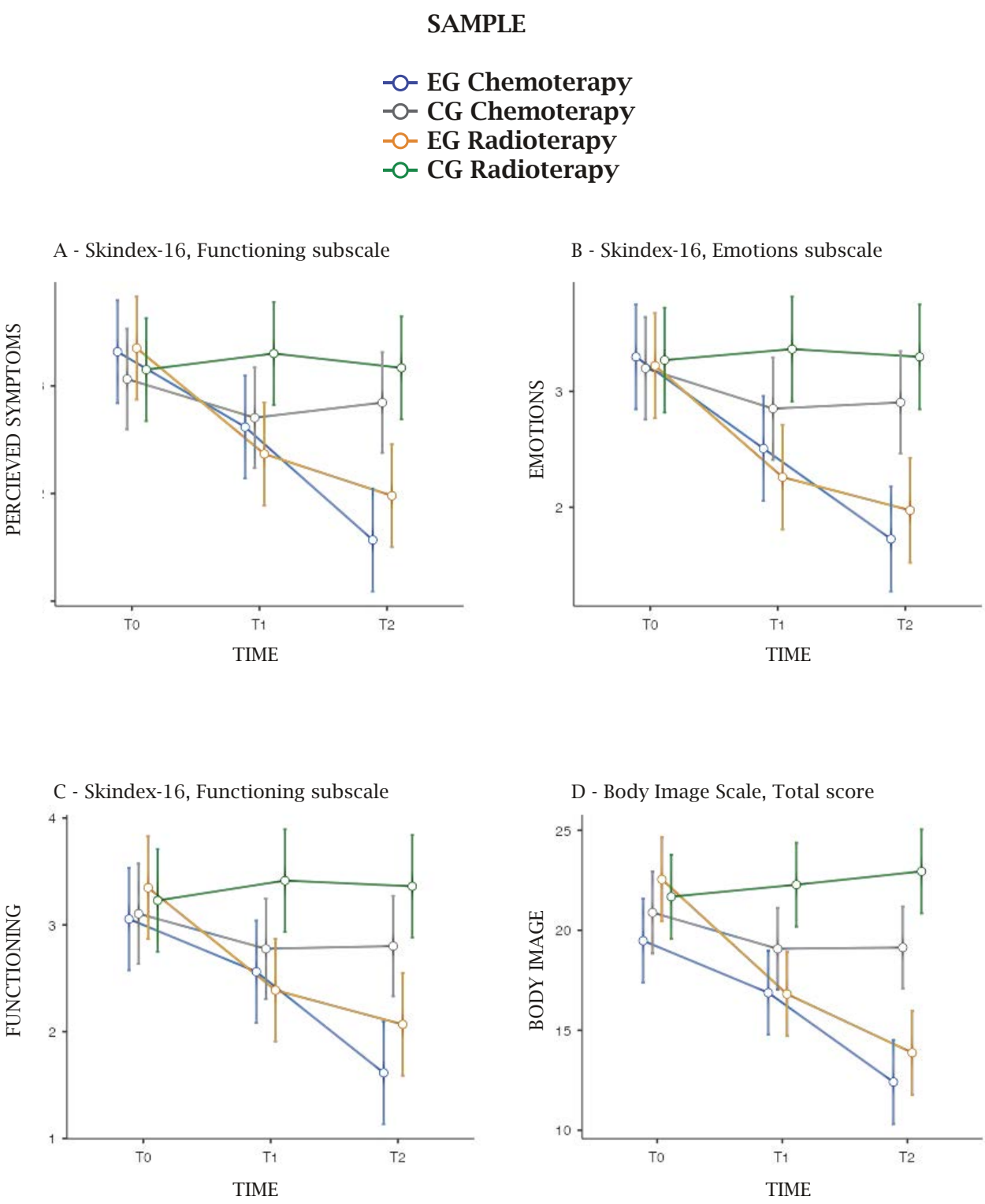

Figure 1 *- Interaction between time and aesthetic treatment effects on Skindex-16 and Body Image Scale scores in different cancer treatments groups.*

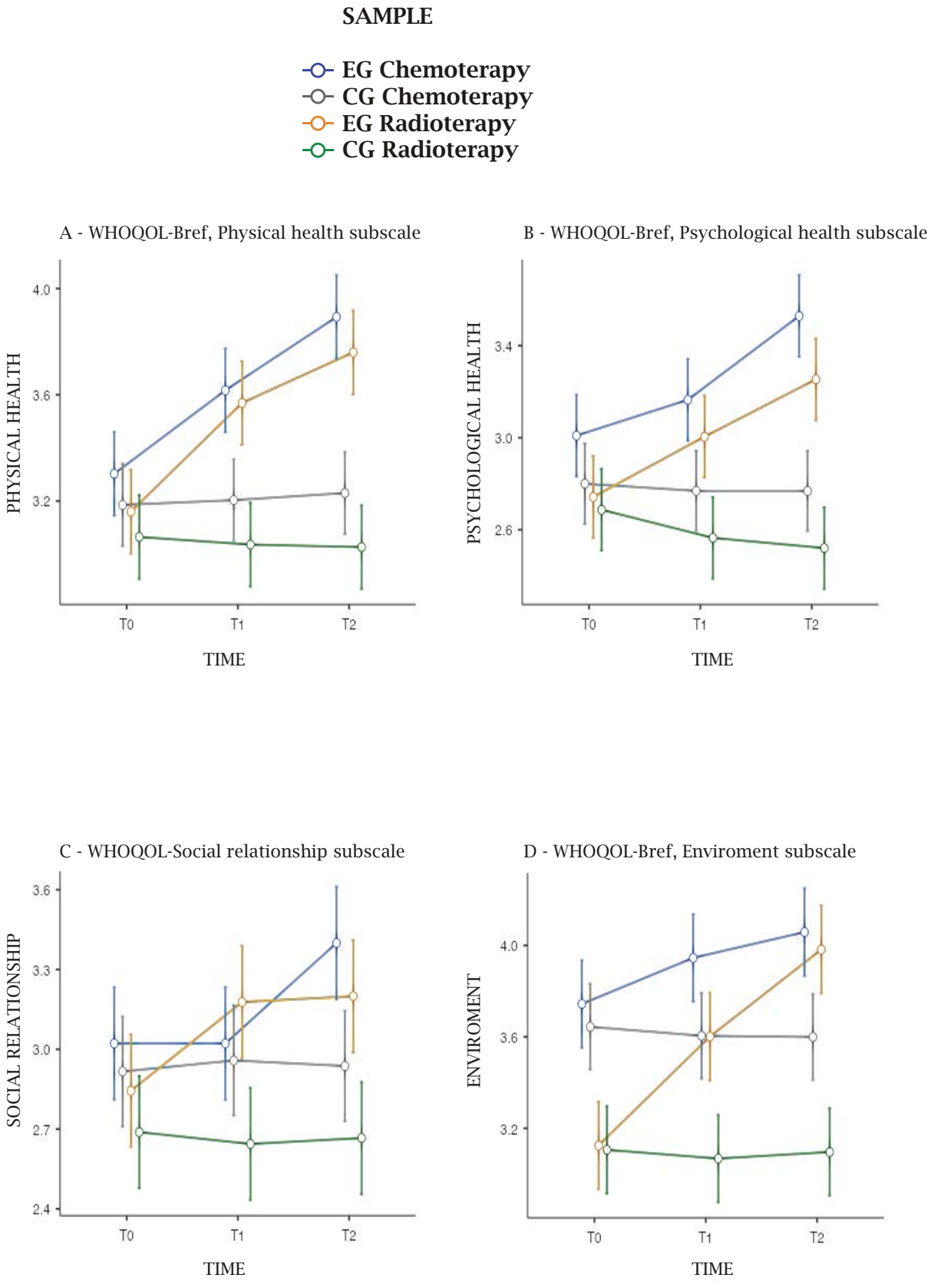

Figure 2 *- Interaction between time and aesthetic treatment effects on WHOQOL-Bref scores in different cancer treatments groups.*

Discussion and conclusions

The oncological literature emphasizes that both chemotherapy and radiotherapy can cause different side-effects, often in cutaneous layers and its appendages. These side effects alter not only the physiology of the skin, but also the physical appearance of the oncologic women. Changes in physical aspects have a negative impact on the patient's perception of Body Image10, with the resulting risk of shame, lower self-esteem and social avoidance for the oncologic patients[20,21], and a consequent worsening of anxiety and depression[22,23].
It was also reported[3,5] that the use of specific dermatological treatments can have a positive impact on the perception of well-being in oncological women.
The aim of the study was to evaluate whether the use of a specific dermatological treatment can improve cutaneous side effects from an aesthetic point of view, thus improving the perception of the Body Image and the QoL of the patient, protecting the onset of anxious-depressive psychopathological disorders.
Regarding the effects of cutaneous lesions on HRQoL, the results underline that the symptomatology, the emotional state and social functioning domains can be predicted according to time, presence/absence of the dermatological product and interaction of both those factors. We know that chemotherapy and radiotherapy are associated with side-effects that could impair the patient's HRQoL[15,23]. In our study, at the time of the first administration the means score in the domains previously described was elevated for both study groups. After 28 days of treatment, both EG showed an improvement of skin lesions, with a decrease in itching, burning and pain. Emotional well-being was also improved, with less frustration and embarrassment related to their skin condition. Patients treated with radiotherapy belonging to the EG had visible improvement since the first week of cutaneous treatment and even more after 28 days of treatment. Conversely, CG patients did not show a significant improvement in their dermatological condition. Our results confirm that the use of a specific dermatological cosmetic product is a key factor in reducing skin related symptomatology[5,33-35] and, consequently, in improving the patients' emotional state and ability to function socially. The daily use of cosmetic products had a positive impact not only on dermatological symptoms, but also on the affective, behavioural and cognitive aspects related to Body Image perception. At T0, all women showed high scores on the Body Image Scale, meaning that before starting the dermatologic treatment, patients felt discomfort in how they perceived their body. Recent studies have already highlighted that women treated for breast cancer can experience changes in their physical appearance[19] and it can be associated with shame, low self-esteem or social avoidance[20,21]. In the current study a significant decrease in psychological discomfort have been found in both experimental groups after 28 days of treatment. In addition, our results revealed that patients of an experimental group treated with radiotherapy exhibited a significant improvement after 7 days. Thus, women who applied the specific topical treatment felt more aware and satisfied with their body during the study period. The control groups instead did not show any improvement in the way in which they perceived their body.
Evidence found in scientific papers revealed that women diagnosed with cancer must fight various difficulties and challenges[36] which can bring an indelible negative impact on their life. Oncological women can experience bad consequences in various physical, social, emotional, psychological and practical aspects[37]. In our study, at the baseline there was a significant difference between the groups for the QoL domains concerning physical health, psychological health and the environment.
Women treated with radiotherapy showed a lower level. This may be due to the fact that radiation therapy can cause worse side effects, particularly those rising on the skin. During the study period, women who used the specific dermatological product showed a gradual improvement in QoL, in terms of physical and psychological health, social relationship and environment. The use of the cream lead women to experience less pain and discomfort, improving their quality of sleep, their self-esteem and their social relationships. Thus, the change in QoL seems to be influenced by the improvement of skin lesions. This fits with the idea that good health no longer simply represents the absence of the physical disease[38], but also a level of wellbeing on physical and psychosocial levels. Our results seem to confirm what literature has already affirmed: taking care of the body, and specifically the skin, helps to increase not only physical health, but also psychological well-being. The data also showed that only the use of dermatological products specifically designed for the treatment of cutaneous side effects of oncological therapies leads women to a better psychological well-being and perception of their Body Image, decreasing negative impact of skin-related symptoms on HRQoL. Consequently, the decrease of dermatological side effects and the improvement of the QoL could lead to a better adherence to the therapy[39,40]: since it is already known that in case of side effects the compliance decrease[41,42]. In conclusion, it is auspicable that dermatologists cooperate with oncologists to prevent and alleviate the cutaneous side effects of treatments and to improve patients' QoL.

Conflicts of interest

There is no conflict of interest, otherwise please complete the 'Conflict of Interest' form.

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Original article

Evaluation of the effect of using hyaluronic acid for lip enhancement on the amount of vertical tooth exposure in smiling

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Abstract

Background: well-defined plump lips display a young and attractive appearance. In the last few years, lip filler injections have become rather popular amongst female patients. One of the main features involved in a well structured smile is The amount of vertical tooth exposure whilst smiling. This study aims to evaluate the effect of hyaluronic acid lip fillers on the vertical tooth exposure in a smile.
Methods: a total of 25 females between 19 and 40 years old were involved in this study. Hyaluronic acid was injected to enhance their lips. The amount of vertical tooth exposure in smiling (lip line) was evaluated by comparing the photographs taken before, two weeks after, and two months after the injection. An AutoCAD 2017 engineering drawing program was used for image processing and dimensional calculations. The T-Student test for a paired sample was used to compare the measurements of the studied variables between the three time periods of the study using SPSS V24.
Results: there was no statistically significant difference (p value <0.05) when using hyaluronic acid in lips augmentation on the amount of vertical tooth exposure in the enhanced smile.
Conclusions: the injection of hyaluronic acid for lips augmentation does not affect the amount of vertical tooth exposure in smiling.

Keywords
Dermal fillers, lip line, fillers injection, hyaluronic acid

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Introduction

Both botulinum toxin "Botox" and dermal fillers have made their way into the world of aesthetic dentistry, which is a branch of aesthetic medicine which has developed in recent years[1,2]. The perioral region is the framework through which the teeth appear[3]. Well-defined and full lips give a youthful and attractive appearance[4]. A variety of absorbing and permanent fillers were used to shape the lips[5]. In recent years, the fillers derived from hyaluronic acid have become the most effective medium to correct soft tissues, and the best filler for lips augmentation[6]. Like other parts of the face, lips lose their attractiveness with time. They lose their volume and become thin and flat as well as loosing their defined borders. The main question that this research raises is: what rules should which doctors follow to achieve the perfect lip augmentation? When looking at aged lips, there are two essential points to observe: the first is the shape of the lips and the second is their relationship with the other parts in the lower third of the face, especially the support provided by the bone structures and teeth[7]. Lip augmentation includes the reshaping and / or increasing the size of the visible part of the lips, the vermilion, changing the shape of the Cupid's bow and the relationship between the vermilion and the skin below the columella of the nose, all of which is considered within lip filling[5]. The lips augmentation can be done using either surgical or injection procedures to increase the size and obtain well-defined borders of the lips[8]. Fillers are products that are injected into soft tissues to increase volume, correct defects, fill wrinkles, and shape the face. Fillers are classified into absorbent and non-absorbent (permanent) materials, and may also be classified according to the injection site (within the dermis or under the skin), to the source of the material (autogenous, animal, industrial, semi-industrial) or to the duration of its effect (temporary: less than six months, long-term: from six months to two years, semi-permanent: two to five years, permanent: more than five years)[9]. Today, hyaluronic acid is commonly used to fill the lips due to its hydrophilic properties and the natural appearance that it gives. Its effect lasts between 3 and 6 months and can continue in some patients for extended periods of time[10]. The lip line as shown in *Figure 1* is the amount of vertical tooth exposure in smiling. In other words, the height of the upper lip relative to the maxillary central incisors. The lip line is one of the most important components of a balanced smile[11]. This study aims to evaluate the effect of injecting fillers in lips using hyaluronic acid on vertical tooth exposure whilst smiling.

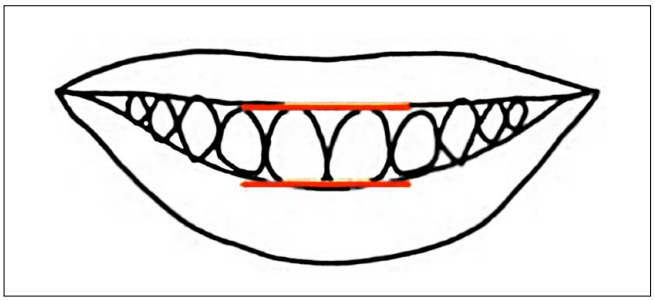

Figure 1 *- Lip line.*

Materials and methods

The Scientific Research Committee of Damascus University approved this research on 12/6/2017 with the ID: 2094. The study was carried out at the department of Oral & Maxillofacial Surgery, Faculty of Dentistry, Damascus University. Informed consent was obtained from patients before the start of this study. The study sample consisted of 25 female patients who were injected with hyaluronic acid in the lips. The effect of the injection on the amount of vertical tooth exposure in the smile was studied by comparing the variables before the injection, two weeks after the injection and two months after the injection.

Inclusion criteria (control variables):

a - All patients were females.
b - Age of patients between 18 and 50 years old.
c - Patients have lips that are full from degree (0) to degree (2) on a Merz scale* as shown in *Figures 2* and *3*[12], where two photos (one frontal and the other of the profile) were taken of the patients before the injection. When the photos were taken, the patients were in a standing position and looking forward, their lips were in a comfortable position, and the Frankfurt plane (a plane which reaches the distal canthus of the eye and the tragus) was parallel to the ground. The camera was on the level of the Frankfurt plane[13]. The two pictures were reviewed by three residents in the Oral and Maxillofacial Department doctors -who were trained on the scale- to choose patients according to Merz scale where the patient approved by at least two doctors were chosen.
**Merz Scale for upper and lower lip fullness at rest: 0=very thin, 1=thin, 2=moderately thick, 3=thick, 4=full.
d - Patients who have an appearance of central incisors in smiling.

Exclusion criteria:

a - Patients who had injected fillers before or during the period of study.
b - Patients who had any surgical lip procedure before or during the period of study.
c - Patients who are pregnant or breastfeeding.
d - Patients with a history of autoimmune diseases.
e - Patients who suffer from severe allergies or have had a severe anaphylactic accident.

Research protocol

The patient's medical history was acquired through a questionnaire for the study and was handed to each participant with printed pictures of the injection technique used in the study and written information about the study and the possible complications. All participants had signed an informed consent form before the injection session.
Patients were given the following Pre-injection instructions:

a) Not to use makeup before the injection session.
b) Stop taking anticoagulants (aspirin, NSAIDs, vitamin E) for 10 days before the injection.
c) Inform the doctor about any medications taken before the injection.

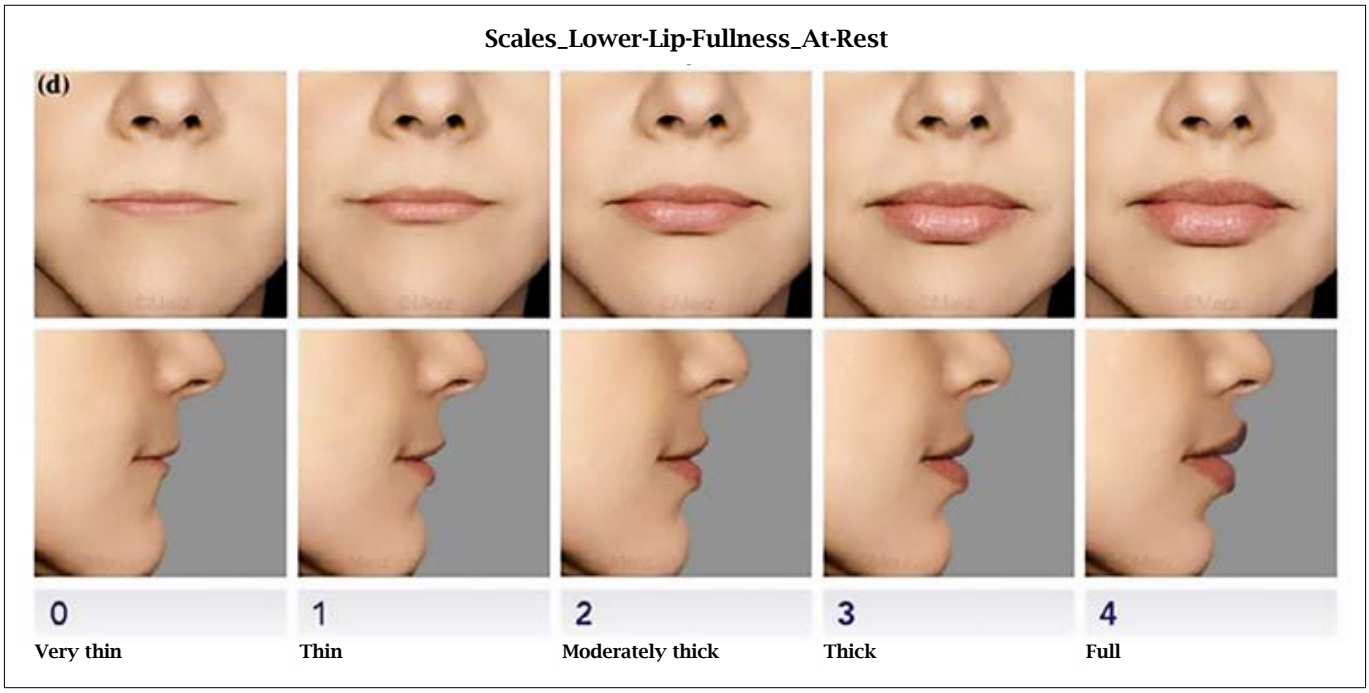

Figure 2 - Merz scale of lower lip fullness.

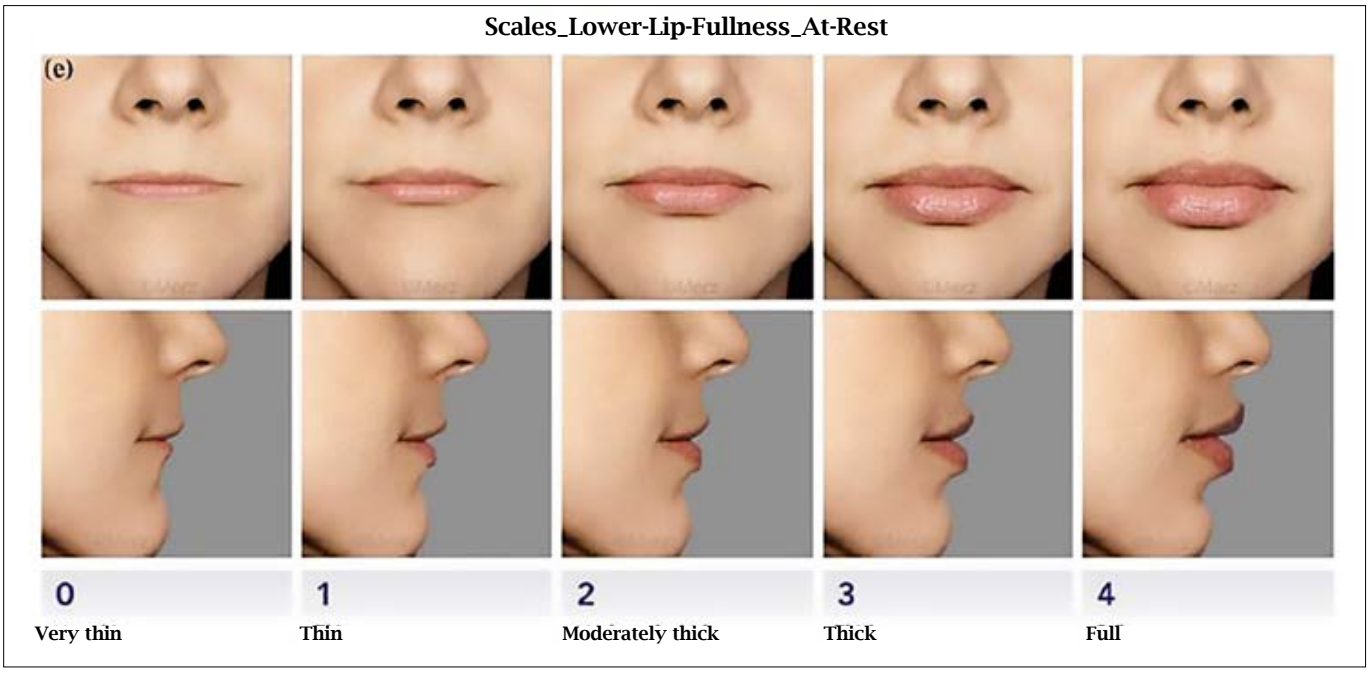

Figure 3 - Merz scale of upper lip fullness.

During the injection session, a frontal photograph for the patient was taken while smiling as shown in *Figure 6*. The patient was standing, and the Frankfurt level was parallel to the horizontal level and the patient was looking forward and the distance between the camera's lens and the patient's head was 150 cm. It should be noted that the photographs were taken without flash in the room's light. Then, regional anesthesia for upper and lower lip was performed using lidocaine 2% with an adrenaline 1/100000. The infraorbital injection was performed to anesthetize the upper lip, while the mental foramen injection was performed to anesthetize the lower lip. After that, the lips and surrounding area was disinfected with the topical antiseptic solution hexamidine. Then, Emla cream (AstraZeneca, Switzerland) was applied to the area for 20 minutes with a layer of 1 mm thickness. Cross-linked hyaluronic acid with a concentration of 23.5 mg/ml (Hyaluronica 2, Vital Esthetique, France) was injected in the lips according to Paris technique. The needle was inserted with an angle of 45 degrees with the outer line of the lip. The depth of the insertion is 1 mm. Then the needle becomes parallel

to the outer line of the lip and the full length was entered. The filler was injected along the needle's way slowly with a retrograde threading method. It is important to maintain a gradual rate of injection to an equal flow of filler material, and stretching the lip and tightening it during the injection, which helps to regulate the flow of the filling material. After the injection, the area was gently massaged to control the distribution of the filler material and to avoid the formation of lumps in the lips. Injecting the lips with hyaluronic acid (1 cc for each patient) is done according to the following steps:

a. Injecting the filler in the lateral subunit of the Cupid's bow in the upper lip as shown in *Figure 4*.
b. Injecting the filler in the medial subunit of the Cupid's bow in the upper lip as shown in *Figure 5*.
c. Creating philtrum columns: It is important to recognize that the philtrum columns are not parallel to each other. They form an inverted (V) that narrows as it comes toward the nostril sills and columella of the nose.
d. Define the vermilion borders of the central part of the lower lip.
e. Little filling for the body of both the upper and lower lips.

After injection, patients were given post-injection instructions. The most important one was to apply an ice pack intermittently and immediately after the injection for 48 hours to reduce edema and bruises. The second important point was not to take anticoagulants (aspirin, non-steroidal anti-inflammatory, vitamin E) for 24 hours post injection. The first follow up was two weeks after the date of the injection session, where a frontal photo in smiling position was taken as shown in *Figure 7* according to the same conditions in which the photograph was made before the injection. The second follow up was two months after the date of the injection session, where a frontal photograph of the lips smiling was taken as shown in *Figure 8* according to the same conditions in which the photographs were made two weeks after the injection and before the injection. Also, no smiling pre and post treatment photos were taken as shown in *Figure 9*. The AutoCAD 2017 Software was used for image processing, dimensional calculation and the unit of measurement was in cm. The optical images were also matched using a ruler included when capturing the optical images in all stages of the research and calculating the percentage of zoom in images using the (AutoCAD 2017) program.

Statistical Analysis

A T-Student test for a paired sample was used to compare the measurements of the studied variable between the three-time stages of the study using SPSS V24.
The Microsoft Excel program was used to clarify the results by organizing them in tables.
The estimation of the statistical differences was based on the significance level (0.05).
Therefore, any value (P-Value) above the significance level (0.05) implies that the observed difference is statistically insignificant. Whereas, any value (P-Value) below the significance level (0.05) would mean that the observed difference is statistically significant and is therefore a real difference.

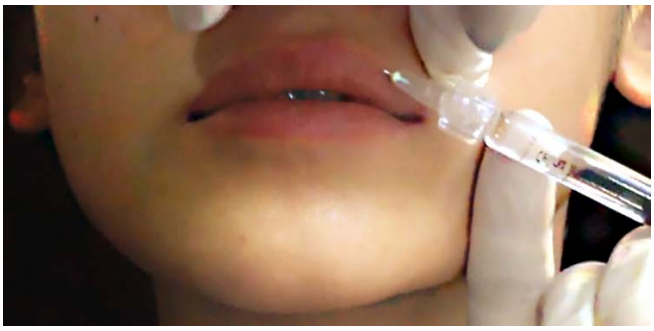

Figure 4 *- Injection of the lateral part of the upper lip.*

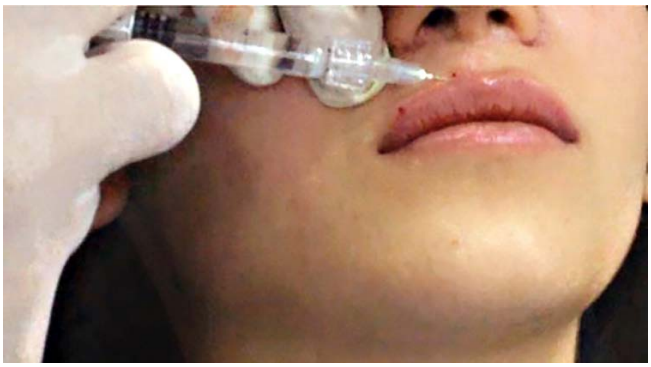

Figure 5 *-Injection of the medial part of the upper lip.*

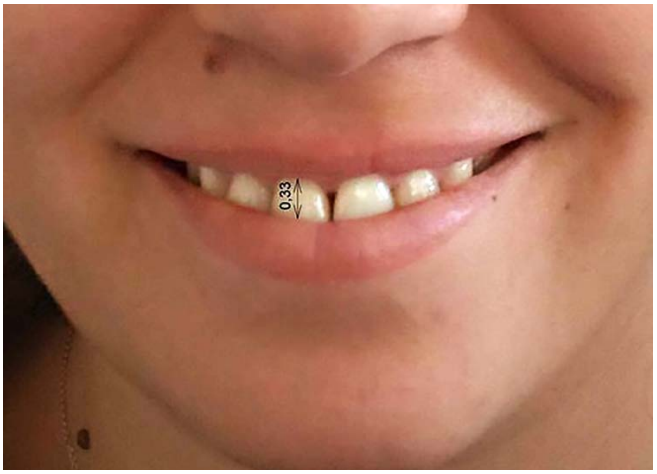

Figure 6 *- Frontal photography before the injection in smiling.*

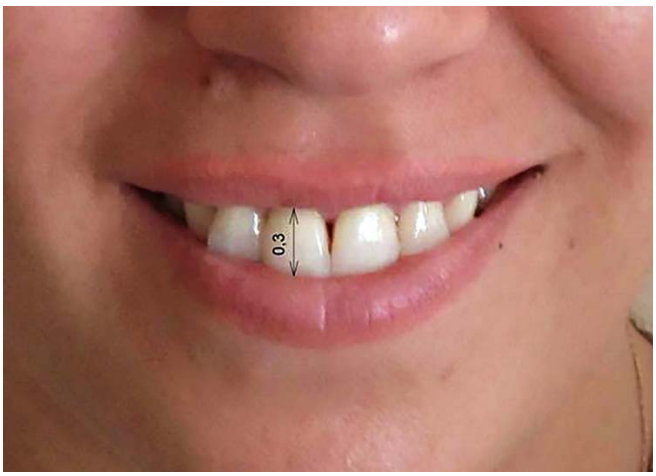

Figure 7 *- Frontal photography after 2 weeks from the injection in smiling.*

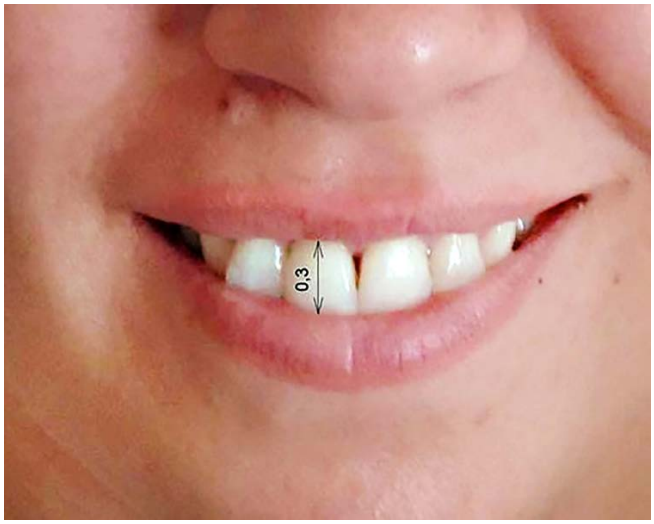

Figure 8 *- Frontal photography after 2 months from the injection in smiling.*

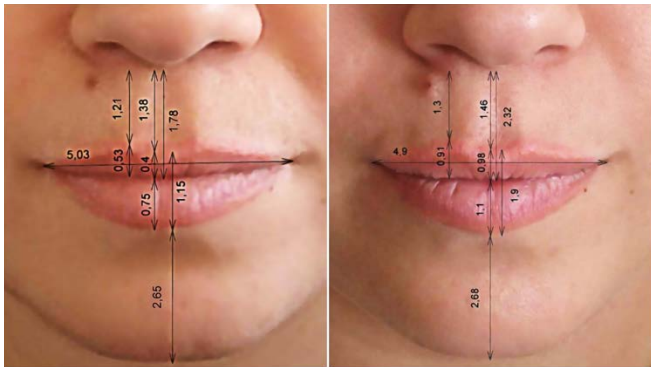

Figure 9 *- No smiling pre and post treatment photos.*

Results

No complications occurred during any filler injection. The arithmetic mean of the apparent amount of the upper incisors in smiling of the sample of this study before the injection of hyaluronic acid was 6.37 mm. After the injection of hyaluronic acid, the arithmetic mean was 5.61 mm. After two months of injection it was 5.60 mm. This indicates that the injection of the lips using hyaluronic acid leads to a decrease in the apparent amount of the upper incisors by an average of 0.77 mm. The results of this study are shown in *Table 1*.

Discussion

Dental aesthetics has become one of the most interesting fields for most dentists. When talking about cosmetic dentistry, that means harmony between the teeth, the gingiva, the lips and the face[14]. In the past years, there has been an increase in the desire for minimally invasive procedures, which include injections of botulinum toxin type A and dermal fillers[15].
Lips play an important role in the aesthetics of the face for their shape and fullness[16]. Lips augmentation with hyaluronic acid fillers have become relatively popular[17]. The lip line, the amount of vertical tooth exposure in smiling, is one of the important components of a balanced smile[11]. Excessive gingival display while smiling has been a cause of aesthetic dissatisfaction for many patients[18]. Most of the patients ask for a natural result when injecting fillers into the lip, this does not mean that patients are looking for a more faint result, but rather they want an increase that looks natural and suitable for their faces[19].

Differences in measuring the apparent amount of the upper incisors in smiling between study stages						
	Stage	**Mean**	**SD**	**(t-test)**	**P-Value**	**The decision**
First comparison	**Before**	0.637	0.258	2.027	0.062	**no statistically significant difference**
	After 2 weeks	0.561	0.167			
Second comparison	**Before**	0.637	0.258	2.051	0.059	**no statistically significant difference**
	After 2 months	0.560	0.166			
Third comparison	**After 2 weeks**	0.561	0.167	1	0.334	**no statistically significant difference**
	After 2 months	0.560	0.166			

Table 1 *- Results of the t-test to study the differences in measuring the apparent amount of the upper incisors in smiling between the studied stages in cm.*

This study evaluates the effect of injecting hyaluronic acid fillers on the amount of tooth exposure in smiling. In a retrospective study Thomas et al.[20] presented a description of filler lip injections on the design of a smile. 35 patients who had undergone lips augmentation with hyaluronic acid were taken up for retrospective analysis. They observed that the lips were more visible, and the fillers enhanced the volume resulting in an attractive smile. Thomas et al. study did not provide numerical results for the effect of lip filler injection on a smile[20]. In our study, we aim to evaluate the effect of injecting fillers into the lips on the smile design. Our study provided numerical results. The injection of the lips using hyaluronic acid in our study leads to a decrease in the apparent amount of the upper incisors by an average of 0.77 mm. From a statistical point of view, the P-value is higher than the significance level (0.05). Therefore, the observed difference is considered statistically insignificant. In this study, we chose patients with very thin to moderate lips. we didn't choose the full lips. In most patients, approximately 1 cc to 1.5 cc of HA filler will be adequate to augment the lips and achieve aesthetically pleasing results[12]. We therefore chose the minimum amount of filler needed for our desired effect. Thus, we standardized the criteria of the research sample whilst obtaining the desired cosmetic results. Furthermore, cross-linked hyaluronic acid with a concentration of 23.5 mg/ml was chosen as our filler, as it was mentioned by Mario Goisis et al, in 2013 that medium viscosity hyaluronic acids are efficient for deep wrinkles and lips[21]. Further studies with different hyaluronic acid concentrations and quantities are required to evaluate whether those two variables could play a role on vertical teeth exposure.

Conclusions

The results of this study show that the injection of hyaluronic acid into the lip does not affect the apparent amount of the upper incisors during smiling. Furthermore, the injection of fillers into the lip using hyaluronic acid does not improve the gingival smile.

Acknowledgment

Damascus University Funded this research.

Conflict of Interest

The authors declare that there is no conflict of interest.

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aesthetic medicine

Original Article

Topographic labiaplasty a new concept to improve aesthetic and functional results

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Abstract
Labia minora Hypertrophy is multifactorial but in general terms is a normal variation of anatomy. The demand for surgical treatment is increasing exponentially year after year. Labiaplasty is a surgical option whic haims to improve functional and aesthetic concerns. Unfortunately, most of the surgeons lack of enough experience, in order to achieve good results in the preservation of anatomical functions and sexuality. Moreover, the number of secondary or revision labiaplasties is also increasing. There is a lack in literature, of a standardized system to identify anatomical variants and plan a surgical procedure according to the patient's needs. Our group has developed a structured idea that divides the components of labia minora hypertrophy and its anatomical landmarks. We have named it "TOPOGRAPHIC LABIAPLASTY", and has been applied on 45 patients from July 2017 to July 2020. GAS (Genital appearance scale), a validated tool used prospectively to our study group, demonstrated statistically significant changes.
Topographic labiaplasty, allows the surgeon to clearly identify all the anatomical variants and topographic landmarks involved in a labia minora hypertrophy. According to our group experience, we believe that this system will be a game changer among labiaplasty surgeons, in order to provide an adequate balance, regarding anatomy, function, and sexuality.

Keywords
Labiaplasty, techniques, ninphoplasty, labia minora reduction, laser labiaplasty, labia minora reduction

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Introduction

Labia minora hypertrophy has been studied and described by many authors. Perhaps the first report found in literature was performed by Mauriceau[1] many years ago. Labia minora hypertrophy called our attention regarding the need of a standardized classification, and description of labia minora hypertrophy. We developed a structured classification that encompasses all the components of labia minora hypertrophy as well as unification of size and symmetry[2]. After, proposing this system our group developed an idea which will be named "topographic labiaplasty" which divides the vulvar components in four quadrants, and also identifies anatomical remarks that require the surgeon's attention. In order to avoid complications, several techniques have been described in literature. Our philosophy is that there is no such technique, but there is a need to adjust surgical principles and follow anatomical remarks in order to approach the huge anatomical variability found in cases of labia minora hypertrophy.

There are anatomical variants described by Hunter in 2015[3], which clearly describe the presence of a division between the clitoral hood components and the labia minora hypertrophy, as previously mentioned inside our classification. Ostrensky et al. reported anatomical variants and aberrations regarding the frenulum of the clitoris and its relations with labia minora and clitoris glans[4]. Mujde et al described eleven surgical approaches to labiaplasty inside his review, meaning that no gold-standard technique exists[5]. Anyhow there are standard techniques described in literature from many years ago, such as the classical linear resection of tissues at the free edge of the labia minora, with important disadvantages, such as the impossibility to remove skin at the level of the clitoral hood, that often requires reconstructive procedures[6]. In 2008 Gary Alter described a technique combining a central wedge resection with clitoral hood reduction, which allowed better aesthetic results, but unfortunately without clearly describing the importance of the anatomical variants, and safety remarks[7]. Fengyong li et al in 2020 described a technique that also combines labia minora reduction with clitoral hood approach, although it seems like a modified version of previously described techniques. It divides the labia minora hypertrophy from the elongation of clitoral hood, in order to allow an independent but complimentary procedure[8].

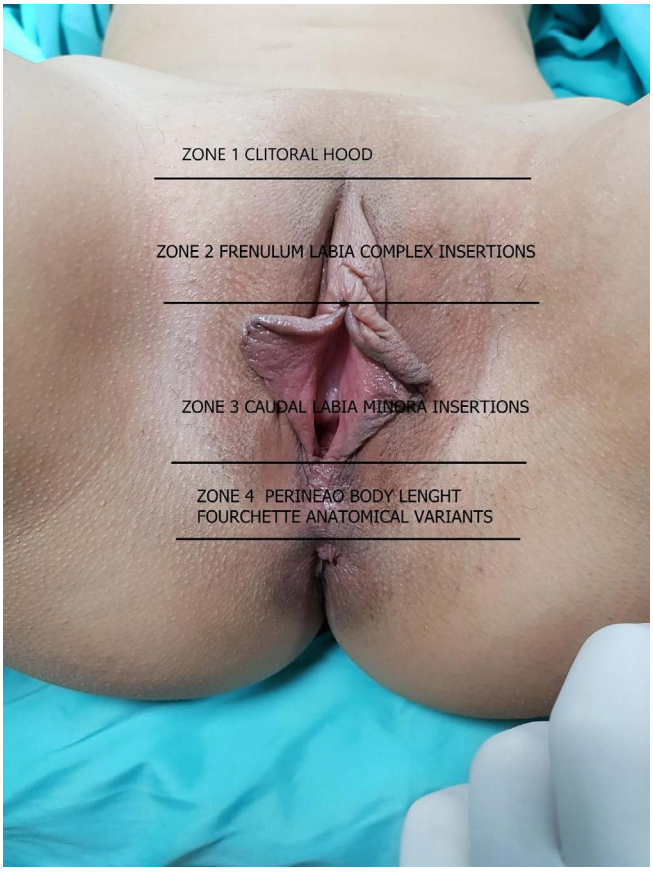
We believe that there is a need to divide topographically all the components involved, as follows (*Figures 1* and *2*)

ZONE 1: Clitoral hood (safety remarks:Interlabial fold)

ZONE 2: Clitoral frenulum insertions complex (safety remarks frenulum insertions)

ZONE 3: Caudal labia minora insertion (safety remarks interlabial folds)

ZONE 4: Vulvar fourchette Perineal body (safety remarks perineal body length)



Figures 1 and 2 *- Topographic zones, anatomical safety remarks.*

Methods

A structured literature review was conducted to identify current evidence regarding labiaplasty techniques and clinical outcomes; the literature search began in November 2018 and concluded in November 2019. The search conducted by the librarian included randomized controlled trials (RCTs), systematic reviews, clinical trials, and practice guidelines publications in English from PubMed (MEDLINE), National Guideline Clearinghouse, CMA Infobase (Canada), NHS Evidence (United Kingdom), NICE (United Kingdom), SIGN (Scotland), New Zealand Guidelines Group, TRIP database, Guideline International Network (GIN), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, AMED,Web of Science, BIOSIS Citation Index, CAB Abstracts, and AHRQ it included the following terms:
-labiaplasty, labia minora plasty, nynphoplasty, clitoral hood reduction.
Publication Dates: No limit
The search of all databases mentioned 41 articles.
No similar proposals of topographic labiaplasty were found in literature.
After signing informed consent, dedicated markings and a standardized surgical technique were performed to 45 cases of labia minora hypertrophy patients, with a mean age of 30, 65 years from July 2017 to July 2020, (*Figure 3*), GAS[9] (Genital appearance satisfaction) scale was our outcome measure. This validated tool contains 11 questions, and total scores ranging from 0 to 33. Higher scores represent greater dissatisfaction with external genitalia. A pulsed shaped designed carbon dioxide laser Deka M.E.L.A from Florence, Italy was used to tailor the technique. Suturing was adapted according to clinical conditions, monofilament material was preferred, outpatient procedures were performed under general anesthesia, a follow up was performed one month after the surgical procedure then after one year after the surgical intervention.

Surgical technique

After identifying all the components of labia minora hypertrophy we proceed to perform a standardized marking (*Figures 3* and *4*) which allows the surgeon to be familiar with the anatomical variants, in order to plan the best technique that fits the patient's anatomy.
The main idea after an adequate marking is to:

1. Identify all the components of labia minora hypertrophy such as:
   A. Anatomical variants (horizontal plane/vertical plane, duplications, trifurcations, fenestrations.
   B. Excess skin at the level of vulva fourchette.
2. Identify safety anatomical remarks (interlabial fold,clitoris frenulum complex and insertions, labia minora insertions, and perineal body length).
3. Adjust surgical technique according to the patient's vulvar anatomy.

We have standardized our technique, it is performed as an outpatient procedure under general anesthesia, after topographic markings (*Figure 5*) and identification of anatomical variants, we proceed to do a topographic hydrodissection (*Figure 6*) with a mix of 3 cc bupivacaine

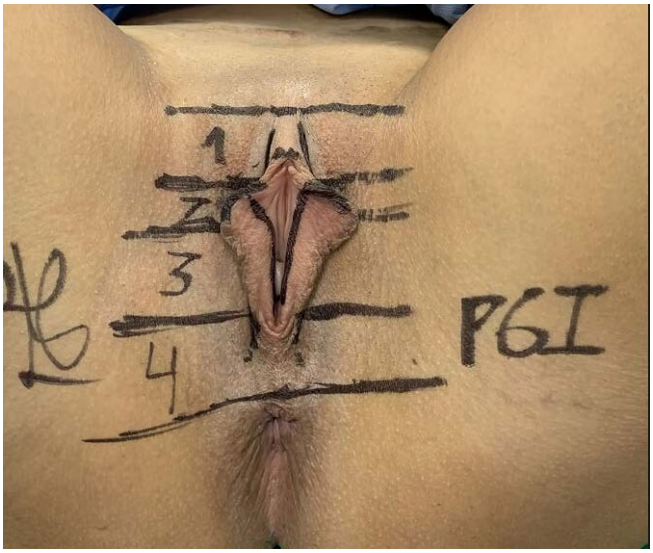


Figure 3 *- Topographic markings.*

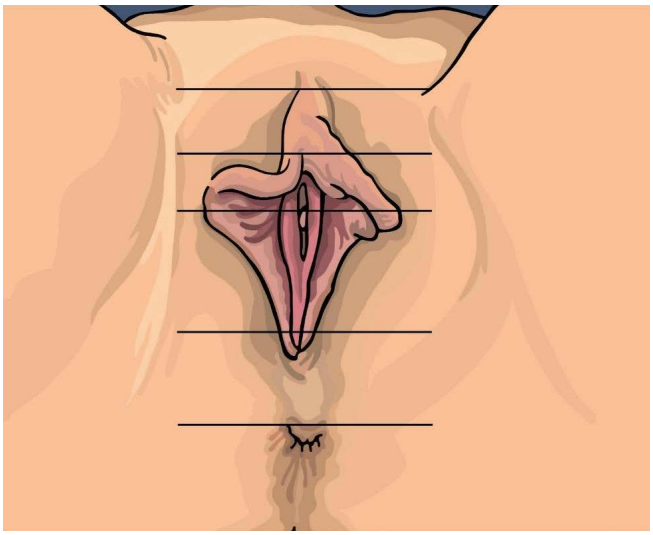


Figure 4 *- Topographic markings.*

cc of lidocaine + epinephrine 2% (6mg/ml 0.6%) + 4 cc Tranexamic acid 5%(40 mg/ml 4%), then afterwards we start to tailor the cuttings and approach of anatomical variants with a pulsed shape design Carbon Dioxide Laser DEKE M.E.L.A from Florence, Italy (*Figures 7* and *8*). If there is a need for coagulation we change the pulse mode and use the beam in a defocused mode. For suturing we prefer to use monofilament, such as Monocryl 00000, (poliglecaprone 25) | J&J Medical Devices.
Our suturing protocol is adapted according to the site and extension of the incisions, in general terms we prefer interrupted suture avoiding tension and excess of suture material, for better survival of the flaps (*Figure 9*).
At the moment of patient discharge we prescribe a gauge soaked with Nitrofurazone, and intermittent ice packings for 72 hours, conventional NSAID or paracetamol plus a short course of first generation cephalosporin (cefadroxil).

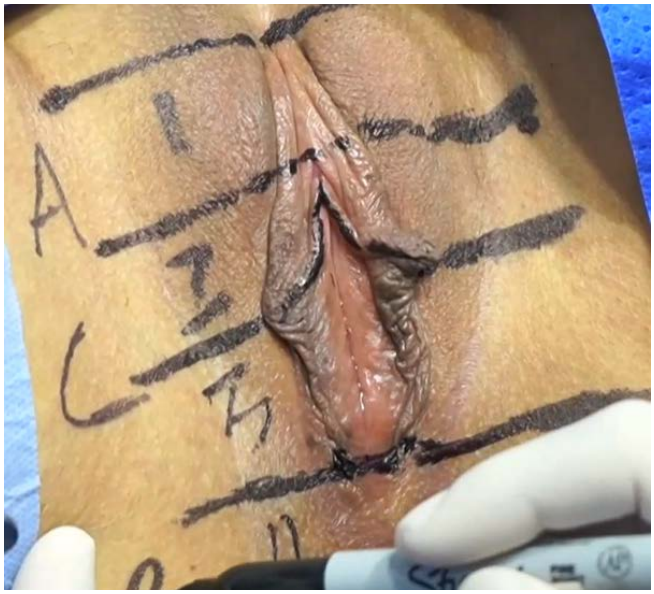


Figure 5 *- Topographic markings.*

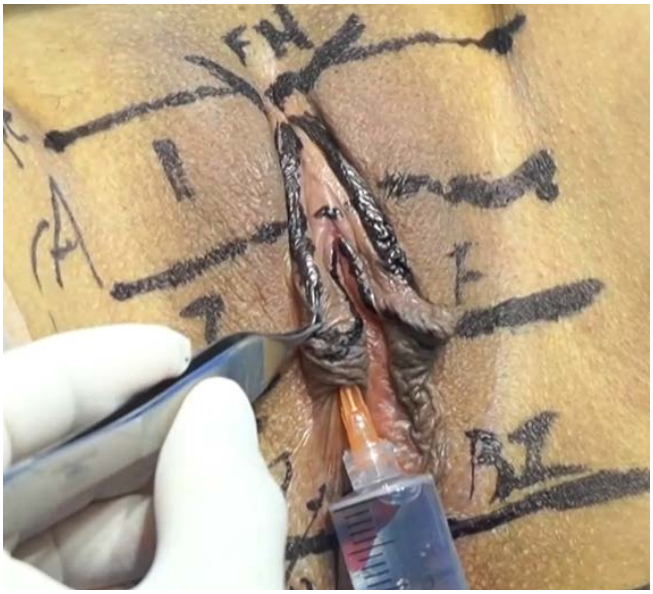


Figure 6 *- Topographic hydrodissection.*

Figure 7 *- Tailoring the wedge on the left side.*

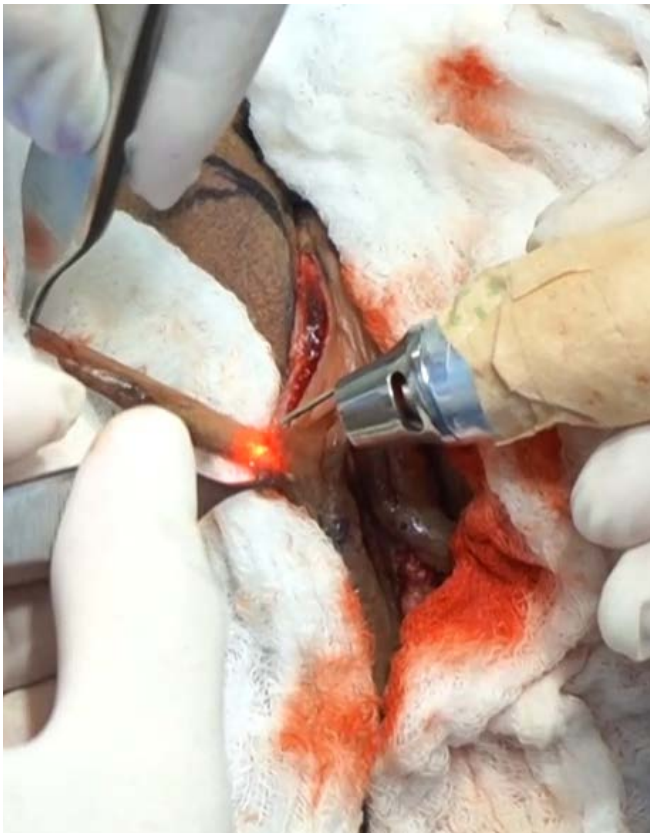
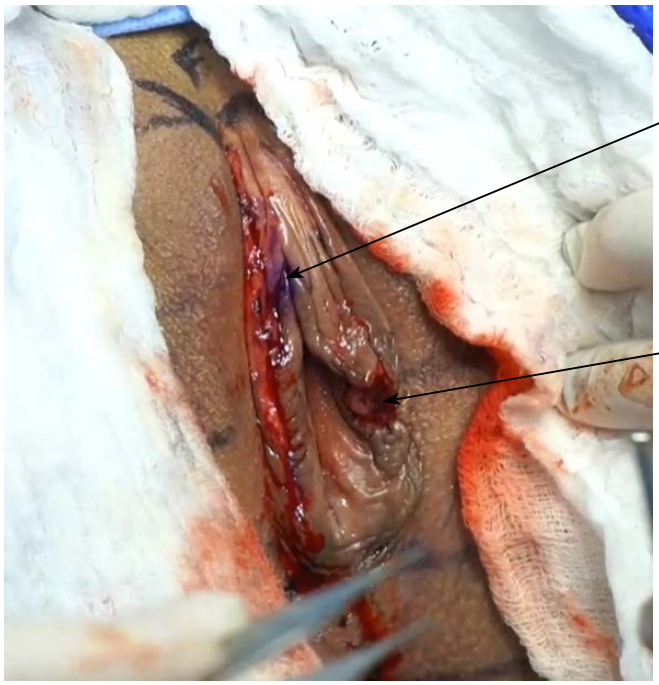


Figure 8 *- Approach of anatomical variants on the right side.*



View of a structured topographic labiaplasty technique (central wedge on the left side and linear resection on the right side approaching anatomical variants.

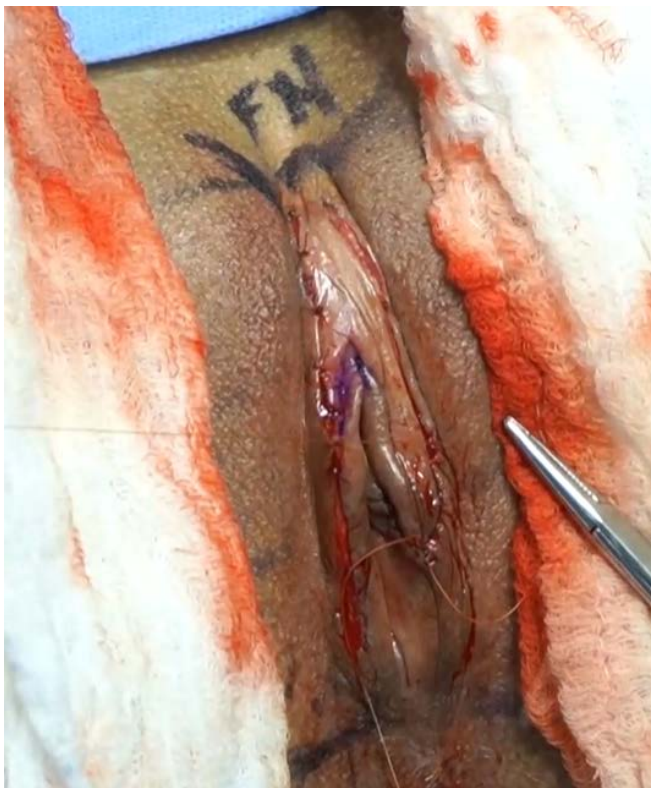
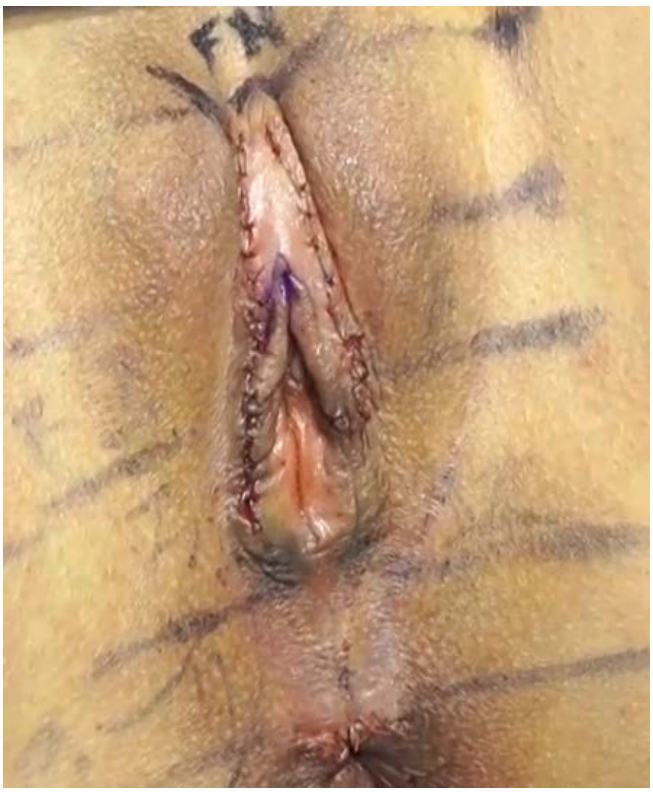


***Figure 9** - Suturing steps.*



Final view of a topographic labiaplasty.

Results

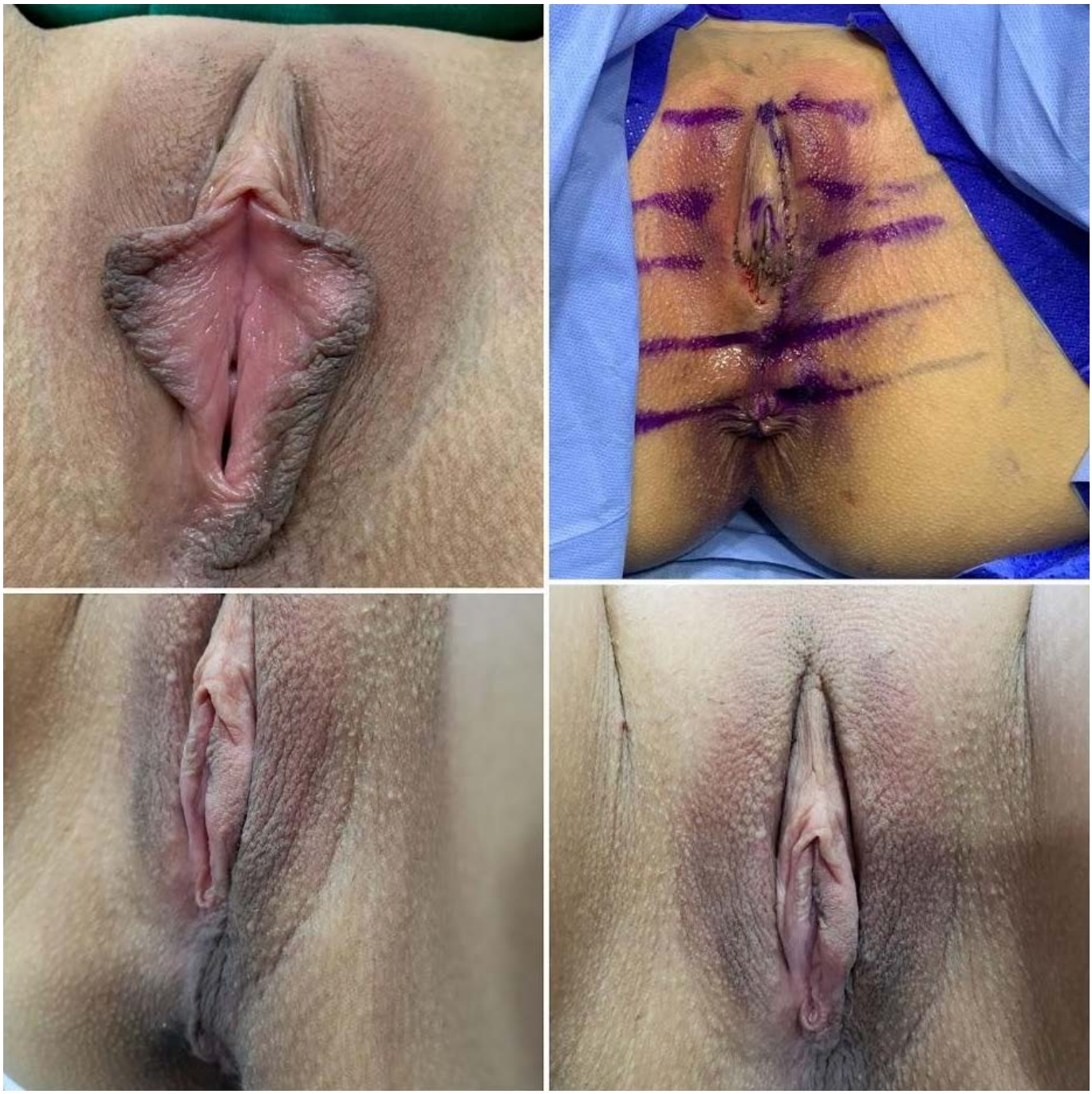
45 patients underwent topographic labiaplasty and completed the GAS scale before the procedure, and at a follow up 36 months after the procedure. At the time of labiaplasty, the women had a mean age of 30-65 years. The most common preoperative complaint for undergoing labiaplasty was functional limitation for performing sports and using tight underwear.
At one year of follow-up, a high satisfaction rate was reported by all subjects, GAS scores before the surgical procedure were 21,26 +/-2,66 and after 36 months, 5,1 +/=1,48, (*Table 1*). No surgical complications were found inside our study group.

GAS SCALE	BEFORE	AFTER
	21,26+/-2,66	5,1+/-1,48

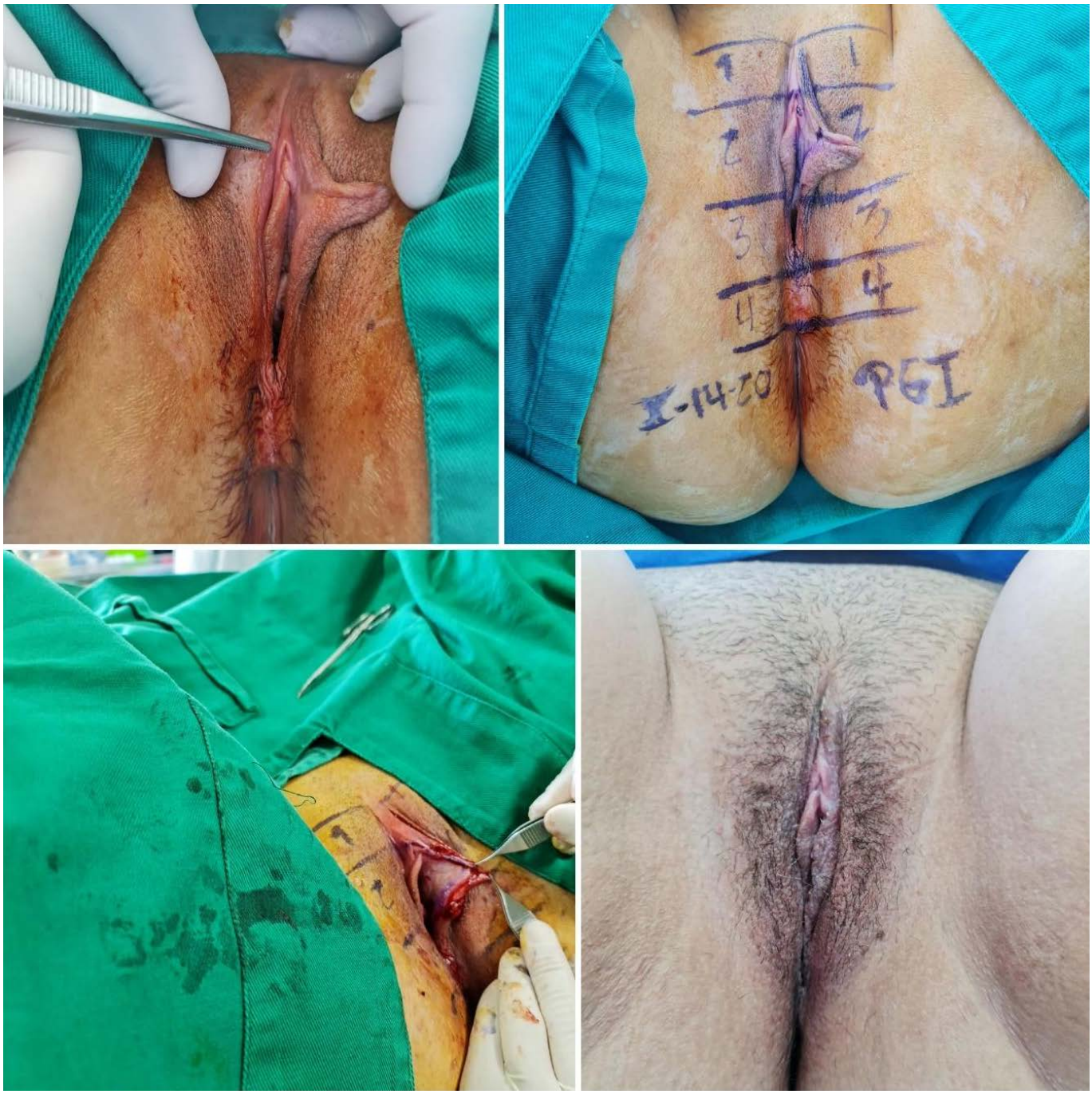
Table 1 *- GAS scores before and after 36 months of follow up.*

Discussion

Labia minora hypertrophy, is considered a variation of normal anatomy[5], however, consultations regarding this clinical condition are increasing everyday. Labia minora labiaplasty is a surgical option that addresses aesthetics and function. Unfortunately reports regarding complications and poor aesthetic outcomes are appearing in the literature[10], which can be explained, by a lack of expertise among surgeons. Our novel technique "Topographic Labiaplasty" can be considered a reproducible and structured strategy that allows the surgeon to improve surgical outcomes, due to a correct evaluation of anatomical variants, for a proper approach. Our findings were confirmed by the use of validated clinical tools. We recommend that surgeons work to understand the huge anatomical variants related to labia minora hypertrophy, and clitoral frenulum complex in order to have a better approach, that can be related to better outcomes from the aesthetic and functional point of view.



Topographic Labiaplasty results:-upper left Pre -upper right inmediate post op -lower left 1 month post op lateral view -lower right 1 month post op front view.



Topographic labiaplasty outcomes.

CLICK HERE FOR FULL SURGICAL TECHNIQUE LINK

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aesthetic medicine

Case Report

Case Report of Delayed Hypersensitivity Reactions to Hyaluronic Acid Dermal Filler Agents following Viral Infection with the SARS-CoV-2 Virus

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Abstract

Introduction: presentation of two case studies where documented SARS-CoV-2 infection preceded delayed-type hypersensitivity reactions to hyaluronic acid (HA) dermal filler agents.
Case Presentation: two cases of delayed-onset hypersensitivity, with symptoms including pain and swelling, in sites of previously injected HA filler agents are described. Both of our patients had reported an active COVID-19 infection within 2-12 weeks of symptom onset. These adverse events are thought to be secondary to Type IV, cell mediated, hypersensitivity reactions in response to a viral illness.
Management and Outcome: both patients were successfully treated with a 6-day course of methylprednisolone with complete resolution of swelling in the treated areas.
Discussion: SARS-CoV-2 seems to cause similar delayed-hypersensitivity reactions to those previously seen in response to other influenza-type viruses and a similar management strategy with oral steroid taper appears to be effective.

Keywords

Dermal fillers, COVID-19, hyaluronic acid, hypersensitivity, SARS-CoV-2, T-lymphocytes

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Introduction

The occurrence of delayed-onset hypersensitivity reactions after dermal filler injections has been well documented in relation to exposure to influenza-type illnesses[1,4-7,9]. Much of the currently available literary sources focus on documented or subjective viral illness, however, given the current pandemic-level of circulating SARS-CoV-2 (COVID-19) virus, we wanted to document two unique cases seen in our practice, located in Phoenix, AZ, USA where documented SARS-CoV-2 infection preceded hypersensitivity reactions to dermal filler agents. On March 11th, 2020, the WHO (World Health Organization) declared that the novel coronavirus (SARS-CoV-2), known as COVID-19, had reached pandemic levels across the United States and much of the world. T-cell immunity is known to play a role in protection against SARS-CoV-2 by helping to generate neutralizing antibodies. CD4 T-cell responses to various structural proteins of SARS-CoV-2 have been studied with the majority of patients appearing to mount at least one CD4 T-cell response to these proteins[2-3]. We hypothesize that it is this T-cell mediated activity that is responsible for the occurrence of delayed hypersensitivity reactions to dermal filler agents as seen in our two patients.

Case Presentation

Two female patients, ages 41 and 58, presented to our office in October 2020 and December 2020, respectively, complaining of localized erythema and swelling on their faces at the sites of previously injected dermal fillers. In both cases, the reaction had started within 48 hours of presentation and began with a diffuse, erythematous, pruritic, macular or welt-like, rash on the trunk and extremities (*Figure 1*). Both patients subsequently developed localized swelling and pain at the sites of prior dermal filler placement with 12 hours of initial rash onset (*Figure 2*). Marked angioedema of the lips were noted in the two individuals, both of whom had previously received dermal filler injections into their lips (*Figure 3*). Neither patient reported difficulty breathing or stridor.

In both cases, our patients had been previously diagnosed with COVID-19 infections by either positive RT-PCR immunoassay or rapid antigen testing within 12 weeks of presentation. Both patients had symptomatic COVID-19 infections consisting of fever, chills, cough, fatigue, in addition to loss of taste and smell. Neither patient required supplemental oxygen and both recovered fully after 14-15 days post-symptom onset. Two months after her initial COVID-19 diagnosis,

Figure 1 *– Patient 1 (left) and Patient 2 (right) initial presentation of rash on trunk.*

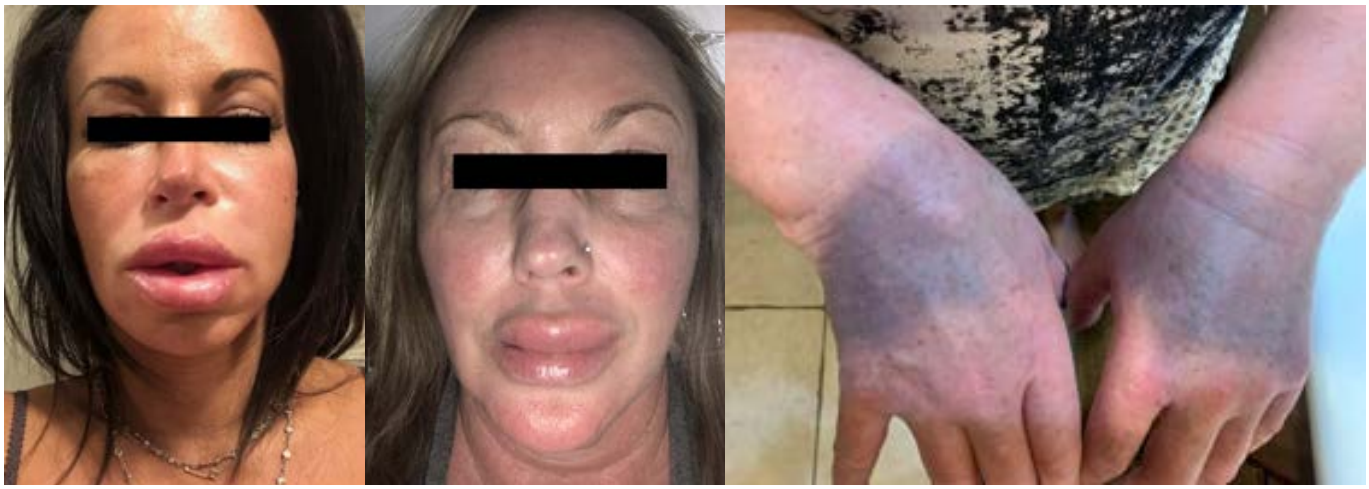

Figure 2 *– Patient 1 (top left), Patient 2 (top right and bottom – hands) showing swelling and erythema at sites of previous HA dermal filler injection.*

Patient 1 experienced recurrence of illness consisting of fever, cough, and gastrointestinal symptoms for 2 days with subsequent rash development and swelling at her injection sites. She had received a dermal filler most recently 6 weeks prior to symptom onset.
Repeat RT-PCR testing for SARS-CoV-2 was performed 2 days after symptom onset and yielded a negative result. Patient 2 was recovering well 13 days after an uneventful course of illness diagnosed as COVID-19 when she presented with hive-like rash on her trunk and extremities as well as swelling and pain at her previous injection sites. At the time of symptom onset, she remained afebrile reporting resolving cough and fatigue (*Table 1*).
Both of our patients had a history of receiving multiple injections with various dermal filler agents over the past 10 years prior to presentation. Only the sites of previous injections of hyaluronic acid based filler products were involved in both cases. Patient 1 had received filler composed of calcium hydroxylapatite (Radiesse+® - Merz Therapeutics, North Carolina, USA) in the mid-facial region and reported no sign of swelling or erythema in these areas. All injections were performed in our clinic, using an aseptic technique, with either cannula or needle delivery. No prior history of allergic reactions to any of the dermal filler agents utilized had been previously reported by either patient. Filler brands included ones such as Juvederm® (Allergan Inc, Dublin, Ireland) as well as Restylane® product lines (Galderma, La Tour-de-Peilz, Switzerland), in addition to Radiesse® as described, above (*Table 2*).

Patient Info	Date of Onset COVID- 19 Illness	Date of Positive COVID Testing/Testing Type	Time interval between COVID-19 diagnosis and onset of HS reaction at dermal filler sites	Time interval between most recent dermal filler injection and onset of HS reaction
Patient 1 41 year old Female	6/29/2020 *re-occurrence of viral illness 8/23/2020	7/1/2020 Cobra(R) SARS-CoV2 test	12 weeks (10/5/2020)	6 weeks
Patient 2 58 year old Female	11/30/2020	12/2/2020 SARS-COV2 Ag Testing (manufacturer unknown)	2 weeks	24 weeks

Table 1 *- Timing of COVID-19 Infection in relation to symptom onset.*

Patient Info	Date(s) of most recent dermal filler injection	Dermal Filler products used, volume injected, site/location	Sites involved in hypersensitivity reaction/areas of swelling
Patient 1 41 year old Female	8/25/2020 3/28/19	Juvederm Volbella XC 0.55 cc - Lips/Oral Commissures/Nasolabia Folds Radiesse + 1.5 cc – cheeks Radiesse+ 1.5 cc cheeks Restylane Refyne 0.2 cc - lips	Lips, oral commissures, nasolabial folds (+diffuse erythematous rash on anterior chest wall)
Patient 2 58 year old Female	5/21/2020 10/30/2019 7/29/2019 9/27/2018	Restylane Kysse 0.8 cc - tear troughs, 0.2 cc Lips Restylane Lyft 1 cc - 0.6 cc cheeks, 0.4 cc chin Restylane Refyne - 1 cc perioral/lips Juvederm Volbella – 0.55 cc tear troughs Restylane Lyft - 1.0 cc to left hand, 2.0 cc to right hand	Lips, chin, cheeks, hands (+ diffuse hive-like rash on trunk and extremities)

Table 2 *- Dermal filler type, volume and anatomical site involved in each patient.*

Management and Outcome

Both Patient 1 and Patient 2 had reported taking over-the-counter anti-histamine medications at the onset of their rash symptoms without relief. While these medications, which included Benedryl® and Allergra®, had not resolved the symptoms in either case, both patients opted to continue these treatments for 2-3 days after initial symptom onset.

Upon presentation, both patients received a 6-day course methylprednisolone starting with 12 mg on day one and tapering to 2 mg on day 6. In addition to methylprednisolone, Patient #1 received a course of doxycycline 100 mg twice daily x 14 days due to more recent history of injection and acute onset of fever in combination with swelling at her injection sites. Patient 2 also received hydroxyzine due to intense itching related to her rash.

In each case, symptom improvement was noted within 12 hours after initiating therapy with complete resolution reported 3 days later. Typical treatments for filler-related nodules such as hyaluronidase, triamcinolone, or fluorouracil injections were used in case of a lack of response to oral steroid taper and were not required in either case.

Discussion

With approximately 2.7 million dermal filler procedures performed by physicians in 2017, as reported by The American Society of Plastic Surgeons (ASPS)[10], in combination with the high-rates of COVID-19 exposure and infection, in addition to the unknown immunogenic effects of the COVID-19 vaccination, we are likely to see a significant rise in the rates of hypersensitivity to these aesthetic agents.

The HA molecules found in these products are thought to be similar to the polysaccharide molecules found in human skin tissue and would, therefore, not be thought to stimulate immunogenic reactions. As HA technology has advanced, however, to create gels that are more stable (including crosslinking and improved cohesivity) we have seen increasing rates of immunogenic reactions such as late onset nodule formation[4]. These reactions are typically thought to arise from a T-cell mediated/CD4+ immunogenic response (Type IV hypersensitivity reactions), as opposed to allergic-type reactions mediated by histamines and IgE antibodies (Type I - Immediate Hypersensitivity response)[4-7,9]. This would correlate with the fact that in our two cases, neither patient responded to anti-histamine medications. Interestingly, Patient 1 did not react similarly at the site of injection of the product consisting of calcium hydroxylapatite (CaHA), suggesting that this product may not have the same immunogenic potential, though prior studies have indicated no significant difference in adverse events between HA and CaHA products[8].

In addition, recent studies have provided evidence that T cells are important for viral clearance and disease resolution after SARS-CoV-2 infection[2,3]. Specifically, it appears that peripheral T follicular helper cells (pTfh) have been identified responding to the SARS-CoV-2 membrane, spike, and nucleocapcid proteins. The pTfh response has been correlated with the production of neutralizing antibodies to these proteins[2]. The activation in T cell response resulting from COVID-19 viral infection, is hypothesized as the likely cause for the immunogenic response seen in both of our patients. While repeat RT-PCR testing to SARS-CoV-2 was negative in Patient #1, based upon her symptoms and exposure history, it is possible that her new symptoms represented a re-infection with the COVID-19 virus. Her negative test may have resulted from prior antibody formation to the virus from her initial infection, testing too early in the course of the illness, or illness resulting from exposure to another influenza-like virus. Co-testing for the influenza virus was not obtained due to a low incidence of circulating virus in the area we focused on at that time.

The delayed hypersensitivity reactions described here, and in other scientific papers[1,4,5,9], as a result of exposure to viral illnesses, seem to occur months-to-years post-injection, involving all injection sites of hyaluronic-based filler, regardless of the duration of time passed since the initial injection took place. In the case of Patient #2, above, reaction at the site of dermal filler injection into the hands occurred despite the fact that her injection had taken place over 24 months prior to symptom onset. This would suggest that these fillers last longer in tissue than is clinically evident. It is also important to note that there is no evidence that those who have a history of infection with the SARS-CoV-2 virus, are more likely to develop reactions to fillers than those who have had other viral infections.

We have already begun to hear of the incidence of similar reactions to the COVID-19 vaccine. In particular, 3 patients enrolled in the clinical trials of the Moderna mRNA vaccine to COVID-19 reported facial and/or lip swelling and 2 of those patients had a history of receiving dermal fillers previously. One patient had been injected 2 weeks prior to immunization and the other had been injected 6 months prior to receiving the vaccine. No cases have been reported with the Pfizer COVID-19 vaccine despite similarities in technology used to manufacture both of these vaccines. It is yet unknown how patients will respond to the forthcoming vaccinations against the SARS-CoV-2 virus that utilize other technology, however, the frequency of these delayed hypersensitivity reactions to dermal filler agents are likely to become more frequent. As such, clinicians should remain vigilant in counseling patients on the potential for these reactions to be seen not only after acute COVID-19 infection but, potentially, after receiving vaccination against this viral agent, as well.

Disclosure

Author has no conflicts of interest or payments for this publication.

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Case Report

Subcutaneous Fractional Microneedling Radiofrequency for the Treatment of Abdominal Striae Gravidarum in Asian Skin: a case study

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Abstract

Fractional microneedling radiofrequency (FMR) is a novel non ablative technology that is frequently used for skin rejuvenation. The aim of this case study is to evaluate the use of FMR to non-invasively improve abdominal striae gravidarum (SG) in a 29-year-old Asian female. The Profound (Syneron Medical Ltd., California) device was used and the level of efficacy of the treatment was evaluated by visual appraisal and a physical examination of the patient and two blinded doctors. The overall appearance of striae was improved 3 months post-treatment and the associated low incidence of side effects suggests that FMR may be considered an effective treatment for SG in Asian skin.

Keywords

Radiofrequency therapy, needles, striae distensae, skin, rejuvenation

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Introduction

Striae or stretch marks are common dermatologic lesions[1] and when related to pregnancy, are defined as striae gravidarum (SG). Affecting up to 90% of pregnant women[2], SG is the connective tissue which undergoes most changes during pregnancy[3]. It can cause significant psychosocial stress to patients, which often leads to a decreased quality of life[4,5].

A variety of approaches have been applied for the prevention or improvement of striae, including topical therapies, chemical peels, microneedling, lasers, and other energy-based technologies. However, no single therapy has been identified to consistently treat these lesions with high efficacy and minimal adverse effects for all skin types[6,7]. More recently, fractional CO2 laser has been tried but is not strongly supported in the literature, with variable clinical outcomes, and risk of postinflammatory hyperpigmentation (PIH) that increases in patients with Fitzpatrick skin types III-IV[8,9,11-13]. In response to the increasing demand for noninvasive therapies with less downtime, fractional microneedling radiofrequency (FMR) represents a novel non ablative technology. This therapeutic modality has gained traction in the treatment of various dermatologic indications, including atrophic scars, hypertrophic scars, wrinkles, and cellulite, by combining efficacy, safety, and a rapid recovery time[10]. We present a case to demonstrate the clinical results and adverse effects of this method, using Profound (Syneron Medical Ltd., California), on an Asian patient.

Case presentation

A 29-year-old Asian woman with Fitzpatrick Skin Type III and no significant past medical history, came to the aesthetic clinic concerned, with postpartum stretch marks on the lower abdomen and bilateral flanks. These concerns developed during her third trimester of pregnancy, with the birth of her first child via lower segment caesarean section (LSCS) 6 months before. She was not on any regular medications. On physical examination, the patient had good skin quality, mild skin laxity and multiple linear purple-red striae distensae on her lower abdomen and bilateral flanks. Her LSCS was visible and showed good healing. Her baseline BMI was 22.1 kg/m2 and clinically, abdominal adiposity was low. She had not received previous treatment to the areas concerned and requested a nonsurgical treatment to improve the appearance of her stretch marks. This patient was considered a suitable candidate for Profound with no contraindications.

Standardised digital photographs of frontal, bilateral oblique and profile views of the treatment areas were documented pre-treatment and seven days, one, two, and three months post-treatment. Perioperative discomfort was reduced through a combination of topical local anaesthetics, followed by a local infiltration in the deep dermis. The Profound treatment protocol is outlined in *Figure 1*. One session of subcutaneous Profound was performed on the area below the umbilicus and bilateral flanks with informed consent. FMR was administered in two passes, one vertical and

Anaesthesia:

Topical Anaesthesia	Infiltration Protocol	Final Total Injection Volume
Approximately 10ml in total: Lignocaine 2.5%, prilocaine 2.5% Evenly applied over the whole treatment area	Total of 20ml 2% lidocaine with 0.4ml 1% adrenaline 1:1000, 3ml 8.4% sodium bicarbonate diluted with 60ml 0.9% sodium chloride.	83.4 ml

Profound Treatment:

Step	Treatment Area	Cartridges Used	Temperature Used	Pulse Duration	Insertion Spacing	Total Insertion
One	Below the umbilicus	SubQ	67oC	Three seconds	3mm	19 insertions, in two passes cross-hatched
Two	Left flank	SubQ	67oC	Three seconds	3mm	30 insertions, in two passes cross-hatched
Three	Right flank	SubQ	67oC	Three seconds	3mm	75 insertions, in two passes cross-hatched

Figure 1 *- Profound Treatment Protocol.*

one horizontal, over the treatment areas for a total of 124 radiofrequency (RF) injections at a depth of 5.8mm, with the device set at 67ºC, three seconds, and pulses administered 3.0mm apart at a frequency of 5±460 kHz (*Figure 1*). Post-procedure, ice packs were applied on the treatment area for 20 minutes and the patient was advised to re-apply the ice packs every two hours, for 20-minutes on/off intervals for the rest of the day to help decrease the likelihood of indurations, extended bruising, and increase comfort. Thereafter, avoidance of rigorous exercise for 24 hours and sun exposure to the treatment area for four weeks was recommended.

The patient was evaluated seven days and three months post-treatment by two independent and blinded, board-certified doctors. Doctor ratings were done through visual appraisal and palpation of the treated areas.

The treatment was well tolerated, with only minor adverse effects during and after the treatment, including pain, erythema, superficial ecchymosis, and mild oedema. These adverse effects were resolved without medical intervention after seven days and no other side effects were reported. At the three-month post-treatment follow up (*Figure 2*), the length and width of each striae and colour had significantly reduced. The texture of striae was also improved. Overall improvement in the appearance of striae was marked and described as excellent by both patients and doctors. Furthermore, the patient noted visible reduction in subcutaneous adipose tissue, tightness, and improved skin texture, especially in the lower abdominal region. The patient was satisfied with the results.

Discussion

Striae have presented a considerable therapeutic challenge as despite the many treatments proposed, clinical outcomes have usually been unsatisfactory. The Profound System is a minimally invasive device that directly delivers bipolar, nonablative RF energy through an array of microneedle electrodes to the selected skin layer. In this case, the SubQ cartridge was selected to target the seven pairs of microneedle electrodes in the superficial aspects of the subcutis at 2.9-5.8mm below the epidermis, at an angle of 75º. The proximal part of the electrodes are electrically insulated to restrict applied energy to the target tissue. Temperature sensors located at the distal tip of the electrode enable real-time feedback of the target tissue temperature during energy delivery and modulation of the treatment by delivering a precise thermal dose into the tissue for defined time periods. Fractional delivery of RF energy creates zones of thermal injury between areas of unaffected zones, which causes collagen contraction and denaturation. There is evidence to suggest that this induces a wound healing response in the treated areas that leads to tissue remodelling and the generation of new collagen, elastin, and hyaluronic acid[11-14]. FMR has been primarily used for skin rejuvenation with beneficial effects seen from previous clinical studies on cellulite, rhytides and laxity of the face and neck, acne scars and textural irregularity[10,14]. Temperature settings of 67ºC and three-second pulse durations were used for treatment, in accordance with an optimised treatment protocol published in literature[15]. As striae are a form of dermal scarring, we hypothesised that FMR may be effective in the treatment of striae. Moreover, as RF energy is not dependent on specific chromophore interactions, it is possible to use FMR devices in all skin types. This is a major advantage, in contrast to lasers, where associated PIH is a concerning adverse effect[8,9,16-18]. Whilst there is limited high level evidence in literature to confirm our hypothesis, a number of studies using FMR devices on striae on the body showed results similar to ours. Pongsrihadulchai et al.[16] reported improvement of the total surface area, width and length of striae with statistical significance ($p<0.001$) following three FMR treatments at four-week intervals. A significant increase in the number of collagen and elastin bundles when compared with the baseline ($p = 0.005$) was also reported. Similarly, Ryu et al.[17] demonstrated moderate improvement in striae in most patients, with a mean clinical improvement score of 1.8 rated using a visual analogue scale (range 1-4). Patients in this study received three FMR treatments at one-month intervals. In addition, skin biopsies taken revealed epidermal thickening and an increased number of collagen fibres in treated areas. Pongsrihadulchai et al. observed PIH in 18.1% of patients post-treatment, similar to the 20% of PIH observed in the study by Ryu et al. This prevalence is comparatively low to the 81.8% of patients observed with PIH following fractional CO2 laser treatment for striae on the body and 36.4% with fractional Erbium glass laser[18].

Conclusion

This case study demonstrates that a single FMR treatment is a safe, tolerable, and effective approach for improvement of SG in Asian skin. Patients can expect minimal pain, downtime, and no scarring. The most common adverse effects are transient superficial ecchymosis, erythema, and oedema. Further controlled randomised comparative clinical trials are needed to determine the optimal treatment protocol for maximising efficacy, safety, and patient satisfaction. Questions remain regarding optimal patient selection, treatment parameters such as energy level, number of passes, number of treatment sessions and/or combination treatments for long-term clinical outcomes. In order to validate the use of FMR in practice for the treatment of skin laxity and reduction in subcutaneous adipose tissue, additional large-scale randomised trials are necessary.

Acknowledgements

The authors declare that there is no conflict of interest.

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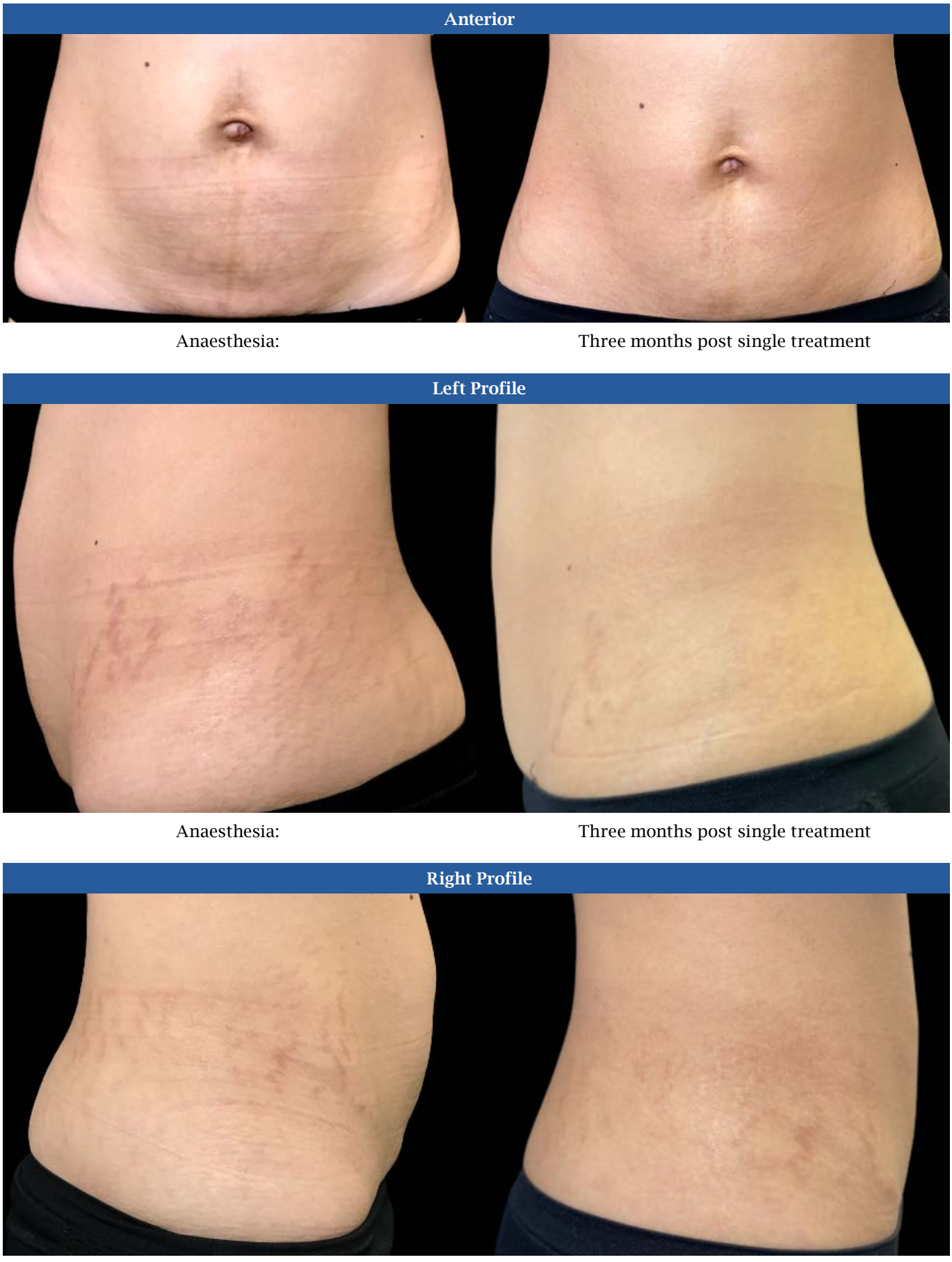

Figure 2 *- Before and three months post single treatment of Profound with SubQ cartridge.*

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aesthetic medicine

Narrative Review

Polynucleotides Highly Purified Technology at the hair follicle level

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The growth cycle of the 100,000-150,000 human hair follicles was defined in the early 1920s: a long (3-7 years) phase of active hair follicle proliferation and growth ("anagen") followed by a short (1-2 months) phase of stasis ("telogen"), and a transitional phase linking anagen and telogen (2-3 weeks) known as "catagen"[1]. During telogen, the fully formed hairs do not proliferate and the papilla of the hair follicle shrinks; hairs appear to be anchored in the follicle, but not too strongly, and may easily fall (on average, 30-100 per day; prominently around autumn and early winter and possibly in spring)[2,3]. The hair follicles are not synchronous, but there is a steady fall of hair proceeding contemporarily with hair growth. Only in 1961 Kligman first described telogen effluvium, one of the most common causes of diffuse hair loss with many suggested potential triggers[4]. Diffuse, non-scarring, usually self-limiting hair loss from the scalp lasting for about 6 month occurs about 3 months after a triggering event, although diagnosis of telogen hair shedding does not allow inferring the lesion mechanism. Kligman hypothesized the transitional event to be the premature termination of anagen; later the follicle precipitates into catagen followed by a resting stage mimicking telogen[4]. Acquiring a completed anamnesis and performing laboratory investigations will allow the exclusion of endocrine, nutritional and autoimmune disorders. Many causes of telogen effluvium are iatrogenic, with drugs like oral contraceptives, anticonvulsants and antithyroid, hypolipidemic agents and ß-blockers that have been implicated. Other major causes are emotional stress, including crash diets and difficult labor, major surgeries and injures[4].

Androgenetic alopecia, which is the common condition in men, is also known as male-pattern baldness. Hair is lost in a well-defined pattern, beginning above both temples. Over time, the hairline recedes to form typically "M"-shaped balding fade. Hair also thins around the top of the head, then often progresses to partial or complete baldness (*Figure 1*)[5].

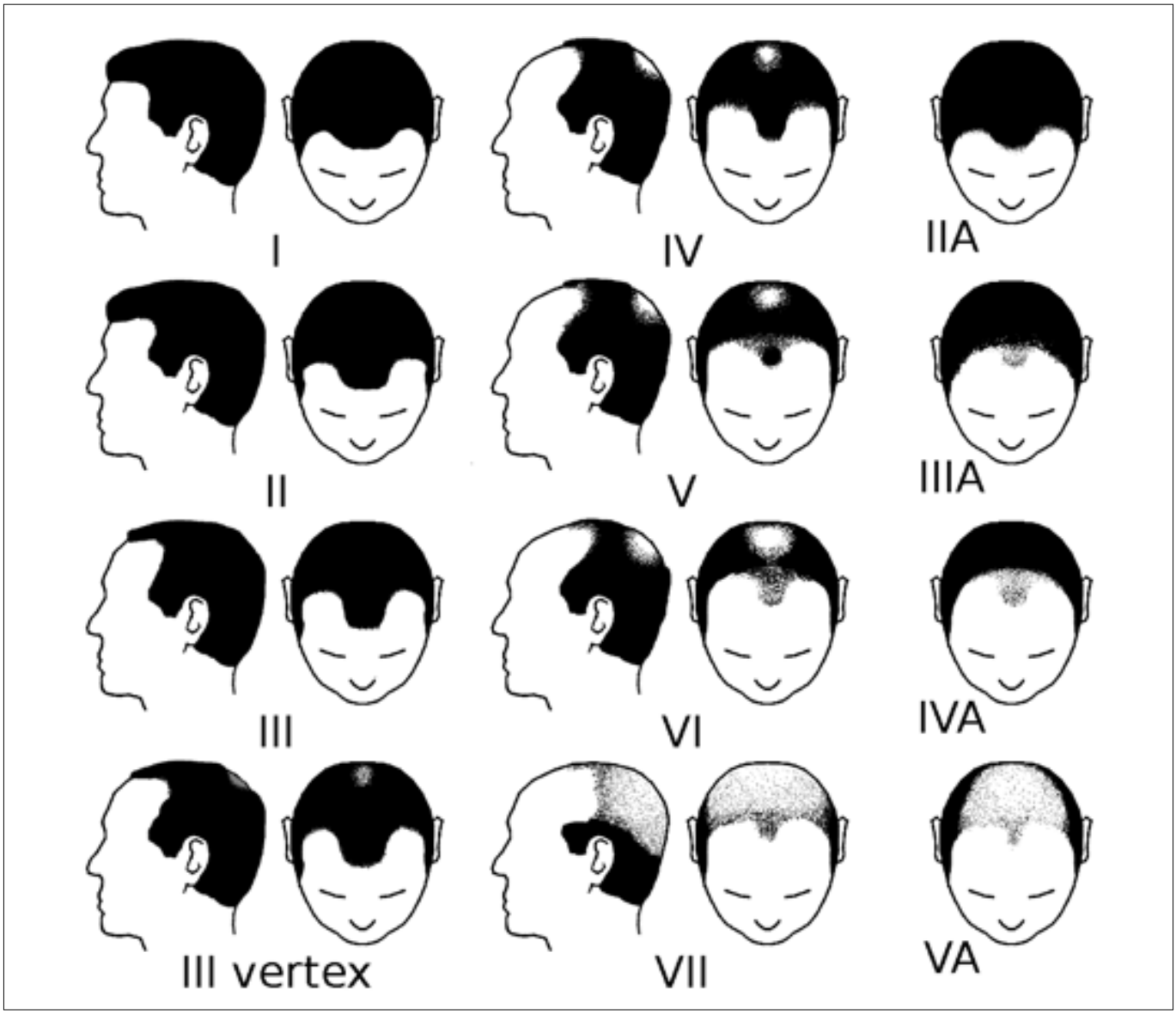

Figure 1 *- The Norwood-Hamilton scale of male pattern baldness, the leading classification system used to sort the stages of male pattern baldness. The stages are described with a number from 1 to 7 (source: https://www.sitri.it/scala-di-hamilton).*

Androgenetic alopecia also affects women. The female hormonal hair loss or female androgenetic alopecia (FAGA) affects up to 40-50% of women with a varying distribution of hair thinning: the most common variant is the "Christmas tree pattern", followed by the less common "Ludwig pattern" (variably severe hair loss in the vertex area) and by the rare male-like "Hamilton pattern" (the receding hairline on the forehead and thinning on the vertex). FAGA occurs whenever the normal estrogen-progesterone balance is severely deranged. This evolution can occur at any age with contraception, pregnancy, stressful events, and dietary deficiencies[6,7].
In the non-androgen-dependent female hormonal hair loss, the less severe lack of estrogens leads to progressive miniaturization of the whole length of hairs (papilla, matrix shaft). The anagen phase is less prolonged than usual with hairs shorter and finer and reduced in numbers, whilst there is a greater amount of them in the telogen phase[6,7]. Actual baldness is uncommon, and areas of hair thinning - hypotrichia rather than full alopecia - commonly present themselves in a mosaic-like pattern. The overall number of hairs is reduced, with an abundant amount appearing as a fine vellus hairs. Menstruation and fertility persist, there is no excess of circulating androgens and no telogen effluvium[8,9].

Polynucleotides Highly Purified Technology, hair follicle activity and hair growth

As always (see also the "Introduction to Polynucleotides Highly Purified Technology" section), after the intradermal scalp infiltration, highly purified, natural-origin polynucleotides (PN-HPT™, Polynucleotides Highly Purified Technology) act at the hair follicle level by promoting the trophism of hair bulb cells[10,11]. An extensive program of clinical studies shows that trophic stimulation is useful in hair loss to reactivate and support the hair growth phase. The following text box represents an example of such studies.

The following text box represents an example of such studies

One-center evaluation (Dermatologic Unit, University of Pisa Medical School) of 20 patients aged between 25 and 65 years suffering from female hormonal hair loss (non-androgen-dependent female hormonal alopecia), with no current or previous history of iron deficiency or endocrine or liver diseases, slimming diets, stress, hormonal contraception or other conditions that could possibly be responsible for hair thinning. Five patients had already experienced local treatments with unspecified stimulating lotions. A proprietary commercial formulation of PN-HPT™ (Plinest® Hair 7.5 mg/mL, Class III CE 0373 Medical Device, Mastelli Srl, Sanremo, Italy) was administered by intradermal scalp infiltrations over 4 month period; following a baseline clinical assessment (T0), evaluations were planned after 1 and 2 months (T30 and T60) and at the end of the 4-month study period (T120)[12].

- As shown in the video dermoscopy (*Figure 2*), the average number of hairs increased from 105/cm^2 to 118/cm^2 after 4 months.
- The female alopecia objectively improved in 72% of treated women with no side effects and high patient's compliance; *Figure 3* illustrates the evolution of the Pull Test and Trichogram Test over the study period.

With the same or similar treatment protocols (individually devised according to the severity of hair thinning), PN-HPT™ infiltrations can also supplement other techniques aiming to enhance hair reconversion to the anagen phase such as autologous platelet-rich plasma (PRP) infiltrations and visible red-light irradiation[13,14].

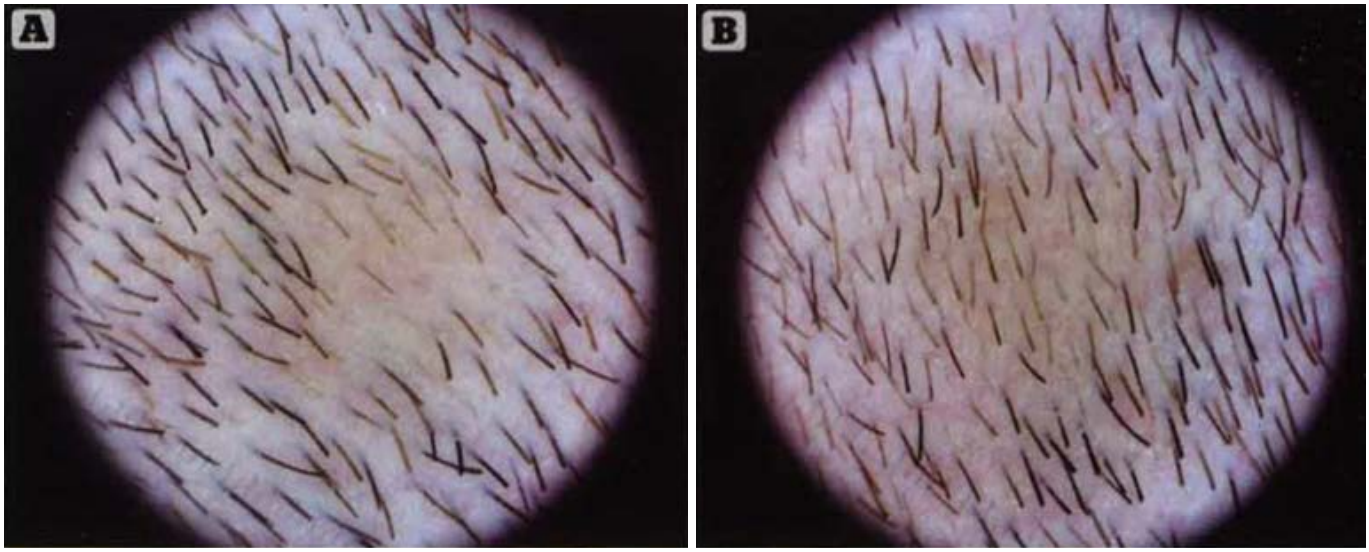

***Figure 2** - Twenty female patients with non-androgen-dependent female hormonal alopecia, average number of hairs at video dermoscopy after 4 months of infiltrative PN-HPT™ treatment: (A) Baseline assessment (T0, 105 hairs/cm^2); (B) end of study period (T12, 118 hairs/cm^2)[12].*

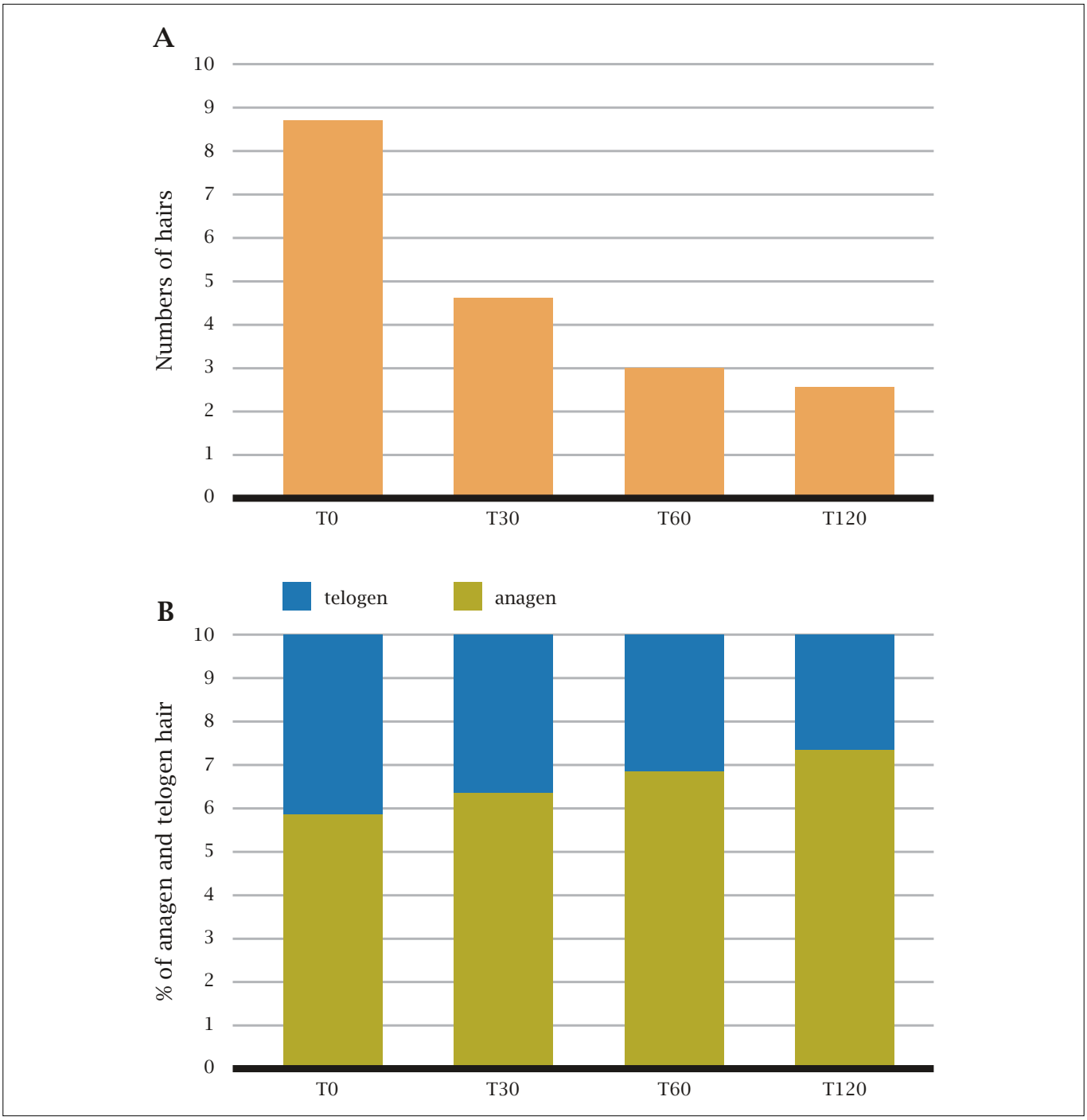

Figure 3 *- Evolution of the Trichogram Test over the 4-month PN-HPT™ treatment period: (A) Anagen/Telogen ratio and (B) direct comparison of hairs in telogen (blue) and anagen (red) phase at baseline (T0) and after 1, 2 and 4 months of PN-HPT™ infiltrative treatment (T30, T60, T120, respectively)[12].*

Suggested PN-HPT™ infiltration technique in the treatment of hormonal hair thinning

As supported by the previously illustrated clinical data, PN-HPT™ are ideally administered by intradermal infiltrations with the serial puncture technique, 0.2 ml per micro-wheal, with injections spaced 3-5 cm.
Using commercial products (validated in clinical studies (a)[11,12], the content of a whole prefilled syringe is distributed equally over the whole hair thinning area at each infiltration session. Available clinical data support an ideal treatment protocol of 8-10 infiltration sessions distributed over a 4-month period: one session per week for the first 4 weeks, followed by one session every 2-3 weeks for 3 months. Polynucleotides at-home supplementation with commercially available nutritional supplements (b) may be advisable as further oral support for the direct follicular efficacy of infiltrative PN-HPT™.

(a) Plinest® fast 7.5 mg/mL, Class III CE 0373 Medical Device.
(b) For instance, Plinest® Care In, 2 tablets per day of, anti-oxidant and pro-trophic nutritional supplement with nucleotides, vitamin C, vitamin E, Coenzyme Q, folic acid, zinc, Mastelli Srl, Sanremo (Italy).

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aesthetic medicine

Narrative Review

Polynucleotides Highly Purified Technology in the biorevitalization of postmenopausal labia majora

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In menopausal women, thinning and drying of the vaginal mucosa with smoothing of vaginal rugae, vulvar atrophy with blundering of interlabial sulci, the depletion of the adiposity of the labia majora and loss of vulvo-vaginal elasticity and flexibility, associate with loss of lubrication and dyspareunia, irritation, and itching. The reduced density of the sebaceous and sweat glands causes the presence of dry and rough skin. Together with dysuria and recurrent urinary tract infections, these symptoms severely compromise the self-perception, self-esteem and quality of life of the menopausal woman[1].
Microscopically, the postmenopausal estrogen deficiency and reduced blood perfusion in the skin lead to collagen hyalinization, loss of elastin fibers, and glycosaminoglycan depletion in the dermal matrix[2]. The symptoms oaf urogenital atrophy affect up to a substantial 15% of premenopausal women[3]. Hyaluronic acid levels in the skin also appear to be depleted[4]. Increasing collagen and elastin deposition to restore thickness in the skin and vulvo-vaginal elasticity and tension is crucial to re-activate the trophism of menopausal vulvo-vaginal tissues.

The Polynucleotide Highly Purified Technology™ / Hyaluronic Acid option

Infiltrated exogenous polynucleotides replenish the dermal and mucosal reservoir of endogenous polynucleotides and support the proliferation of dermal fibroblasts and tissue trophism[5]. Highly purified, natural-origin polynucleotides (PN-HPT™, Polynucleotides Highly Purified Technology™) have a short-term viscosupplementation effect like those of linear hyaluronic acid (HA). This is due to their nature of polymeric molecules that gather large amounts of water. Moreover, after dermal infiltration, PN-HPT™ recompose their structure by directing and coordinating water molecules to form a 3-D gel[5]. In the long run, PN-HPT™ prime the thin and hypotrophic tissues to improve cell viability and to produce new collagen, new elastin fibers and new dermal matrix glycosaminoglycans (see also the section "Introduction to Polynucleotides Highly Purified Technology™")[6].
HA consolidates the early PN-HPT™ benefits by improving the hydration of the extracellular matrix that is crucial for fibroblast trophism; HA also stimulates the production of new collagen and elastin[7]. Several studies in menopausal women with vulvo-vaginal ageing and labia majora hypotrophy demonstrate that HA infiltrations, with either cross-linked or linear HA, can help to counteract the loss of elasticity and volume and restore labial turgidity, volume and tonicity[8,9].
This background justifies the benefits of a two-step sequential strategy starting with PN-HPT™ infiltrations to counteract the symptoms of the genito-urinary syndrome of menopause. PN-HPT™ acts as the primer of the vulvo-vaginal bio-revitalization cascade. This first PN-HPT™ "priming" step is followed by a second phase of alternating PN-HPT™ and HA infiltrations with HA acting as consolidator of the early benefits induced by PN-HPT™ (*Figure 1*)[10]. Candidates to the PN-HPT™ ("primer") plus hyaluronic acid ("consolidator") procedure herein described are all the women in physiological or surgical menopause experiencing postmenopausal vaginal dryness, mucosal atrophy and thinning, loss of vaginal rugation and related symptoms: mucosal pallor and petechiae, soreness and tenderness of the vaginal introitus, dyspareunia.

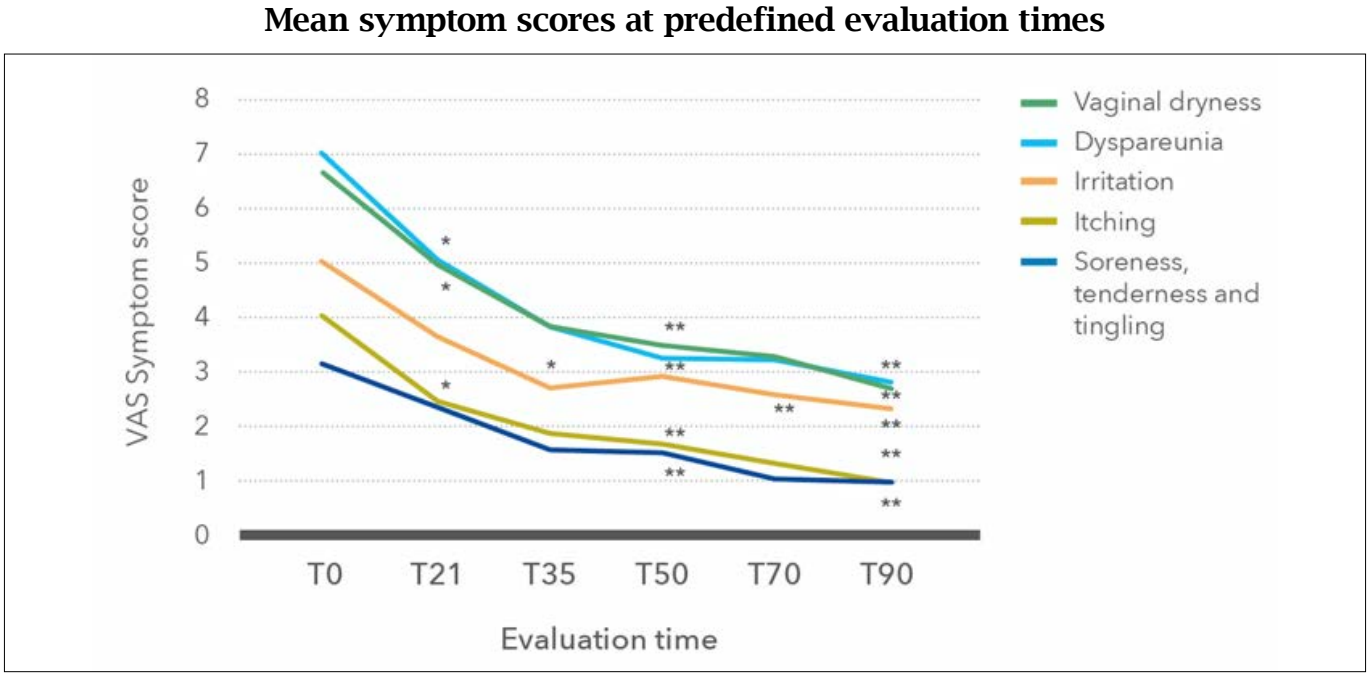

Figure 1 *- Evolution of vulvo-vaginal mean symptom scores over the 90-day follow-up period. T0: baseline assessment; T21, T35, T50, T70, T90: predefined assessment sessions, 21, 35, 50, 70 and 90 days after baseline and the first infiltration. * p <0.05 vs. baseline; ** p <0.01 vs. baseline. Reproduced with permission from the authors[10].*

Suggested procedures and timing

Preliminary disinfection and local anesthesia with an anesthetic gel should be performed 30 minutes before each PN-HPT™ and HA infiltration. The local anesthetic dose should be the smallest amount sufficient to numb the target vulvar area while minimizing the risks of systemic absorption.

Vulvo-vaginal bio-revitalization protocol - PN-HPT™ "priming" sessions

The target of PN-HPT™ infiltrations are the superficial derma of atrophic labia majora, the superficial lamina propria of labia minora and the vulvar areas around the introitus and clitoral hood. Available clinical data suggest using highly purified mixtures of polynucleotides, with an infiltration depth in the labial derma or lamina propria of about 3 mm below the vulvar skin surface.
Commercial PN-HPT™ products in prefilled syringe are available, extracted from salmon trout gonads and titled at 40 mg per 2 mL[(1)]; the ideal dose, according to available clinical data, is 2 mL.
According to available clinical data, the ideal PN-HPT™ "priming" program should foresee at least 3 PN-HPT™ infiltration sessions spaced 2 or 3 weeks. The ideal needle should be 30G/13 mm as in the commercially available prefilled syringe; the needle should be inserted with a 30-45 degrees inclination. As regards the infiltration technique, available clinical data suggest adopting the linear retrograde technique in labia majora and the micro-wheal technique in more internal vulvar areas, labia minora and around the vaginal introitus and clitoral hood. The ideal dose with the micro-wheal technique is 0.1 mL per wheal, with a distance between wheals of 0.5-1 cm. *Figure 2* shows the vulvar infiltration points suggested by clinical experience.

Vulvo-vaginal bio-revitalization protocol - hyaluronic acid "consolidation" sessions

The areas targeted for hyaluronic acid infiltrations are always the superficial dermis and lamina propria of the same vulvar areas previously "primed".
Available clinical data suggest that the labial hyaluronic acid "consolidating" infiltrations should be ideally carried out with a solution of highly purified natural-origin sodium hyaluronate and a molecular weight ranging from 1,000 to 1,500 kDa.
A commercial formulation is available with a HA concentration of 40 mg/2 mL[(2)]; the dose suggested by clinical data is 2 mL. Always based on clinical experience so far, the hyaluronic acid "consolidation" program should foresee at least 2 sessions every 2 weeks starting 15 days after the last PN-HPT™ "priming" session.
Once again, the linear retrograde technique should be adopted in labia majora and the micro-wheal technique in the more internal vulvar areas. Benefits are still appreciated after 6 months and a complete vulvo-vaginal bio-revitalization cycle should be repeated twice yearly. The supportive at-home topical application of polynucleotides, formulated as either vaginal pessaries or cream, has been used in several clinical experiences, up to relatively recent times[10]. Supportive topical PN-HPT™[(3)] are useful to help compliance to PN-HPT™ and hyaluronic acid infiltrations until the conclusion of the two-step vulvo-vaginal bio-revitalization program.

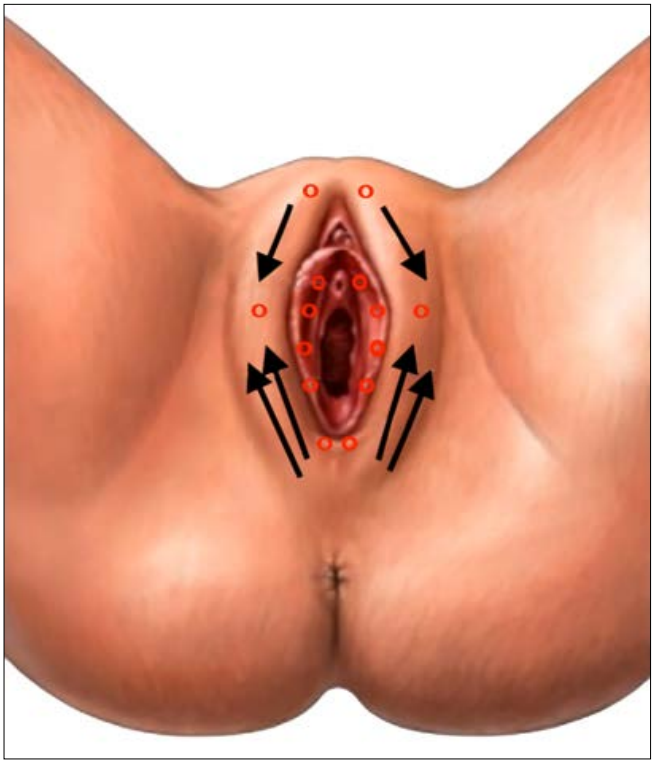

Figure 2 *- Points on vulvar labia where PN-HPT™ and HA infiltrations should be performed based on available clinical data (woman normally positioned on a standard gynecological examination chair). Infiltrations should be performed linearly and retrogradely, beginning with no more than two infiltrations below the posterior labial commissure overlying the perineal body and one or two infiltrations at the anterior labial commissure below the mons pubis. What is left in the syringe should be infiltrated in several small wheals on labia minora at the side of the vestibule and rising up to the clitoral hood. In spite of adequate local anesthesia, women sometimes experience some (bearable) discomfort during this second part of the procedure. Reproduced (image and caption) with permission from the authors[10].*

[(a)] Plinest®, Class III CE 0373 Medical Device, Mastelli Srl, Sanremo (Italy)

[(b)] Ialest®, Class III CE 0373 Medical Device, Mastelli Srl, Sanremo (Italy).

[(c)] Commercial formulations: Turnover® ovuli (vaginal ovules CE 0373), Turnover® intimo (mucoadesive vaginal cream CE 0373), Mastelli Srl, Sanremo (Italy)

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aesthetic medicine

Letter to the Editor

Non surgical fat reduction with dehoxycholate: an update regarding available solutions in the European market

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Non surgical fat reduction can be achieved with Energy Based Devices (EBD) such as cryolipolisys or by dehoxycholate (DC) injections; moving an EBD can be difficult and cumbersome, therefore, these systems may not be practical for physicians who work in multiple locations. Injectable treatments do not have this disadvantage and can therefore be performed on demand[1-3]. Moreover, EBDs must be purchased upfront, whereas a supply of injectables can be purchased as needed, when needed[2]. Nowadays ATX-101 is the only approved drug containing DC: the sole purpose of this drug is to reduce unwanted submental fullness. ATX-101 was introduced into the US and Canadian markets in 2015 and into the European market in 2017[2,3].

The effectiveness of DC injection in nonsurgical fat reduction was first described by Rotunda et al.[4] in 2004; when DC is injected into fat, it alters the permeability of fat cell membranes, causing progressive cellular swelling that ultimately results in the break-up of fat cells. This process can take several days to several weeks[2,5,6]. After cellular break-up, macrophages enter the site and eliminate cytoplasm and cell membranes, while the healing process is carried out by the development of fibrotic tissue. The entire process, including healing, usually takes several months[2].

A DC-based solution with a lactose-based delivery system formulated for the purpose of controlling and enhancing the action of external ultrasound waves, for the microcavitation of adipose tissue for the medical treatment of localized adiposity reduction (Aqualyx, Marllor International, San Giovanni in Marignano, Italy) has been sold in Italy since 2009 (*Table 1*)[6].

This solution developed by Dr Pasquale Motolese, although containing DC, obtained CE certification as "medical device"[6]. Several studies have shown its effectiveness in body fat reduction even when external ultrasound waves are not performed[6-9]; this is easy to be explained: DC, once injected into the fat, doesn't need "activation" by external ultrasound waves, DC has got its own pharmacological activity.

In 2013, in a letter published on *Aesthetic Surgery Journal*, Duncan compared Aqualyx with a PC/DC solution and with placebo (saline solution alone); the first solution showed to be the most unselective and cytolytic[10].

In 2014, Rauso and Salti, on the same journal, published their positive 4-year experience with Aqualyx injections, showing that contrary to the indication for this solution (to enhance and control the action of external ultrasound waves for the microcavitation of adipose tissue), Aqualyx appears to be effective and safe for localized fat reduction in this off-label fashion (ie, without ultrasonography)[6]. No unexpected side effects occurred, such as skin necrosis; however, typical DC injection-related transitory effects, such as reddening of the skin, bruising, and edema, were experienced by all patients[6].

In 2016, Amore et al. released their study regarding the effectiveness of Aqualyx injections in a large sample of patients (1832 patients), also in this study external ultrasound waves were not applied after the injections[7]. The main focus of the study was not to show Aqualyx effectiveness, but authors tried to standardize the injection technique called intralipotherapy, firstly proposed by Dr Motolese, then published by Rauso and Salti in their earlier experience with the off label injection of Aqualyx[6,7]. Amore et al. concluded that intralipotherapy, when performed properly with an appropriate adipocytolytic device and when proper precautions are taken, can be effective and safe for reducing undesirable subcutaneous fat deposits[7].

Moreover, Amore et al. in 2018, released another paper showing the effectiveness of a 1.25% DC-based compound (manufactured by Industria Farmaceutica Galenica Senese s.r.l. - Via Cassia Nord, 351 - 53014 Monteroni d'Arbia – Italy) delivered with the intralipotherapy technique in order to reduce localized adiposity[11].

It is rather unusual that a DC-based solution (Aqualyx) gained approval as a medical device, and subsequently had issues arise.

In 2011, the Italian Ministry of the Health asked for an explanation to Marllor International (Aqualyx manufacturer) about the recording of Aqualyx as "III class medical medice" due to the presence of DC[12].

The same clarification was then demanded by the Italian Ministry of the Health in November 2013 and February 2015[12]. In February 2016, the Italian Ministry of the Health performed a request for opinion to the Italian Technical Health Committee about the presence of DC into Aqualyx and its record as a medical device[12]. Professor Bernardini of the Italian Technical Health Committee stated that Aqualyx contained DC as Kybella, a drug recently approved by the American Food and Drug Administration (FDA)[12]. In May 2016, the Italian Ministry of the Health denied the merchantability of Aqualyx[12].

Aqualyx manufacturer made legal recourse to the Regional Administrative Court of Lazio (T.A.R. del Lazio) asking for the cancellation of the provision released by the Ministry of the Health regarding the merchantability of Aqualyx; however the legal recourse was rejected[12].

Table 1. Italy's Ministry of Health card Regarding Aqualyx Registration

Medical Device	Medical Device	Medical Device	Medical Device	Medical Device	Medical Device	Medical Device	Medical Device	Manufacturer	Manufacturer	Manufacturer	Manufacturer
Device's type	Identification number	Inventory subscription	Manufacturer's code	Brand name	CND	CE class	Date of the first publication	Manufacturer's role	Name	Fiscal code	Nation
Device	286598	N	PFLX0010	Aqualyx	K020280 - surgical device with ultrasound generator	III Class	28.01.2010	Producer	GHIMAS S.P.A.	290990373	IT

Table 1 *- Italy's Ministry of Health card regarding the registration of Aqualyx: this DC solution is recorded as an injectable medical device formulated for the purpose of controlling and enhancing the action of external ultrasound waves for the microcavitation of adipose tissue for the medical treatment of localized adiposity reduction.*

Moreover, Aqualyx manufacturer made appealed to the State Court, the third degree of justice required by law. In January 2018, the State Court cancelled the provision released by the Ministry of the Health regarding the denial of merchantability of Aqualyx with the following reasons: "The contested provision was issued in the absence of suitable participation by the manufacturer to the related procedure, as it never received the notice of rejection with a simultaneous request for counter arguments, nor the request for documentary production of February 2016, in order to make the cross-examination and the right of defense of the private party effective, nor finally note of May 2016, with which Ghimas s.p.a. (Aqualyx manufacturer) was asked to transmit its counter-arguments to the issuing of a prohibition measure"[12]. Due to this measure, after January 2018 Aqualyx was sold again[12].

The effectiveness of Aqualyx without external ultrasound waves application has been also recently shown on a non surgical lipoma treatment; the injection was administered with a high frequency ultrasound guide injection and not with the intralipotherapy technique firstly described by Motolese[9].

Nowadays, January 2021, Aqualyx is still sold in Europe and others country such as Russia, Hong Kong, U.A.E., etc. recorded as class III medical device (not as drug) and is used for non surgical fat reduction[13]. The only 2 solution containing DC actually sold in Europe are Aqualyx and Belkyra (called Kybella in U.S.A.), respectively recorded as medical devices and drugs. Both the solutions contain DC, although DC concentration is reported only for Belkyra (10 mg/mL); Aqualyx package leaflet reports: the solution consists of a polymer of 3:6-anhydro-l-galactose and D-galactose, buffer systems, 3⟨, 12⟨-dihydroxy-5®-24-oico cholanic acid sodium salt, and saline solution[14].

Belkyra/Kybella is indicated for the non surgical treatment of submental fullness (SMF), Aqualyx for non surgical treatment of all body adiposity, buffalo hump deformity and lipoma[3,14]. A restricted indication for Belkyra/Kybella (just SMF treatment), is related to the difficult and long course to get a drug approval. In order to let the readers to understand how difficult obtaining an indication for a drug is, just think how many years passed from glabellar lines treatment (2002) to forehead lines treatment (2017) using botulinum toxin type A. On the other hand, it is easier to expand indications to a medical device compared to a drug. Another big issue is related to the cost difference between the medical device Aqualyx and the drug Belkyra/Kybella: a vial of Aqualyx contain 8 mL of solution and costs around 20 euros, a vial of Belkyra/Kybella contain 2 mL of solution and costs around 150 euros.

From a scientific point of view, Belkyra/Kybella has several published scientific papers, characterized by randomized and non randomized studies, regarding its efficiency and effectiveness[15-17]; on the other hand some large clinical studies also support efficacy, effectiveness and low rate of side effects injecting Aqualyx without external ultrasound waves application[6-9,18].

It is actually a paradox having 2 European solutions, one recorded as a drug, and one as class III medical device, both containing DC, who have both shown effectiveness and safety for submental fullness treatment and, for the "medical device", efficacy also for body adiposity treatments. Nowadays, a European aesthetic physician, involved in non surgical fat reduction with DC solution, could face all the questions that arise reading this paper.

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Web: http://asocime.com.pe/congreso-cientifico-de-medicina-estetica/

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President: P. Vega
Email: seme2021@pacifico-meetings.com
Web: https://www.seme2021.org/index.php/es/

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Argentinian Society of Aesthetic Medicine SOARME
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Email: info@soarme.com
Web: https://www.soarme.com

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