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Contents

Lasers for the treatment of rosacea

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key words: *rosacea, laser, telangiectasias, erythema, inflammation*

Abstract

Rosacea is a very common dermatosis, which affects almost 6% of the general adult population, and is characterized by the appearance of flushing, telangiectasias, stinging, papules, and pustules. Due to the heterogeneity of clinical appearances, there are many therapeutical modalities that can be applied. In the last decades, the mainstream of rosacea therapy consists of the use of highly selective laser systems. The objective of this review paper is to access the efficacy and safety of different light sources and lasers in treating rosacea.

Introduction

Rosacea is a chronic, inflammatory disorder that includes abnormal cutaneous innate immune responses and neurovascular dysregulation (1). Clinical features varied, with key components being frequent facial redness and inflammatory lesions (2). Increased reactivity of blood vessels leads to transient erythema and flushing, and persistent centrofacial erythema and telangiectasia (3). Inflammatory response induces papulopustular, phymatous changes, and ocular inflammation. Chronic inflammation may present in the thickening of areas such as the nose, ears, and cheeks, as the result of oedema, sebaceous hyperplasia, and fibrosis. In the granulomatous variant, more monomorphous, persistent skin-colored to dull red-brown facial papules are seen (4).

Rosacea is a very common dermatosis, first appearing during middle age, more often in lighter skin phototypes individuals (5). In the

systematic review, L. Gether, et all. found that 5,46% of the adult general population is affected by rosacea, with no prevalence between men and women (6). Since rosacea is chronic, facial dermatosis with such high incidence, it represents a big psychological and sociological burden on the patients (7).

Several different, but interrelated, pathological mechanisms have been proposed in rosacea. Along with genetic predisposition that plays a significant role in the pathogenesis of rosacea, environmental triggers are considered as important contributing factors, like ultraviolet light and other factors (e.g., spicy food, heat, alcohol, dome medication, etc.) (8). Additional important pathomechanisms of rosacea imply skin barrier dysfunction and penetration of sensory irritants, as well as greater follicular infestation with commensal microbes Demodex mites (folliculorum and brevis), associated with an intense perifollicular inflammatory infiltrate (9, 10). Furthermore, several clinical features of rosacea (including transient erythema, persistent centrofacial erythema, telangiectasias, and flushing) indicate the important role of the vascular system dysregulation in its pathogenesis, like increase angiogenesis and blood flow (11).

Considering the heterogeneity of skin changes and clinical manifestations, that is pathognomonic for rosacea, many therapeutical options can be applied in the treatment, such as regular skincare regiments, a local and oral antibiotic, different anti-inflammatory and anti-parasite treatments, isotretinoin, etc. (12). Usually, the inflammation (papules and pustules) responds well at the local or oral medical therapies. On the other hand, vascular disturbance presented as erythema, telangiectasias and a rhinophyma, are very persistent and commonly require additional physical modalities, such as laser treatments (13). Vascular laser therapy represents the main therapeutic option for rosacea with dominantly erythematotelangiectatic skin presentation, along with topical $_1$adrenoreceptor agonists, electrocautery, and radiofrequency (13).

The use of lasers in dermatology has in general increased in the last decades. The name LASER is an acronym that stands for Light Amplification of Stimulated Emission of Radiation, which describes the process of light generation (14). The foundation of laser-tissue interaction is defined mainly by the theory of selective photothermolysis, which was first introduced by Anderson and Perish in 1983 (15, 16). In their study, it has been shown that selective heating of target tissue can be achieved by an appropriate choice of laser wavelength and pulse duration, which allows heating of the target cells, but not the surrounding tissue. The desired effect only occurs when light is absorbed by a target chromatophore (i.e., hemoglobin, water, melanin), converting light to heat. Theory of selective photothermolysis made possible the development of different selective tissue lasers.

There are several types of light sources and non-ablative lasers that can be used for erythema and telangiectasias in rosacea, the ones with the most success are: pulse dye laser (PDL), Long pulse Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG), Intense pulsed light (IPL), Potassium-titanyl-phosphate (KTP). In treating changes that are the result of hyperplasia and fibrosis, good results have been achieved in using ablative lasers (CO2 laser) (17).

Material and Methods

In our research, we have focused on the following electronic databases - Science Direct and PubMed/MEDLINE for published articles. Furthermore, we have included reference lists of different articles on which we focused. Databases were limited to the period 2000–2020, but studies that represent a turning point in the application of lasers in dermatology and surgery were also included in the research process (papers from 1981, 1983, and 1996). Only studies in English were included. The following search terms were used to generate the data: Rosacea laser treatment, Effectiveness Safety, Undesirable effects, Pulse dye Lasers (PDL), Long pulse Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) Laser, Intense pulsed light (IPL), Potassium-titanyl-phosphate (KTP), CO2 laser.

Results

Pulse dye Lasers

Pulse dye Lasers (PDL) are the most usually implemented lasers for treating rosacea, and there are over 500 clinical articles supporting its efficiency and safety in treating rosacea (18). PDL emit a wavelength of 585nm and 595nm and targets hemoglobin as chromatophore, which provokes conduction of heat from erythrocytes inside the lumen to the entire wall of the blood vessel, and so it causes complete coagulation in superficial dermal vessels (19).

It has been shown that usage of a 5- or 7-mm spot size, fluences between 5 and 7 J/cm2, and pulse duration of 0.45 milliseconds, produce good to an excellent reduction in telangiectasia, erythema, and overall appearance as well as a decrease in papules and pustules (20). It has been noticed that treating rosacea with PDL also leads to decreasing or total absence of Demodex mites in hair follicles, which could explain the clinical improvement in presence of papules and pustules in rosacea patients (21, 22). Also, it has been shown that treating rosacea with PDL causes a decrease in nerve fiber density and the number of substance P immunoreactive nerve fibers, which helps in improving rosacea stinging condition (23). Side effects reported in PDL treatment include edema, erythema, purpura, and pain, but were all defined as transient and mild (24, 25).

Many studies have shown that treating rosacea with PDL is safe and effective, and some authors are considering it as a gold standard for rosacea laser treatments (20).

Long pulse Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) Laser

This laser type emits wavelengths of 1064nm and has 3-5 times greater absorption of methemoglobin than oxyhemoglobin (26). Pulse durations for the long-pulsed Nd:YAG may range up to 300 milliseconds and the fluences up to 900 J/cm2 (27). Spot sizes range from 3 to 10 mm. The mechanism of action is based on the theory of selective phototermolysis, which explains how the laser energy leads to local vascular necrosis, and collagen destruction, and at the same time sparing the surrounding tissue (28). Although PDL has greater absorption for haemoglobin than Nd:YAG laser, the long pulse of Nd:YAG allows deeper penetration and so treating deeper and larger caliber telangiectasias (29). Nd:YAG laser shows some affinity to local melanin which helps in conducting the heat and local destruction of blood vessels, but also increases the possibility

of hyper or hypopigmentation (30). Because the risk of scarring is increased, it is essential not to overlap the pulses and to use adequate skin surface cooling methods. For treating facial telangiectasias Nd:Yag laser has shown to be very effective, especially for deeper and resistant dilated blood vessels in comparison with PDL (27).

Potassium-titanyl-phosphate

Potassium-titanyl-phosphate (KTP) emits wavelengths of 532nm and has high affinity for oxyhemoglobin. Pulse durations range from 1 to 150 milliseconds, fluences up to 240 J/cm2, and spot sizes up to 5 mm (27). In comparison with long lapse Nd:YAG laser, because of its shorter wavelength, KTP shows more affinity for melanin absorption. Potassium-titanyl-phosphate is very effective in treating telangiectasias in rosacea, but also provokes more dyspigmentation formation (31). Depending on vessel size laser spot, fluence, and pulse durations are chosen to ensure the highest possible chromophore absorption, while minimizing possible side effects. Comparative studies of KTP and PDL have shown more swelling, purpura, and pain with the KTP, but KTP appears to be more effective (32).

Intense pulsed light

Intense pulsed light (IPL) uses xenon flash lamps and emits unfiltered broad-spectrum (500-1200nm), which by filtering can be customized for specific disorders (27). For rosacea inflammatory and vascular lesions, shorter wavelengths are applied (33). Some IPL-s allow multiple pulsing with different pulse durations and pulse intervals, which permit treating both superficial and deeper telangiectasias. In comparison with PDL treatment, it has been noticed that IPL provokes less purpura formation (34). Some studies have shown that IPL for rosacea-associated erythema is safe and effective, with high success rate in treating papulopustular rosacea and erythemotelangioectatic rosacea (35).

CO2 laser

In recent years, laser treatments have been included in treating sebaceous hyperplasia and fibrosis in rosacea and have taken the place of surgical procedures and electrocauterization. CO2 laser emits wavelengths of 10600nm and has a high affinity to water (36). Tissue destruction is nonselective with CO2 laser and it is performed by vaporization in skin cells, which leads to local destruction of tissue. Advantages in using CO2 laser opposed to surgical procedures for treating rhinophyma are shorter downtime, lesser bleeding, better control of the depth of the injury, and in all better aesthetic results (36). By the study results, it has been shown that CO2 laser treatment for rhinophyma produces good cosmetic results with minimal complications development.

Discussion

Given the literature presenting results of clinical studies (35), and by our personal clinical experience, the use of highly selective lasers can be considered as highly effective in the treatment of rosacea with a high safety level. For the treatment of papuloeritematous form of rosacea, as well as for diffuse erythema, the best results could be achieved by using PDL. To treat

telangiectasia, slightly better results could be attained by using Nd: YAG or KTP lasers. In recent years, IPL devices have been upgraded to be more user friendly, so they could be very successfully used in the treatment of both telangiectasia and diffuse erythema, with minimal chances of developing side effects.

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Letter to the Editor

Non-surgical abdominal fat reduction procedure, with the use of a monopolar radiofrequency device: a useful and non-invasive method.

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key words: *radiofrequency, fat reduction, body circumference, body contouring, truSculpt*

Introduction

The demand for the use of non-invasive methods for body circumference and fat reduction is growing year by year. Accordingly, different non-invasive body contouring modalities exist. We presented a therapeutic response in 20 patients to a device that reduce abdominal circumference and fats, without overheating the application sites or causing other discomfort to patients. The ease of use and versatility make it a valid non-invasive technique for body remodeling.

In the last decades, several non-invasive body contouring techniques started to be increasingly used as procedures in esthetic medicine (1). Specifically, the significant risk of invasive body contouring procedures has led to 521% growth of non-invasive techniques since 1997, with an increase of 21% every year (1). At the same time, in the general population, there is an increase in the incidence of diseases associated with overweight and obesity (2). Accordingly, there is an increase of subcutaneous fat, that is an indicator of peripheral fat mass, which could be evaluated by circumference and skin fold measurements and variation in these parameters could be considered as an indicator of cellulite changes (1). In this regard, different non-invasive

body contouring modalities are available for reducing the volume of subcutaneous adipose tissue, such as cryolipolysis, radiofrequency (RF), low-level laser therapy (LLLT), and high-intensity focused ultrasound (HIFU) (1).

In this article we report a case series of abdominal fat reduction using a novel device, which takes a multi-dimensional approach to decrease circumference and eliminate fat cells, by delivering and holding clinically therapeutic temperatures to the subcutaneous adipose tissue to achieve the efficacy in the shortest possible treatment (3).

Methods and case series

A total of 20 Caucasian female patients (median age: 58 years, ranging between 43 and 72), with an increase of abdominal fat, which caused discomfort to patients, have been included in this report. None of the selected patients had also other relevant medical diseases. All patients did not perform any previous treatment for the increase of the abdominal fat and were included in treatment with truSculpt® iD (Cutera, Brisbane, California, USA), a body sculpting device that offers personalized non-surgical fat reduction treatments based on patient needs. Specifically, it is a monopolar radiofrequency device in which electric current flows between a single electrode and a grounding point. The 2 MHz treatment frequency create hyperthermic conditions within the subcutaneous fat layer but the handpieces maintain a comfortable skin temperature (between 43.0°C and 44.0°C). The temperature inversion effect acts on the adipocytes without damaging to the cutaneous layers (4).

The treatment was performed on 8 areas simultaneously, specifically in abdomen and flanks. Up to six 40 cm^2 hands-free handpieces placed simultaneously over multiple localized fat pockets. Handpieces covered up to 300 cm^2 treatment area on the abdomen and flanks in 15 minutes. Each treatment session consisted of 2 cycles of 15 minutes for each session, for a total of 5 sessions every 15 days. After 5 sessions all treated patient reached with a fact reduction, resulting in a reduction of the abdominal circumference, with a mean circumference reduction of 1.8 cm (ranging between 1.5 cm and 2.8 cm). (Fig. A1, fig. B2) No adverse events have been recorded, but the patients experienced only mild to moderate local erythema and edema after the treatment, for a period ranging between 1 hour and non-more than 24 hours.

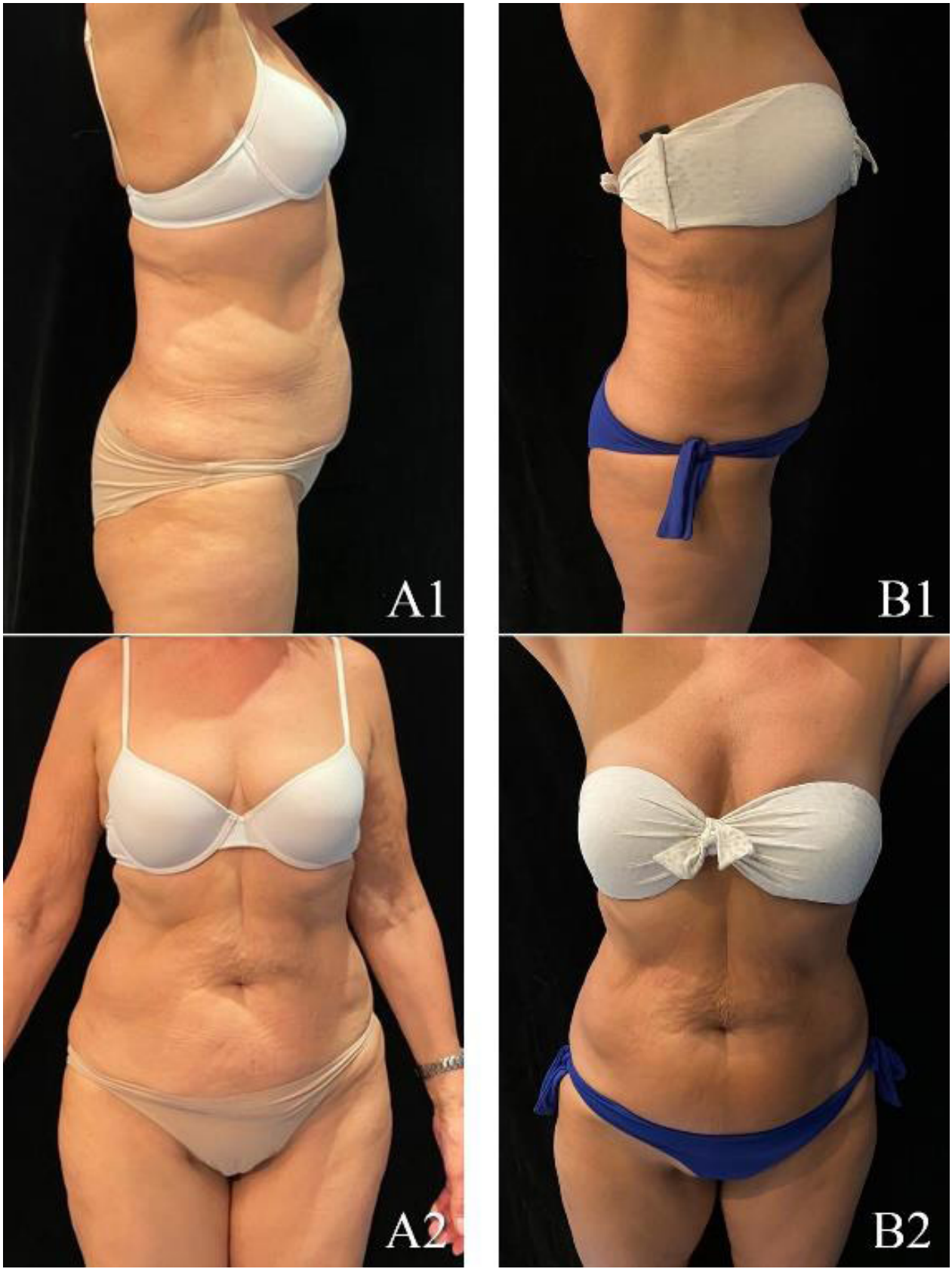

Fig. A1-B2. *Each session consisted in 2 cycles of 15 minutes. After 5 sessions the patient showed a reduction of the abdominal circumference, with also a reduction of the abdominal fat. No specific side effects have been recorded.*

Discussion

According to the existing evidence, the non-invasive techniques have shown statistically significant effects on body contouring and on removing unwanted fat., however, with little or no effect on body weight reduction and total percentage of body fat (1). According to the literature (1), the average circumference reduction after noninvasive methods is of 2 cm, and our results confirmed these data. Furthermore, the patient satisfaction following the treatment, with the minimum possible discomfort for the patients, remains to be a valid treatment for abdominal circumference and fat reduction.

Radiofrequency (RF) is an electromagnetic wave that was initially used for body contouring (4-6). It may induce heat in different tissues by transforming energy through three main mechanisms: orientation of electric dipoles; polarization of atoms and molecules to produce dipole moments and displacement of conduction electrons and ions (1, 7) truSculpt® iD is a non-invasive, monopolar RF platform, characterized by high tolerance and compliance by the patient, with excellent aesthetic results. Specifically, truSculpt® iD allows for customized treatments to multiple body areas simultaneously based on patients need in as little as one 15-minute treatment protocol, delivering heat to the entire fat layer, without skin overheating (3, 7). Indeed, a therapeutic temperature of >45ºC in the fat is reached, while maintaining a cutaneous temperature of 3-4ºC cooler (3). In this way, an average of 24% fat cells are irreversibly damaged and fat cells are slowly removed and excreted through the body naturally over a 12-week process (3, 7, 8).

Conclusions

The demand for the use of non-invasive methods for reducing body circumference, fat reduction and muscle sculpturing is growing year by year (9-13). We have presented a therapeutic response to a device that does not cause discomfort to patients and does not overheat the application sites. The ease of use and versatility make it a valid non-invasive therapy for body contouring.

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Therapy of common acquired melanocytic nevi by shaving followed by touch with diathermy

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key words: *ordinary nevi, melanocytes, heat diathermy, shave excision*

Abstract

Background: The ordinary surgery of common acquired melanocytic nevi (CAMN) is excision and suturing when nevi are small, but when large, excision is followed by graft or flap. Objective: To find simple alternative modes of treatment like shaving and simple touch with diathermy for small nevi especially when are multiple or numerous. Patients and Methods: This is a prospective interventional study where seventeen patients were enrolled in the study, 13(76.47%) females and 4(23.52%) males, their ages ranged between 12-36 years with a mean 22years with a total of 52 ordinary common acquired melanocytic nevi on their faces which were removed. The area was cleaned with spirit and povidone-iodine and under local anesthesia, a number 15 surgical blade was utilized to carry out the shave excision, followed by simple touch cautery with diathermy. All patients were seen after 2 weeks and then every two months for four months. Oral antibiotics were used for five days. Topical mild corticosteroid cream was used for one month to prevent pigmentation. Results: Two weeks after surgery, post-surgical erythema was noticed and this gradually gone leaving no scar or pigmentation during follow up period 2 - 4 months following excision. No complications or relapse were observed in any case treated.

Full satisfaction with the result outcome was achieved in all patients. Conclusion: Shaving of ordinary nevi followed by touch with diathermy needle is an excellent surgical technique without complications or repigmentation.

Introduction

Common acquired melanocytic nevi (CAMN) is a common ordinary type, largely acquired, disorder resulting from benign proliferation of nevus cells. This disorder, also referred to as "signature nevi" (1), has been variably categorized depending on the architectural, anatomic, and cellular histological pattern (2).

CAMN appear after 6 months of age. They enlarge in size and increase in number through the third and fourth decades and then slowly vanish. They are mostly less than 5 mm in diameter.

Based on the location of the nevus cells in the skin, CAMN are subdivided into: junctional, compound, and dermal. The three types represent sequential developmental stages in the life history of a nevus. During childhood, nevi begin as flat junction nevi in which the nevus cells are localized at the dermoepidermal junction. They progress into compound nevi when some of the cells migrate into the dermis. Migration of all of the nevus cells into the dermis results in a dermal nevus and these are commonly seen in adults (3).

The junctional nevus is a macular lesion with slight accentuation of skin markings. Compound nevi have a lighter shade of brown and show variable degrees of elevation than do junctional nevi. Dermal nevi are a lighter shade of brown or even skin-colored and are usually more elevated compared with compound nevi (3). The treatment of CAMN is in most scenarios dictated by cosmetic necessity (4). Surgical excision is the oldest and involves various techniques like shave excision, razor-blade excision, deep excision, and round excision (5-9). Shave excision is a simple and easy to perform procedure that is commonly used for the removal of ordinary nevi by cutting its base parallel to the skin, using scissors or scalpel (8, 9).

A novel and safe procedures using a needle of diathermy has been introduced by Sharquie KE in the treatment of different types of acne scarring and nose volumeplasty for bulky nose under local anesthesia in one session with minimal or no adverse effects (10-14). The lasers used for CAMN range from pigment-selective lasers to ablative lasers (15, 16).

The aim of the present work to find simple alternative modes of treatment like shave excision followed by simple touch with diathermy for small nevi especially when are multiple or numerous.

Patients and Methods

This is a prospective interventional surgical study where seventeen patients were seen during the period from April 2014 to August 2020, 13 (76.47%) females and 4 (23.52%) males, while their ages ranged between 12-36 years with a mean 22years.They had single or multiple nevi, junctional and compound type of CAMN on their face with a total of 52 nevi. By utilizing naked eye examination, we excluded any nevus with atypical clinical features such as asymmetry,

border irregularity, and color variability. Also, patients who underwent clearance of nevus by any type of intervention were also excluded.

The study followed the Declaration of Helsinki Principles and formal written consent was taken from each patient or his/her parents before starting the therapy, after full explaining about the nature of the disorder, course, and the method of management, complications, follow-up, and prognosis. Close-up photographs were taken before the treatment session, at the end of the session, and each visit during the follow-up period. A proper history was taken including, sex, age, duration, age of onset, associated symptoms, and past medical and drug history. A full clinical examination was performed to identify the site, size, border regularity, color, and associated signs.

The area was cleaned with spirit and povidone-iodine. Under local anesthesia with sub-lesional 2% lidocaine, a number 15 surgical blade was utilized to carry out the shave excision at a mid-dermal level, followed by simple touch cautery with diathermy to stop bleeding and to remove any residual melanocytes. All nevi were treated with one session. All patients were seen after 2 weeks and then every two months for four months. Oral antibiotics were used for five days. Topical mild corticosteroid cream was used for one month to prevent pigmentation. Any complications or occurrence of adverse effects were recorded at each post-session visit.

Patient's satisfaction in response to the treatment was assessed as follow:

1) Full satisfaction.
2) Partial satisfaction.
3) No satisfaction.

All statistical calculations were carried out using statistical package for the social science (SPSS) version 19. Data were statistically described in terms of range, mean, frequencies (no.of cases), percentage (%), and male to female ratio.

Results

The location of nevi in all cases was the face with variable sizes (2-10mm) and different types. Ten patients with multiple pigmented nevi while seven patients had single pigmented nevus. All treated nevi exhibited clinically full clearance of pigmentation. Transient crusting and erythema immediately after the treatment session were observed in all treated patients.

Two weeks after surgery post-surgical erythema was noticed and this gradually gone leaving no scar or pigmentation during the follow-up period 2-4 months following excision. No complications or relapse were observed in any case treated. Photos of patients before and during follow-up period are shown in Fig. 1-3. There was no difference regarding response to therapy, complications, or relapse between different types of treated nevi. Full satisfaction with the result outcome was achieved in all patients.

Fig. 1. *Twenty-one-year-old female with multiple ordinary nevi on the both sides of the face. Right side before treatment (a); 4 months after treatment session (b); left side before treatment (c); 4 months after treatment session (d).*

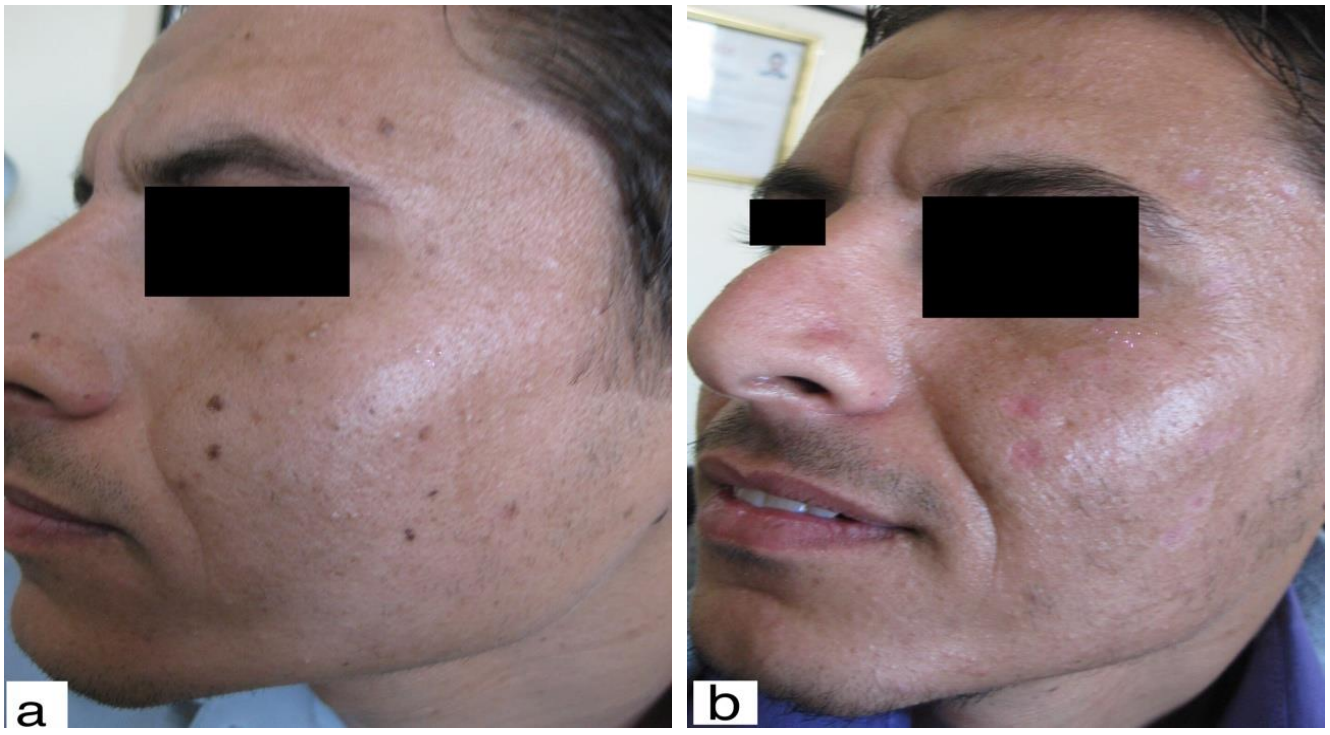

Fig. 2. *Nineteen years old male with mixed types of ordinary nevi (junctional and compound) on the left side of the face. Before treatment (a); 2 weeks after treatment session (b).*

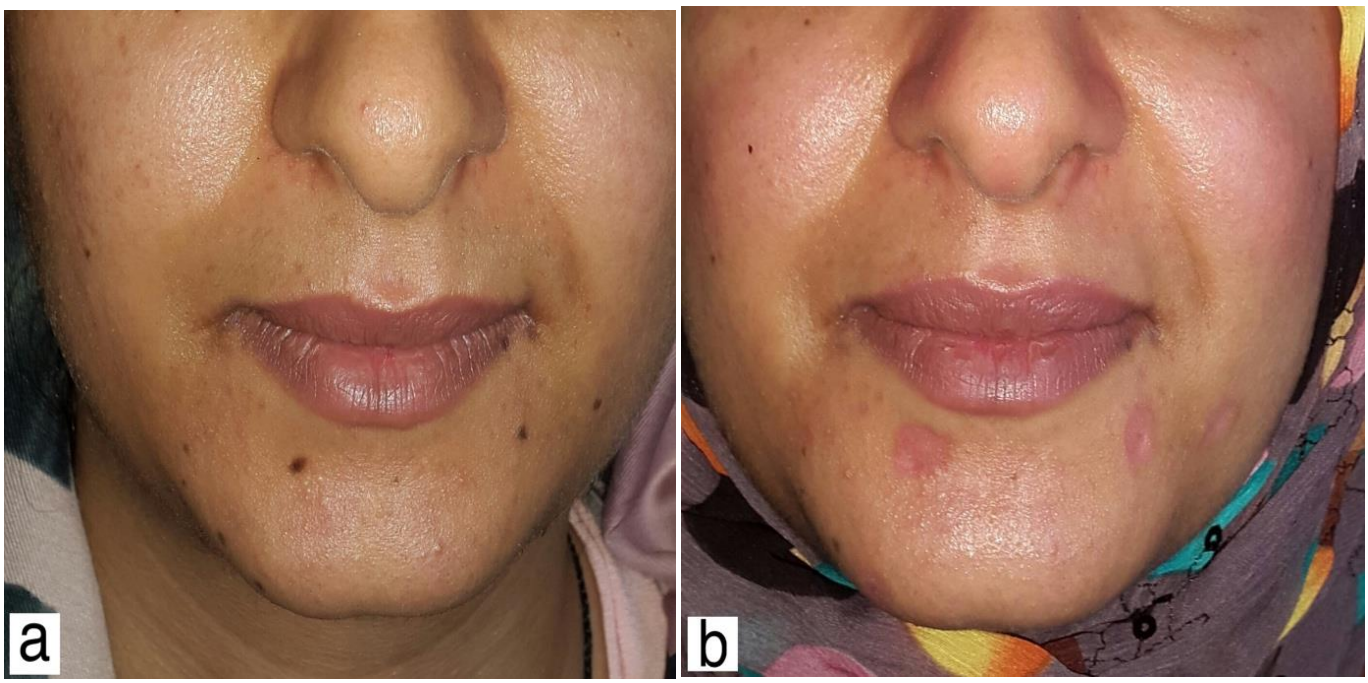

Fig. 3. *Eighteen-year-old female with multiple ordinary nevi on the chin. Before treatment (a); 2 weeks after treatment session (b).*

Discussion

To the best of our knowledge, this is the first study of shave excision followed by touch with diathermy needle for the treatment of ordinary common acquired melanocytic nevi. It is postulated that heat diathermy used to get hemostasis and to destroy residual melanocytic cells and thus an important component of successful shave excision. There are many methods for removal of ordinary nevi. However, surgical excision by classical fusiform excision is one of the methods used in the treatment of ordinary nevi (17). But this method needs resuturing after excision and surgical scars may be unpredictable even in the hands of experienced surgeons.

Different kinds of laser such as ablative or pigment lasers have been used for the treatment of the melanocytic nevi. However, there is a high incidence of repigmentation following laser therapy of melanocytic nevi especially with CO2 laser (18). Q switched NdYAG laser and Q-switched Ruby laser, as a pigment-specific laser, can cause an incomplete clearance of the nevus cells (19-21). Theoretically, laser may induce malignant transformation of nevus cells (22). Finally, cost implications of laser therapy should also be considered when choosing management options for the removal of melanocytic nevi as it may need many sessions to achieve the final cosmetically acceptable outcome.

Shave excision of the nevi followed by simple touch cautery with diathermy provides certain advantages in the form of no scar, no recurrence or complications, minimal expertise in performing this simple procedure, done in outpatient basis under local anesthesia with only one session and cost-effectiveness of the

procedure as compared to fusiform excision or repeated laser treatments.

This study was also confirmed by other studies in which shave excision of acquired nevi was done, but these studies were associated with variable results of recurrence or scar formation (8, 9, 23, 24). While in the present work, neither scar nor regimentation was recorded in any treated patient during the follow up period. This difference between our results and the results in the previous studies could be due to the use of heat diathermy after shave excision in present study as this diathermy cause destruction of residual melanocytic tissue and prevent a recurrence, while previous studies either used shave excision alone or by electrocautery.

All patients were fully satisfied with the result outcome to the extent that patients with multiple nevi requested for the removal of other nevi located on the face or other sites of the body by the same procedure. Limitation of this study is the lack of pathologic study of the ordinary nevi before and after shave excision. Another limitation of this study is a short of follow-up period of 4 months after shave excision. Nevertheless, pathologic study can be performed In the shaved material. In fact, the histological evaluation of pigmentary skin lesions is a must in the daily practice (25-48).

Conclusion

Shaving of ordinary common acquired melanocytic nevi by scalpel followed by touch with diathermy needle is an excellent surgical technique without complications or repigmentation, cost-effective surgery and gave very satisfactory outcome with good cosmetic results, thus avoiding excision and suturing. Histology can be performed in the shaved tissue.

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Today's vision on environment, health and skin care

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Abstract

Due to an earth always more polluted and a continuous health deteriorating for the stressful way of living, consumers are looking worldwide for cosmeceuticals and nutraceuticals more effective, safe and respective of the environment. Thus a continuous increase of the food, cosmetic market and the global wellness economy evaluated USD 4.2 trillion in 2017.Consumers are further looking for natural-oriented and personalized age-agnostic products which, having an holistic approach, are able to maintain the natural skin and global microbiota, reducing the stress condition tho give emotional and physical benefits at short and long time. Thus, the research for innovative and smart cosmetics, diet supplements and services which, characterized for their high technological quality and the natural ingredients used, are able to maintain beauty and wellness of all the body, improving the general skin conditions. Use and activity of natural polymers such as chitin and lignin and their derived compounds to produce innovative cosmetics and diet supplements are reported and discussed. These natural ingredients are actually of great interest because obtainable as by-products at low cost from food and forestry waste by bionanotechnologies.

Introduction

Personal health, wellbeing and climate change are projected to have a greater Impact in the next future. Thus, new models and new products able to bring health and wellness, safeguarding the environment and distributed at low cost and at zero waste, will represent the future global cultural stars. Scientists and consumers, in fact, are afraid of the climate changing and push industries to produce high-quality products and services, for reducing the actual air, water and land pollution. Thus, on the one hand the necessity to save water by a fast-rinse or less rinse time technology for washing skin and hair by a product, characterized for its safe and natural ingredients free of aquatic toxicity and at zero-waste for packaging also. On the other hand, the indispensable need to reduce the greenhouse gas(GHG) emissions, fundamental cause of climate changing and the worldwide disasters (1, 2). As a consequence, the necessity to pass from a linear economy of taking, making and producing waste to a circular economy of reducing, reusing and recycling. Thus, by the circular economy will be possible to obtain the 17 sustainable development goals which requested from United Nations (Fig. 1) since 2015, are fundamental to preserve the Planet' environment and reduce the worldwide extreme poverty by 2030 (1).

Fig. 1. *Linear economy versus circular economy and sustainability [by the courtesy of UN (1)].*

However, the actual global wellness industry, evaluated USD 4.2 trillion in 2017, is composed by 10 sectors. These sectors, including personal and beauty care, healthy nutrition, and fitness (Fig. 2), have shown an annual growth rate (CAGR)of 3.6% from 2015 to 2017, representing 3.3% of the global economic output (3).

Fig. 2. *Global Wellness Economy [by courtesy of GWI (3)].*

The soul, beauty and personal care market was expected to register a CAGR of 5.9 % during the forecast period 2018-2025 with a growing preference for natural/organic ingredients and an higher demand for anti-aging products (4).

Personal health and wellbeing, in fact, are the top-of-mind global concerns, so that consumers spending is massively going toward product value, healthy eating and cosmetics quality. But what are consumer expectations? They are looking for novel skincare experiences, high-value skin- and environmentally-friendly products, specifically tailored to their personal needs so that 40% of Millennial consumers (aged 18-34) and 45% of Generation Z (aged 6-24) buy products that make them to look healthier, enhancing their skin conditions (4).The skin, in fact, exchanging and sending out messages, interfaces continually with other organs and the environment, filtering the stimuli that comes from the outside to maintain its homeostasis. For these reasons, nearly half of US women aged 18-34 years have tried to enhance their appearance combining the use of oral supplements and innovative cosmeceuticals to fulfil the dream of beauty from within (Fig. 3) (5).To realize this dream, therefore, it seems possible "to ingest specific prebiotic and probiotic in order

to associate topical and general treatments for improving skin condition without falling into the drugs category" (5, 6).The food functional market, therefore, has risen from USD 8.0 billion in 1996 up to USD 16.1 in 2006, and to USD 177.7 in 2019 with a compound annual growth rate (CAGR) of 8.1% from 2019 to 2025 (7).

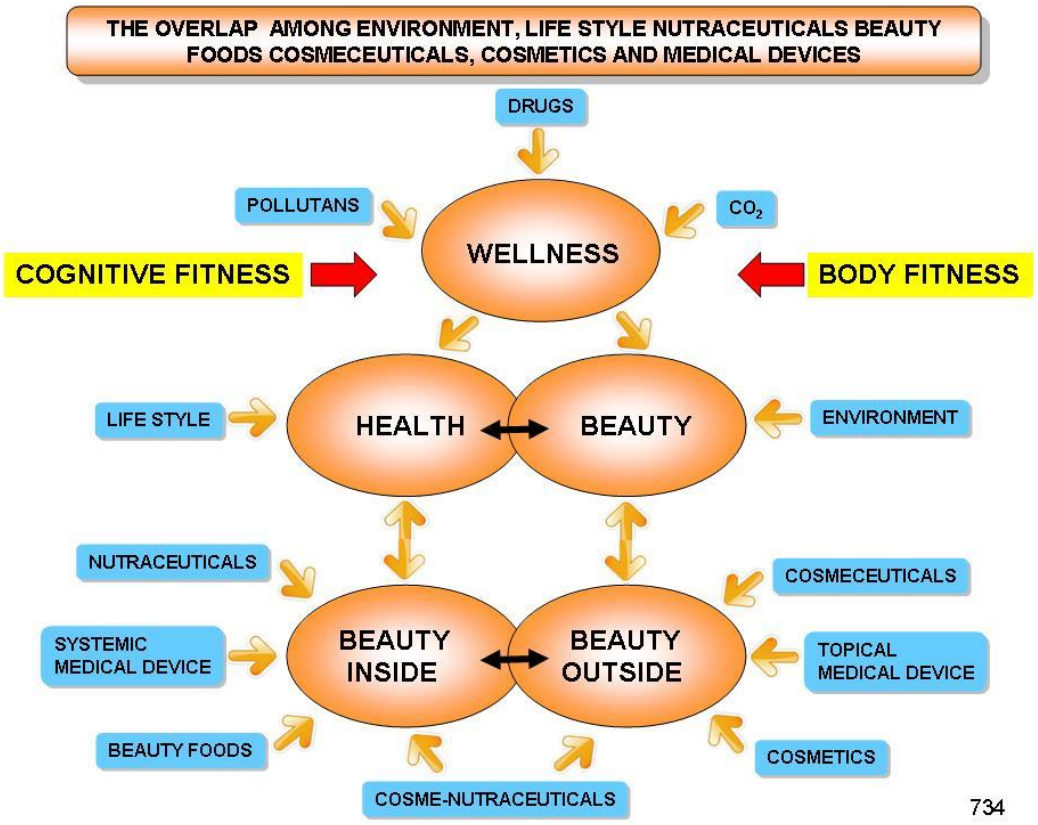

Fig. 3. *Beauty and Health Connection by Cosmeceuticals and Nutraceuticals.*

Thus, the concept of health, wellness and beauty involves not only the skin, but also the entire body. Taking everything into account, this concept is represented by a broad and segmented market, underlined by an emphasis on prevention and maintenance which involve body and cognitive fitness without use of drugs (4, 5). At this purpose it is to remember that human body host 1.5Kg of microorganisms, part of which are located on the skin and scalp surfaces or under the epidermis. Therefore, skin microbiota, represented from pathogen(disease) and saprophytic(helpful) microorganisms, changes throughout a person' lifetime, according to age, diet, environment and lifestyle. Moreover, it may vary from individual to individual and in different anatomical areas, being gender-dependent also (6, 8). It is, therefore, a major player in establishing and maintaining skin health, so that 78% of consumers agree to the necessity to maintain balanced skin and hair microflora by specializes diet supplements or cosmetics. So doing it will be possible to

avoid the bacterial and fungal dysbiosis which, exacerbated by a polluted environment, could cause for example scalp dandruff and seborrheic dermatitis (9). Moreover wellbeing could be considered the result of the many interactions between genetic and external environmental factors which, having the possibility to augment or reduce the gene impact, account 10-15% of the human health outcomes (10).

Human lifespan, in fact, determined by both genes and external influences, acts by means of genetic pathways regulating the cellular processes, cause of aging and death. Thus, the environmental conditions are of great importance for humans also, because no living organism is able to live and survive in an environment completely different from that to which is genetically adapted.

Consumer expectations

As previously reported, consumers are looking for cosmetics and diet supplements which, with a rinsing awareness regarding microbiota balance, can protect health and environment. These products would be characterized by a real clinical effectiveness and safeness, and therefore studied and verified by in vitro and in vivo methodologies (11). Unfortunately, many are the skincare products controlled only by in vitro methods and some time by in vivo ones, too often realized by a small number of subjects. Furthermore, some of these cosmetics, are sold and publicized by marketing claims attesting to possess, for example, anti-aging effectiveness, only because formulated with ingredients effective to positively modify the cell turnover. Thus, the definitions of cosmeceuticals and nutraceuticals which, coined many years ago from Albert Kligman in 1984 and Stephen De Felice in 1989 respectively, should be characterized for their effectiveness and safeness, documented, and verified by the same scientifically correct pharmaceutical methodologies used for the drugs (12).

In any case, these terminologies, while not officially recognized by the international laws governing cosmetics and diet supplements, are normally accepted from dermatologists, nutritionists, and marketing managers to define cosmetic/food products showing a pharmaceutical effectiveness (12-14). Thus, according to current EU and other international laws a cosmetic product is (15):"any substance or mixture intended to be placed in contact with the external parts of the human body.... or with the teeth and mucous membranes ...with a view exclusively or mainly to cleaning them.... changing their appearance ...and/or protecting them or keeping in good condition".

On the other hand, the diet supplements, legally recognized as foodstuffs with the indication to supplement the normal diet by concentrated source of nutrients, may claim their specific effectiveness (as slimming, anti-aging etc) showing and documenting their activity by in vitro and in vivo studies, to be successively approved by a special official EC commission (16, 17). In conclusion for consumers wellness has to be considered as the active full complement of multifaceted activities, encompassing physical, mental, emotional, social, environmental and spiritual dimensions (3, 10). Thus food, cosmetics, exercises, and all the other living activities are considered necessary means for the daily life. Therefore, it must be recognizing the impossibility

to live a full life without a healthy body, mind, and spirit because all humans, animals and plants are interconnected in a natural world. Therefore, wellness is a salutogenic approach focused on prevention and healthy lifestyle, so that longer-term physical and mental benefits are better than looking good. Consequently, in 2018 the global beauty and personal care market and the food functional market have been evaluated to reach from by 2025 USD 717, 6 billion and USD 275, 77 respectively with a CAGR of 5.9% and 7.9%, while, for example, the EU fitness market in 2018 had a growth of 1.2% with a revenue of ₁27.2 billion and a number of 61, 984 clubs, located across all the countries (18-21).

Consumers are trying to personalize both life and products, looking for cosmetics which, allowing them to express their individuality, improve the environmental sustainability eliminating the invasive and dangerous plastic waste (22-24).Therefore, their investments are oriented in high quality products, including reuse and recycling whatever possible, while the mental, spiritual and physical balanced status remain the priority (24, 25).Thus the health habits and attitudes are an important aspect of consumers' lives influencing their decisions so that Generation Z, Millennials and Baby boomers, (54-74 years old) are looking at health with a more holistic view (26, 27). However, Baby boomers, who define themselves as the forever young, have many values and priorities in common with Millennials and younger generations, focusing their life on prevention and enjoyment of life (23-25). They, in fact living much longer, don't want to feel old and may be defined age agnostic for their dream to remain active, contributing to the society progress, thus maintaining an ageless attitude towards life. Over 50% of the global consumers, however, claiming to suffer from moderate and high stress levels, wish to live by a more balanced lifestyle, simplifying their lives and spending more time on themselves (25, 26). Among the other Millennials, accounting for about 32% of the world's' population and being the largest demographic group in USA, show to prefer their "appearance", thus representing the largest potential group buying beauty and personal care products (22, 25). It is interesting to underline that, in 2019 in China also , Millennials and Generations Z, living prevalently in urban areas (60%) and accounting for almost 40% of the population, have spent more than 50% of their income for beauty and personal care cosmetics, looking for high quality products for babies and pets also (27). Moreover they have a strong attachments for smartphones used to buy products and services (27). However, it is to underline once again that global consumers demand and are willing to pay more for products which, preserving the natural resources and maintaining a long-term ecological balance, result necessary to maintain a healthier built environment (10).

Chitin nanofibrils, nano-lignin and derived-complexes

Among the natural industrial bio-ingredients useful to produce innovative cosmeceuticals, nutraceuticals, would dressings, and/or air/water purification agents, there are chitin and lignin, obtainable from waste materials at low cost (28, 29).

They are the most abundant biopolymers present in nature, having an increasing market for their

multiple use in different fields and to be easily obtained from food and forestry waste. Moreover, the possibility to make both chitin and lignin in the nano size and purity form has further increased their utilization in pharmaceutical, food and cosmetic sectors (30, 31).

Chitin

Chitin is synthesized in nature as a linear biopolymer composed of many acetyl-glucosamine units linked by 1-4 beta bonds. It may be easily produced industrially in the form of micro/nano fibrils (i.e. chitin nanofibrils) which, partially deacetylated, are characterized by the presence of 40 to 60 % of glucosamine units, the percent of which is depending from the technological process adopted(Fig. 4) (32).The totally deacetylated, chitin is named chitosan, characterized by 60 to 90% of glucosamine units (Fig. 4) (32).

Fig. 4. *Chemical structure of chitin with glucosamine and acetyl glucosamine groups (left) and chitosan group (right).*

Chitin, present as structural structure in crustaceans shells, insect cuticles and cell wall of fungi, is a biocompatible, biodegradable, and nontoxic polymer made by linear macromolecules joined by hydrogen bonds to form, ordered crystalline and amorphous structure organized by microfibrils (Fig. 5).

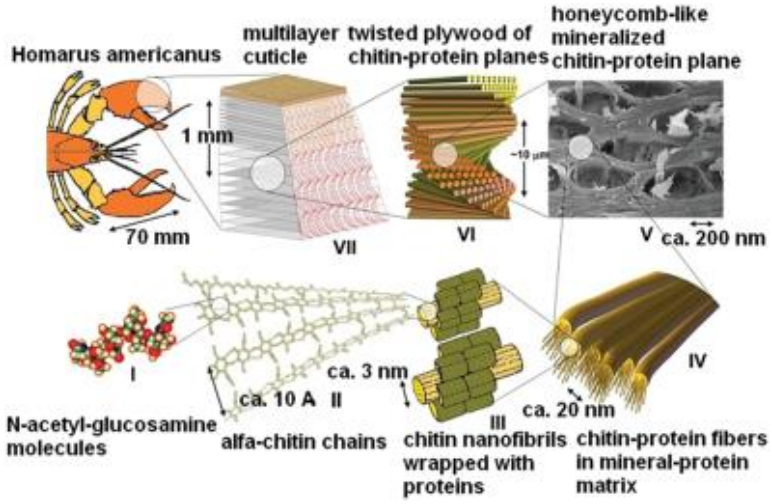

Fig. 5. *Structure organization of chitin nanofibrils in nature (by personal courtesy of D. Raabe et al)..*

The nanofibrils, industrially produced (Fig. 6), have a mean dimension of 240x 5x7nm and a crystalline structure covered by positive electrical charges on their surface. According to fibril size, micro/nano dimension and electrical charges of the carrier-nanoparticle used, CN, the derived compounds and/or micro-complexes may disrupt the skin barrier, penetrating through its layers, releasing the loaded active ingredients.

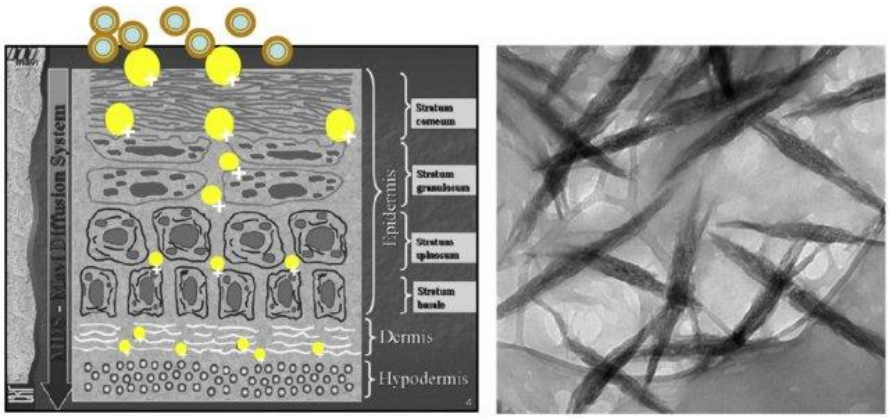

Fig. 6. *Chitin nanofibrils produced in lab at SEM (right) and their skin penetration degree (left). The Brown particles, negatively charged remain on the skin surface, while the yellow ones positively charged may penetrate less or more deeply, according to their dimension also.*

Due to the different polarities, in fact, it is possible to make a CN-nanolignin (NL)compound, complexing, for example, the electropositive CN with the electronegative hyaluronic acid (Fig. 7), which previously can be loaded with different bioactive ingredients. At this purpose it is interesting to underline that chitin: (a)when produced industrially as Chitin nanofibrils, loses not only its pro-inflammatory characteristics becoming an anti-inflammatory agent, but also its allergenic character. During the many purification steps necessary for its production process, in fact, CN loses the protein content wrapping the natural fibrils (fig 8), and it is these wrapped proteins that are responsible for seafood intolerances and allergic reactions, often recovered by dermatologists on many subjects (33, 34).

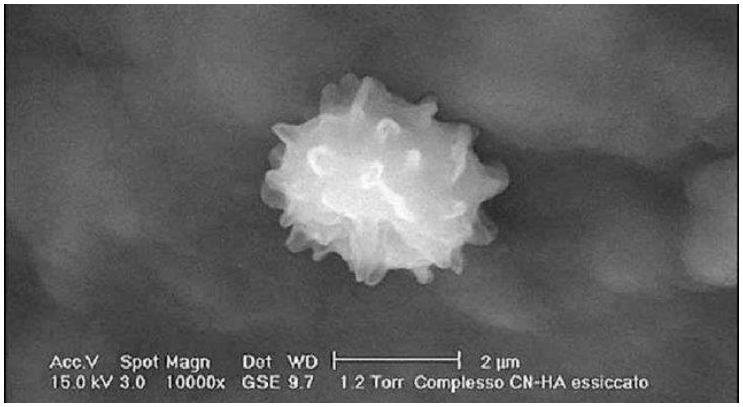

Fig. 7. *Chitin nanofibrils-hyaluronic acid complex at SEM.*

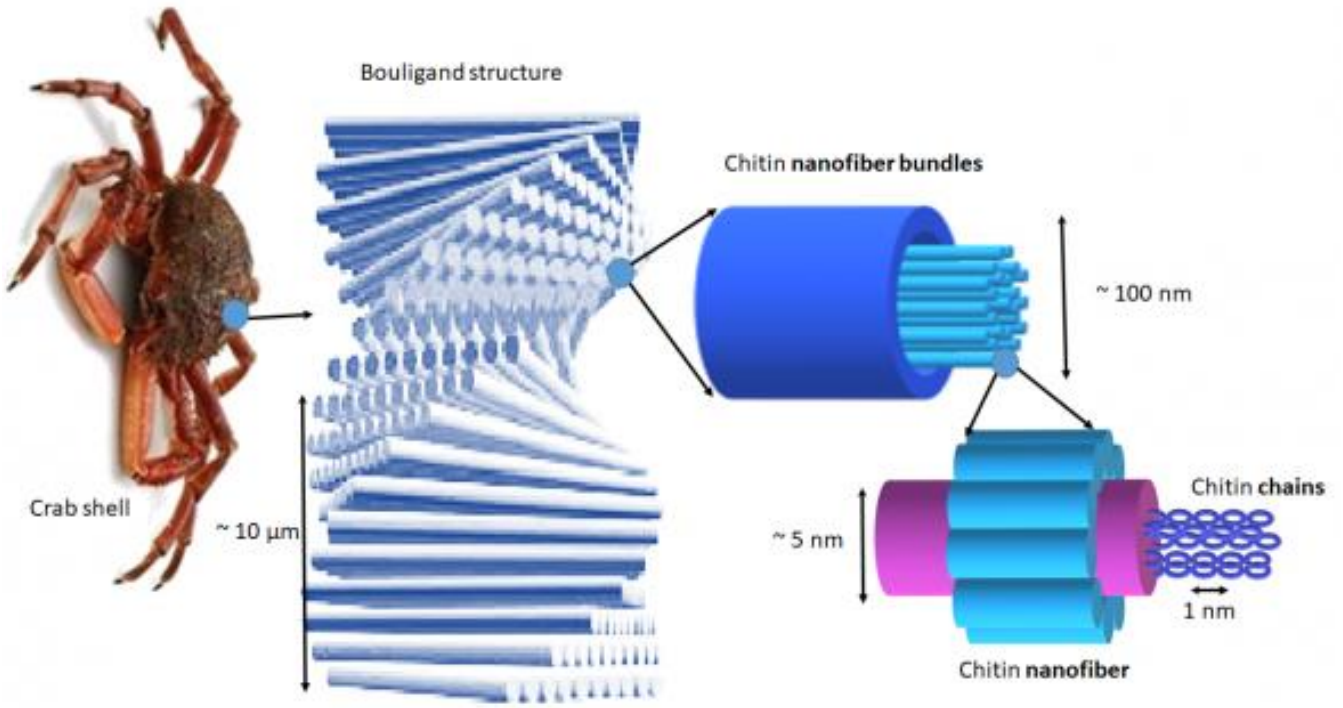

Fig. 8. *The chitin fibril wrapped by proteins.*

The minor or major presence of OH- and -NH2 groups in the chain molecular structure of both chitin and chitosan (Fig. 4) opens the door for their many industrial and biomedical applications by the obtainable derived compounds .Moreover their different use depend not only from the acetylation and polymerization' degree, but also from other important parameters such as molecular weight, crystallinity, solubility, environmental pH, surface area, etc

Additionally, and depending upon the chains' disposition and bonding, chitin may be recovered in nature in alpha, beta and gamma polymorphic form, the more frequent and used resulting the alpha ones (35).

For all the reasons previously reported, the global market of alpha chitin and chitosan evaluated USD 6.8 billion in 2019, is expected to expand at a revenue based CAGR of 24.7% between 2020-2027(36). This growth will be determined from the growing Industrial applications in water treatments, pharmaceutical, biomedical, cosmetic and food. One of the key factors steering the demand of these polymers is their easy availability from the industrial fishery waste and the increasing use as chelating, coagulating and flocculating agent to purify water. Moreover, they are massively used as antimicrobial and anti-inflammatory agents in food packaging as well as cosmetic active ingredient and carrier in the increasing cosmetic natural market .The global Cosmetic natural market size, estimated 34.12

billion in 2018 with a CAGR of 5.01% from 2019-2025 (Fig. 9) (37), has expected in fact to drive the growth of the wellness and beauty sector for the increasing request of natural-oriented, skin-friendly and environmentally -friendly products. About the worldwide involvement, Asia Pacific emerged as the largest regional market in 2019, owing to the rapid development of end-use industries in Japan, China, India and South Korea.

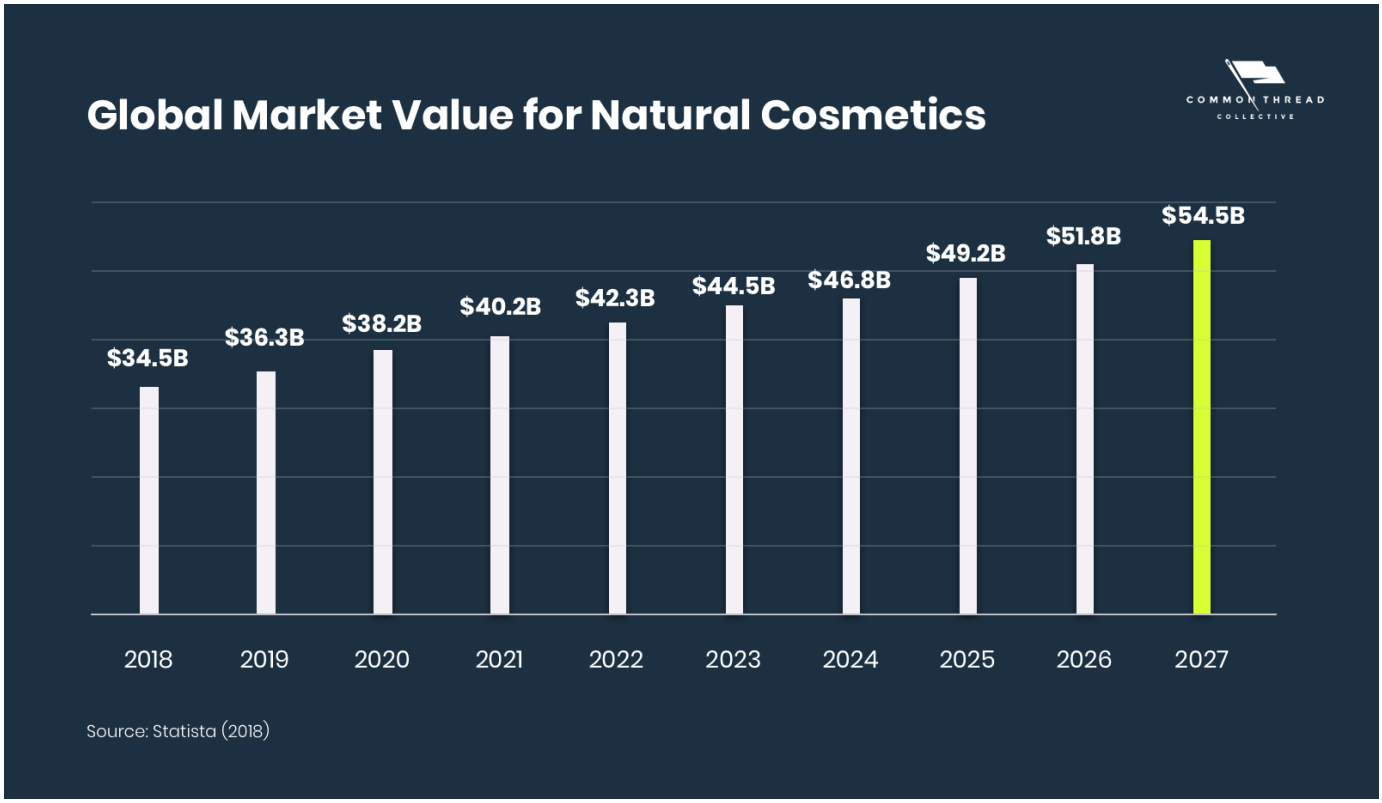

Fig. 9. *Global value of natural Cosmetic (by courtesy of Statista).*

Lignin

Lignin, constituting from 20 to 30% of the earth plant biomass, is a complex structure made of three different type of monolignols :p-coumaryl-, coniferyl- and synapil alcohol, the ratio of which depends from plant type and the extraction method used (Fig. 10) (29). This natural polymer, rich of phenolic and chromophore groups with antioxidant and UV-blocking properties respectively, represents the integral part of the secondary cell wall of living plants like trees and grasses, being one of the most abundant organic polymer in the earth (29).

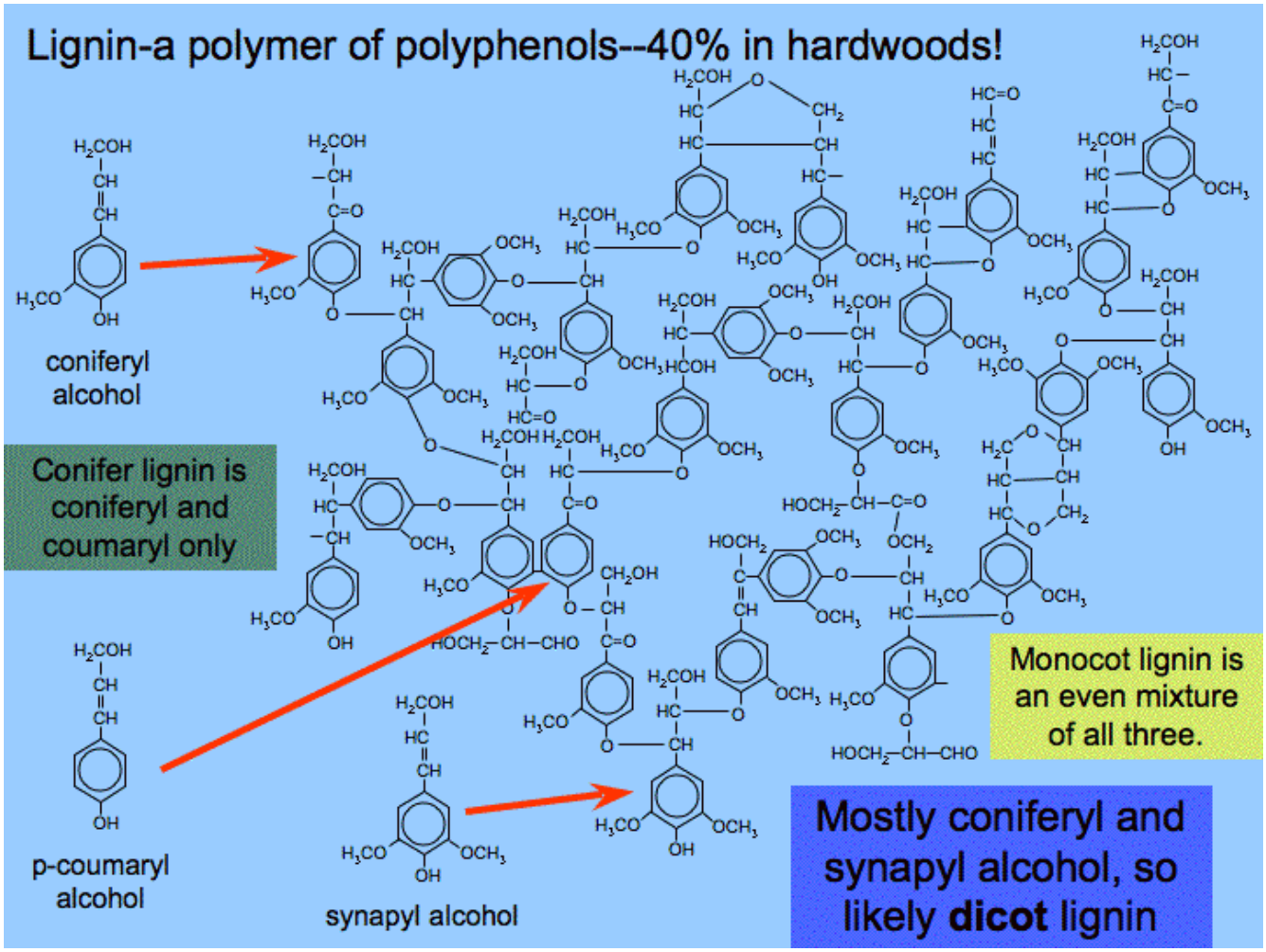

Fig. 10. *Lignin structure.*

Lignin, covalently linked to cellulose and hemicellulose and cross-linked to different plant polysaccharides to form a three-dimensional amorphous structure, acts as a glue and confers mechanical strength to the cell wall, similarly to chitin as principal structural polysaccharide of the arthropods (32). Thus, the polymer, containing a vast amount of the world's carbon and possessing a great antioxidant, antibacterial and light protective properties, may be utilized to replace many petrol chemical-based products used in the everyday life. However, depending also to its structure and purity, the polymer and its derivatives are used principally in the medical and cosmetic sectors, because of their versatility to produce wound dressings, drug and cosmetic delivery systems, and innovative materials to remove air/water toxic ingredients (29-31, 38). Lignin, in fact, modifying its native structure when extracted as a by-product from the plant biomass during the industrial pulp (70 million tons per year) and paper process, is purified before its use and may be transformed in its nano size (39). As such, it may be used as composite or complexed polymeric compound when bound to other ingredients as chitin and chitosan to make

a biomedical or cosmetic gel and tissue, used as high-performance broad-spectrum sunscreen emulsion or drug/cosmetic delivery carrier (39-41). However for a better utilization of the polymer, due to the high chemical variability of its complex molecular structure, it should be necessity to understand how the productive process could affect the reaction mechanisms and structure-properties of lignin, first of all when used in human health for its biological properties.

Thus, the global market size of this natural polymer has been estimated in 2019 at around USD 1/1.5 billion and is expected to expand at a CAGR of 2 % in term of revenue from 2020 to 2027(42).Because of the increasing demand for animal feed and macromolecules and aromatics' production, used in the development of bitumen, biofuels, pharmaceuticals and cosmetics, it is anticipated that lignin will drive the market growth, also if 2% only of the polymer is used for value-added products. About the regions involved, Asia Pacific is anticipated to witness the fastest growth over the forecast period, as a result of its rapid industrialization and rinsing demand for electronics and automobiles also. On the other hand, it has been estimated a rapid growth of the EU market because of the favourable regulatory framework facilitating the use of lignin as alternative raw material to produce biopolymers and bioplastics.

Conclusion

The Beauty and health market has been rapidly evolving with the rise of social media opening an interesting discussion around beauty products, skincare, wellness and the environment, playing an increasing role in educating consumers about the activity of this category of products. The today community is represented by new consumers 30% of which, exploring the push-off between nature and science, and looking for cosmetics effective for their needs, are fitting into the digital beauty consumer segment. However, they show a high interest on the environmental pollution and waste, being particularly worried about the health of both their skin and hair, affected by microbiota, stress and aging (6, 8, 43).

Some bacteria, in fact, providing relief for skin concern that involve a poor barrier activity, could ameliorate its function by the use of smart cosmeceuticals and nutraceuticals. But to find the wright solutions it should be necessary to better understand the condition in which microbes are beneficial or harmful to the skin, what's their unbalance and how to rebalance them (8, 9, 44). Thus, the increasing skincare sustainability is becoming a global consumer priority, pushing beauty products and apparel towards new sustainable innovations (45). Sixty percent of global consumers, in fact, are worried about climate changing and the wrong way of producing and consuming goods, so that 55% think that their purchases could have a positive contribution to ameliorate the general condition of our planet. Moreover, half of them, as previously discussed, claim to use do-it-yourself beauty products at least once a month not only to customize and personalize the products used, but also to take back control over they are putting on their own skin (22, 23). For these reasons,

the necessity to make and use nature-oriented products realized by a circular economy at almost zero waste.

A new productive method could be metabolically engineering the bacteria by biorefinery technologies, involving these microorganisms to produce bio-compounds realized by a low-carbon emissions. This is an innovative method to obtain new ingredients by a molecular machinery able to make them in a safe, inexpensive, and fast way. Moreover, it is possible to produce active ingredients and biological carriers using agro-forestry and food by-products based on the use of waste biological materials. Thus as previously reported, the possibility to produce smart emulsions and tissues (Fig. 11) by polymers such as chitin and lignin which used as active carriers, may be applied on the skin surface or taken by oral route as innovative cosmeceuticals and nutraceuticals (46-48).These smart cosme-nutraceuticals, produced indifferently by water soluble and insoluble natural polymers by innovative bionanotechnologies, are not only biodegradable, skin- and environmental-friendly, as requested from scientists and consumers, but may be also used as drug/cosmetic carriers as well as to produce one day use beauty/surgical masks and medical dresses (48).

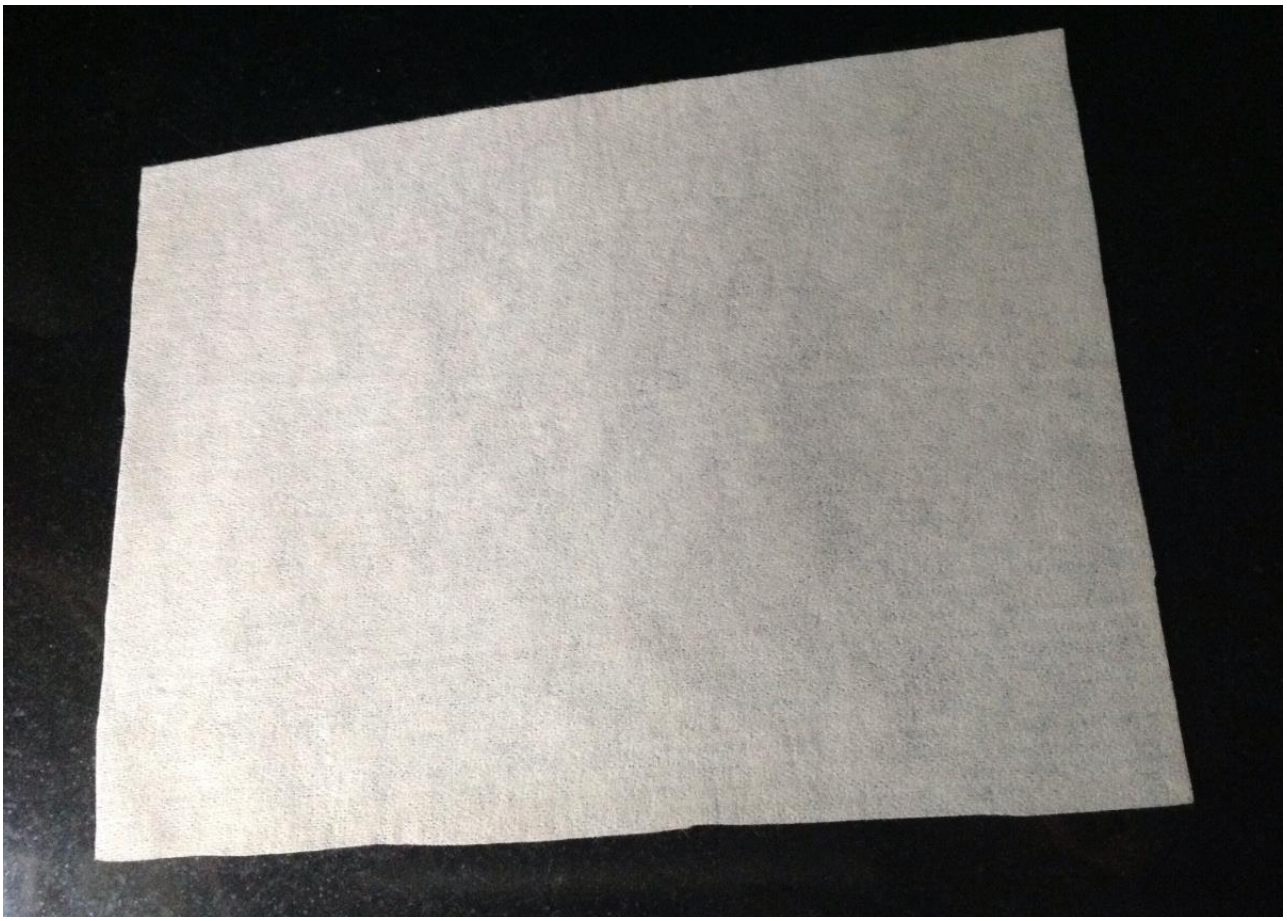

Fig. 11. *Biodegradable natural-oriented non-woven tissue made by chitin nanofibrils-lignin.*

In conclusion protecting health, beauty and the environment by the introduction of a circular economy characterized by a reduced production and consumption of plastics and production of zero waste, is the actual expectations and vision of scientists, industries and consumers. The result will be a more pleasant and living Planet with the maintenance of the natural raw materials and its important genetic, species and ecosystem biodiversity (Fig.12) (49). So doing it will be possible to improve health, food and water security, and mitigate climate changing, thus contributing to a sustainable development (1, 48, 50-52).

Fig. 12. *Global earth biodiversity.*

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Platelet-rich plasma for male androgenetic alopecia: results from an open randomized finasteride-controlled study

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key words: *alopecia, androgenetic alopecia, platelet-rich plasma, finasteride*

Introduction

Topical minoxidil and oral finasteride are widely accepted for the treatment of male androgenetic alopecia (MAA). However, these are not completely effective and have adverse effects. Therefore, the requirement for new treatments becomes imperative. Objective: Evaluate the efficacy of platelet-rich plasma (PRP) compared to oral finasteride in MAA treatment. Methods: An open randomized controlled study, including 20 patients with MAA, underwent 4 sessions every 3-4 weeks of PRP procedure compared with 13 patients receiving oral finasteride. Patient and physician visual analogue scale (VAS), satisfaction scale and photographs were evaluated before and after treatment. Results: Comparison of data revealed that satisfaction with the procedure increased significantly (1.8±0.8 vs 3.35±1.6, p=0.0002), as well as, patients approval measured through VAS (5.85±2.3 vs 7.40±1.7, p=0.0093). Regarding finasteride, no significant difference was observed. The blinded observer score between baseline and after 3 months had an average of +2.0±0.7 with PRP. No changes were observed with finasteride. Mild pruritus was seen in 5 (25%) PRP patients. Conclusion: PRP seems to be a better therapy for male androgenetic alopecia in comparison to oral finasteride, with virtually no relevant adverse effects.

Male androgenetic alopecia (MAA) is a common problem, affecting 12% of men between 18 and

29 years old and 50% of them between 40 and 49 years old (1). In contrast to its high prevalence, the approved pharmacological therapeutic options are limited and thus several unapproved treatments appear to be effective in restoring hair loss. The only treatments approved by the Federal Drug Administration are oral finasteride and topical minoxidil (2). However, the results achieved by these two therapies (finasteride and minoxidil) are still not completely satisfactory, and the presence of adverse effects brings the need to search for new therapeutic options. In this sense, a new method of treatment, platelet-rich plasma (PRP), emerged as an autologous plasma preparation containing more than 1,000,000 platelets/mcL, ie. 4-7 times more platelets than the concentration of blood cells, which secrete growth factors and cytokines, including platelet-derived grow factor, vascular endothelial growth factor, insulin-like growth factor and others (3). Degranulation of these pre-synthesized platelet growth factors occurs after the contact with the tissue collagen. The growth factors then bind to mesenchymal stem cell transmembrane receptors, as well as fibroblasts, endothelial cells, and epidermal cells leading to an activation through intracellular signaling, genes related to cell proliferation, collagen synthesis, and others (4, 5).

Regarding experimental use of PRP in alopecia in animals, Uebel et al. demonstrated that a pre-treatment of hair units with PRP during transplantation, improved hair density and thread hair growth. Furthermore, Li et al. (6) revealed that PRP can induce papillary dermis proliferation, prolongs the anagen phase, delays progression to the catagen phase, increases hair follicle survival and stimulates hair growth in mice.

A study developed in human by Takikawa et al. (7) showed that PRP injections in 26 patients every 15 days, for 5 times, was able to increase the number and diameter of hair follicles. Another study evaluated CD34 + cell PRP injection in 13 patients compared to placebo, although both groups received finasteride 1mg (8). The result of this work demonstrated increased number and capillary diameter of the hairs in patients treated with PRP. However, concomitant use of finasteride has difficult the interpretation of obtained results. Therefore, there is a gap in the literature which did not indicate if PRP therapy alone could reduce hair loss when compared to finasteride.

The aim of the present study is to evaluate the efficacy and safety of PRP therapy in male androgenetic alopecia compared to a group of volunteers receiving finasteride.

Materials and Methods

This is a prospective randomized open controlled study. We followed CONSORT guidelines. Male volunteers aged 18 to 60 years, summoned through radio advertisements and news website, suffering from male androgenetic alopecia were included. Men with type II, III, IV or V of Hamilton-Norwood classification (9), diagnosed by clinical history, physical examination and exclusion of secondary conditions, with availability to attend the outpatient clinic monthly and those who wished to participate were also included.

Exclusion criteria were use of topical or systemic finasteride or minoxidil, individuals who underwent intradermal therapy, carboxytherapy,

PRP or other scalp procedures for at least six months of the study. In addition to these criteria, patients with severe scalp seborrheic dermatitis and those undergoing hair transplant or scalp surgery were also excluded. Those using systemic corticosteroids, anabolic steroids, cyclosporine and zidovudine in the last 3 months were rejected. Patients with a history of coagulopathy, thrombocytopathies, anticoagulant use, neoplasms, autoimmune diseases and keloid tendency were also excluded. Alopecia grades I and VI Hamilton-Norwood were also excluded. If aspirin or non-hormonal anti-inflammatory drugs were used, suspension was requested for 7 days before and 3 days after the procedure.

The control group (finasteride group) consisted of men with MAA who were treated with finasteride 1mg once a day. Subjects were electronically randomized to receive PRP or finasteride.

During the treatment, patients were asked to keep their scalp clean and in the day before the procedure, to use bactericidal shampoo. After the procedure, they should not wash the scalp for at least 24 hours and not engage in physical exertion in order to avoid sweating.

During the study period, patients were advised to not use any medications, and suspend vitamin supplements to avoid confounding elements.

Platelet-rich plasma

We collected 10-15mL of whole blood from the cubital veins in sterile vacuum tubes containing sodium citrate as anticoagulant by sterile technique. All steps to obtain the PRP were performed with appropriated procedure as gloves, respecting asepsis and technical care. Then, the tubes were placed in a centrifuge machine at 3200 rotations per minute for 4 minutes. At the end, the blood was obtained and divided into three layers: the lower one consisting of red blood cells (55% of the total volume), an acellular upper layer that is the PRP itself (corresponding to 40% of the total volume) and an intermediate layer, or buffy coat (5% of the total volume). So, the upper layer was pipetted, and the lower two layers were discarded. The PRP was finally placed in a sterile syringe.

The scalp was anesthetized with topical anesthesia (Pliaglis®, Galderma, France) in the frontal and vertex regions. In the area where there was higher hair density, spray solution containing lidocaine and tetracaine was employed. Topical anesthesia was left for about 30-40 minutes. At the time of PRP application the scalp was cleaned with alcoholic solution and chlorhexidine solution. PRP injections were performed with 30G1/2 needle and 3 ml syringe. Intradermal therapy injections were used through multiple injections with distant points about 1 cm with aseptic technique. A total ranging from 3-6 mL was injected. Treatment was performed on a schedule every 2-3 weeks for 4 applications.

Side effects evaluation

Signs and symptoms, possible side effects, as well as the results presented by patients during and at the end of treatment were recorded in a spreadsheet, and in the medical record.

Photographic control for better monitoring of the results were performed before and at the specified post-procedure moments.

Clinical response evaluation

Patient opinion [visual analog scale - (VAS) 1-10-Lickert] and physician opinion (VAS 1-10) scales were included. Photographs were evaluated by a blinded researcher and compared with pre-and post-treatment results according to the Kaufman et al. (10) scale: 7 points: -3 (very small), -2 (moderately reduced), -1 (slightly reduced), 0 (no change), +1 (slightly increased), +2 (moderately increased) and +3 (greatly increased).

To evaluate the degree of satisfaction, a self-applicable scale were used for patients with the following alternatives: fully satisfied, satisfied, partially satisfied, dissatisfied and prefer not to give their opinion; An open-ended question will appear on the form to obtain a justification from the patient for the degree of satisfaction referred to, if desired. All participants agreed and signed the informed consent form to participate in this study. This study followed Helsinki declaration principles.

Statistical analysis

Data were recorded and obtained as means, medians, standard deviations, intervals, frequencies and percentages. Statistical analysis was performed using Excel and GraphPad InStat version 2.00. Student's t-test, Mann-Whitney's and Fisher's exact tests were used as statistical tests. Results were considered significant if $p < 0.05$.

Results

Thirty-three patients were included, 20 patients undergoing PRP and 13 individuals undergoing oral finasteride. No significant differences were found regarding age (34.05±8.09 vs 29.77±6.95 years, p=0.12), white race (75% vs 61.5% p=0.77), alopecia time (7.98±5.57 vs 8.00±5.26 years, p=0.99), alopecia degree by Hamilton-Norwood scale (3.45±1.09 vs 3.31±1.18, p=0.73). Regarding comorbidities, no differences were also observed in the groups (30% vs 0, p=0.08) (Table I).

Table I. *SDemographic data in male androgenetic alopecia subjects treated with PRP or finasteride.*

	PRP treatment N=20	**Finasteride N=13**	**p-value**
Age, years	34.05 ± 8.09	34.05 ± 8.09	0.12
Caucasian race, n (%)	15 (75%)	15 (75%)	0.77
Disease alopecia duration, years	7.98 ± 5.57	8.00 ± 5.26	0.99
Comorbidities	6 (30%)	0	0.080
Hamilton-Norwood scale			
II	3 (15%)	4 (30,7%)	0.39
III	8 (40%)	4 (30,7%)	0.72
IV	3 (15%)	2 (15,3%)	1.00
V	5 (25%)	3 (23%)	1.00

Data are shown in mean ± standard deviation or percentage **(%).** *PRP: plasma-rich platelets.*

Comparison of data before and after three months of PRP administration revealed that satisfaction with the procedure increased significantly (1.8±0.8 vs 3.35±1.6, p=0.0002), as well as the patient's VAS (5.85±2.3 vs 7.40±1.7, p=0.0093). Regarding the physician's VAS (5.8±2.6 vs 6.9±1.9, p=0.06) a trend was observed. The observer's score blinded by the Kaufman scale, between baseline and after 3 months also showed a significant difference (0 vs +2.0±0.7, p <0.001) (Table II).

Table II. *Comparison between data pre- and post-treatments with PRP or finasteride.*

	PRP treatment N=20			**Finasteride N=13**		
	Pre	**Post**	**p**	**Pre**	**Post**	**p**
Patient satisfaction	1.8 ± 0.8	3.35 ± 1.6	0.0002	1.38 ± 0.65	4.14 ± 0.69	0.46
VAS patient	5.85 ± 2.3	7.40 ± 1.7	0.0093	2.69 ± 2.7	6.71 ± 1.9	0.07
VAS physician	5.8 ± 2.6	6.9 ± 1.9	0.06	2.69 ± 2.7	6.33 ± 2.1	0.71
Photo comparison grade	0	+2.0 ± 0.7	<0.001	0	0	1.00

Data are shown in mean ± standard deviation or percentage (%). ***PRP****: plasma-rich platelets.*

Regarding finasteride, data analysis before and after 3 months showed no significant differences regarding satisfaction (p=0.46) as well as patient´s (p=0.07) and physician's (p=0.71) VAS. The blind observer's score between baseline and after 3 months also presented no significant difference (p=1.00) (Table II).

Comparison between the PRP and finasteride groups revealed significantly greater satisfaction in the PRP group (1.8±0.8 vs 3.58±1.2, p=0.00002), as well as the patient's VAS (5.85±2.3 vs 7.92±1.7, p=0.0005) and the physician's VAS (5.8±2.6 vs 7.7±1.6, p=0.013). Figure 1 demonstrates photography taken pre- and post-PRP therapy. The increase of hair count and density on frontal and vertex regions of these two patients is visible (Fig. 1).

Regarding adverse effects in the PRP group, 5 (25%) patients reported mild pruritus up to 48h after the first PRP and 4 (20%) up to 48h after the second PRP procedure. At the time of application, minimal and brief pain were observed by all patients. There were no other adverse effects or infections in any patient during the study period (Fig. 2).

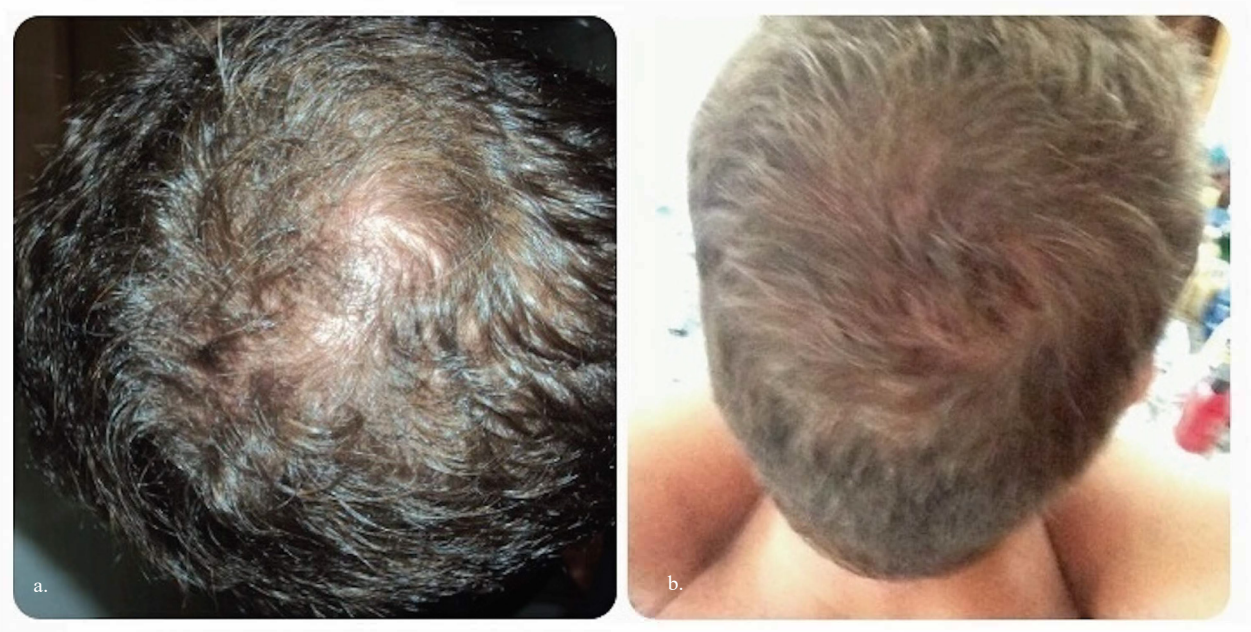

Fig. 1. *a): Pre-PRP; b): Post-PRP.*

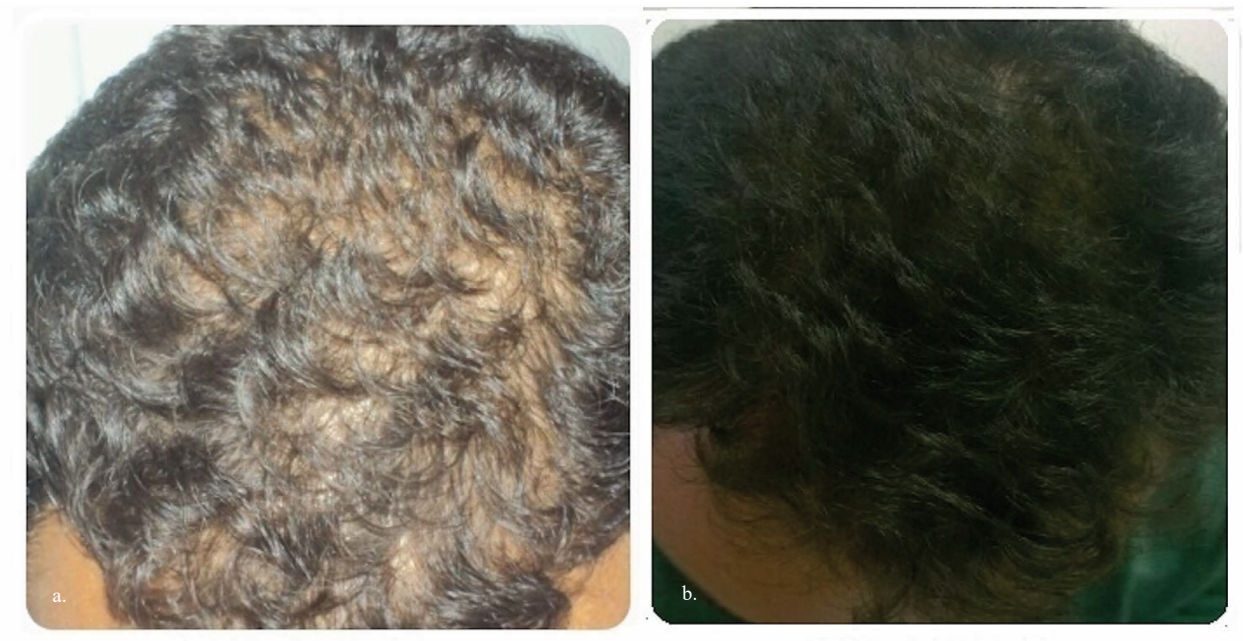

Fig. 2. *a): Pre-PRP; b): Post-PRP.*

Discussion

The present study demonstrated the efficacy and safety of platelet-rich plasma in the treatment of male androgenetic alopecia. As advantage, we can put in evidence the inclusion in the present study of only men, since it is known that the frequency of the disease is predominant in men. In addition, a more homogeneous population in MAA types, with cases chosen in subtypes II to V, excluding very mild cases and those with already indication for hair transplant surgery was

selected. In this line, external variables associated with change in hair loss were also excluded, such as disease exclusion, drug use or scalp surgery. The use of control group with finasteride brings one of the strong points of the current study. In fact, in previous studies there was no control group or finasteride was included together in the group that performed the PRP, making the results difficult to interpret. Another important point of this work is the blind evaluation through comparative photography and result obtained with very high grade after PRP.

Studies show that growth factors, such as epidermal growth factor, which is present in PRP, is capable of promoting papillary dermis cell proliferation and thus preventing their apoptosis (11). A possible adverse effect caused by finasteride on the male sex life – sexual impotence - during alopecia treatment makes PRP an option very attractive instead of finasteride (12). A systematic review has shown that treatment with finasteride presents an increase of 24% in capillary count after 48 months. Otherwise, PRP has excellent advantage of an accelerated response over standard 5-alpha reductase inhibitor treatment (13).

There are some clinical trials using PRP in alopecia, however no study has compared PRP to finasteride as herein performed. All previous trials demonstrated good results with PRP (14-17). A study evaluated PRP in comparison to topical minoxidil and found better results with PRP (18).

Long-term follow-up of patients treated with PRP are inexistent yet. In fact, the majority of the articles have evaluated from 3 months to 6 months in general. Specially, this short follow-up indicates good outcome. However, it is not known the outcome over time, for example one or even 5 years after PRP treatments. Future studies are needed to answer this issue. Data showing little value of PRP treatment have been published (19).

There are still some unanswered questions. For instance, it is not yet known which dosing schedule is most appropriate and regarding the use of PRP in women in comparison to finasteride. These topics urge for further studies with a larger number of female participants.

A limitation identified in this study was the number of participants. Further studies with a large number of participants are therefore desired to confirm the present data. In conclusion, the present study supports the notion that platelet-rich plasma seems to be better in treating male androgenetic alopecia in comparison to oral finasteride, with virtually no relevant adverse effects.

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Case report and short review: Botulinum toxin injection for the treatment of Notalgia parasthetica

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key words: *Notalgia parasthetica, botulinum toxin, neurological, symptomatic relief, neurotoxin, parasthesia, lichenification, hyperpigmentation, non-cosmetic uses of botulinum toxin, onabotulinum toxin*

Notalgia Paresthetica (NP) is seen as a well demarcated hyperpigmented patch on the back usually between T2 & T6, medial or inferior to the scapula. It is said to be a sensory neuropathy of the back and is characterised by itching, lichenification, hyperkeratosis or xerosis. A 48-year-old patient with Notalgia Parasthetica was injected with microbotox and remained symptom free for 8 months. There are very few reports of NP treated with onabotulinum toxin, but it is worth a study.

Notalgia Paresthetica (NP) is seen as a well demarcated hyperpigmented patch on the back usually between T2 & T6, medial or inferior to the scapula (1). It is often unilateral and is said to be a sensory neuropathy of the back. Some patches exhibit lichenification, hyperkeratosis or xerosis (2-4). Patients often complain of intense pruritis. Other symptoms are pain, parashthesia, burning sensation, hypoaesthesia, hyperaesthesia. NP can have a negative effect on the patient's quality of life. Various modalities of treatment in the form of topical and oral medications have been tried and are at their best temporary. There have been 4 reports of botulinum toxin injected in patients with NP. The author injected botulinum toxin in her patient who complained of relentless itching and found improvement in her symptoms.

Case report

A 48-year-old female doctor presented with an itchy dark patch on the back, just below the scapula on the left side in the past 12 years (Fig. 1). The patch was extremely itchy more after bathing and at bedtime. The itch would increase whenever the patient was stressed or whenever any other person spoke of itching as a symptom. The itching was unbearable, and she often had to use long sticks or large sized combs to scratch the patch. It was even uncontrollable and embarrassing at public places. The patient applied topical corticosteroids, capsaicin cream, oral antihistamines but found no relief. She had no other medical history and no history of atopy or injury. Upon examination, a hyperpigmented patch approximately 11x 7 cm was seen in the upper back, below the left shoulder blade. There was erythema and scratch marks on the lesion. The lesion was also lichenified and rough to touch. Radiographic investigation showed no anomaly. The condition was diagnosed as notalgia parasthetica.

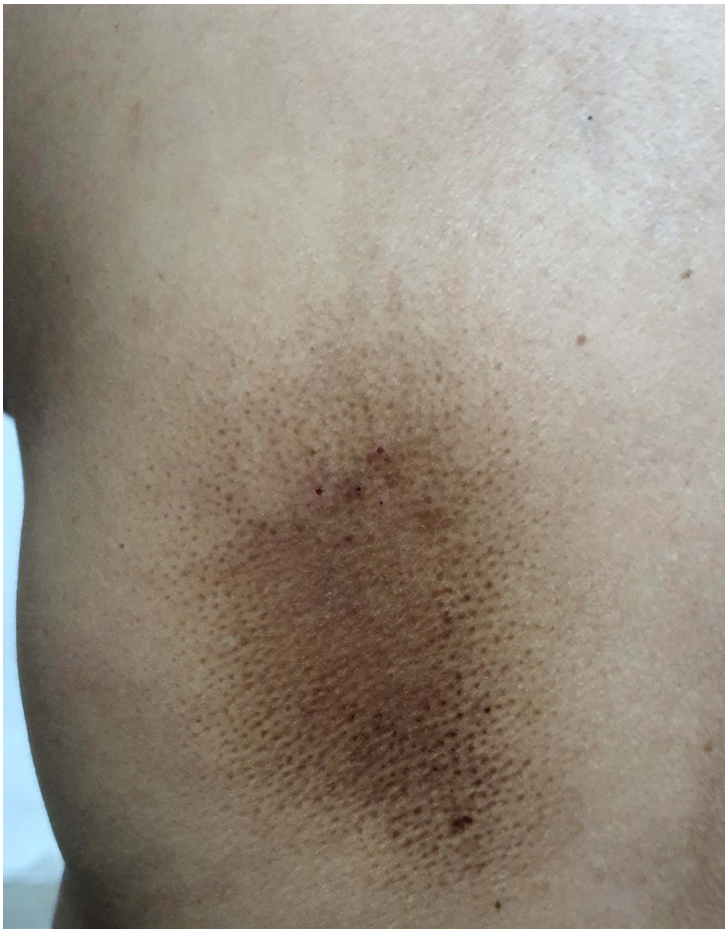

Fig. 1. *NP before Microbotox injection.*

The author treated the patient with botulinum toxin. 100 units of botulinum toxin was reconstituted with 2.5ml of 0.9% preservative free saline. 60 units of onabotulinum toxin was

then taken and further diluted with xylocaine in a 1:1 ratio and described a microbotox.

After taking consent and photographs, the dark patch on the back was thoroughly cleansed. Topical anaesthesia in the form of lidocaine prilocaine was applied for 30 minutes. This was then cleaned using chlorhexidine and alcohol. The dark patch was outlined. Markings were made 1cm apart to cover the entire patch. Using a tuberculin syringe, 2 units of microbotox was injected intradermally, first in alternate points for the lidocaine to act and the points in between were injected. A total of 120 units of microbotox were injected. Care was taken not to inject into the marking to avoid any tattoo formation. Th patient was advised not to massage the area and avoid any activity which involved sweating for at least 24 hours (Fig. 2).

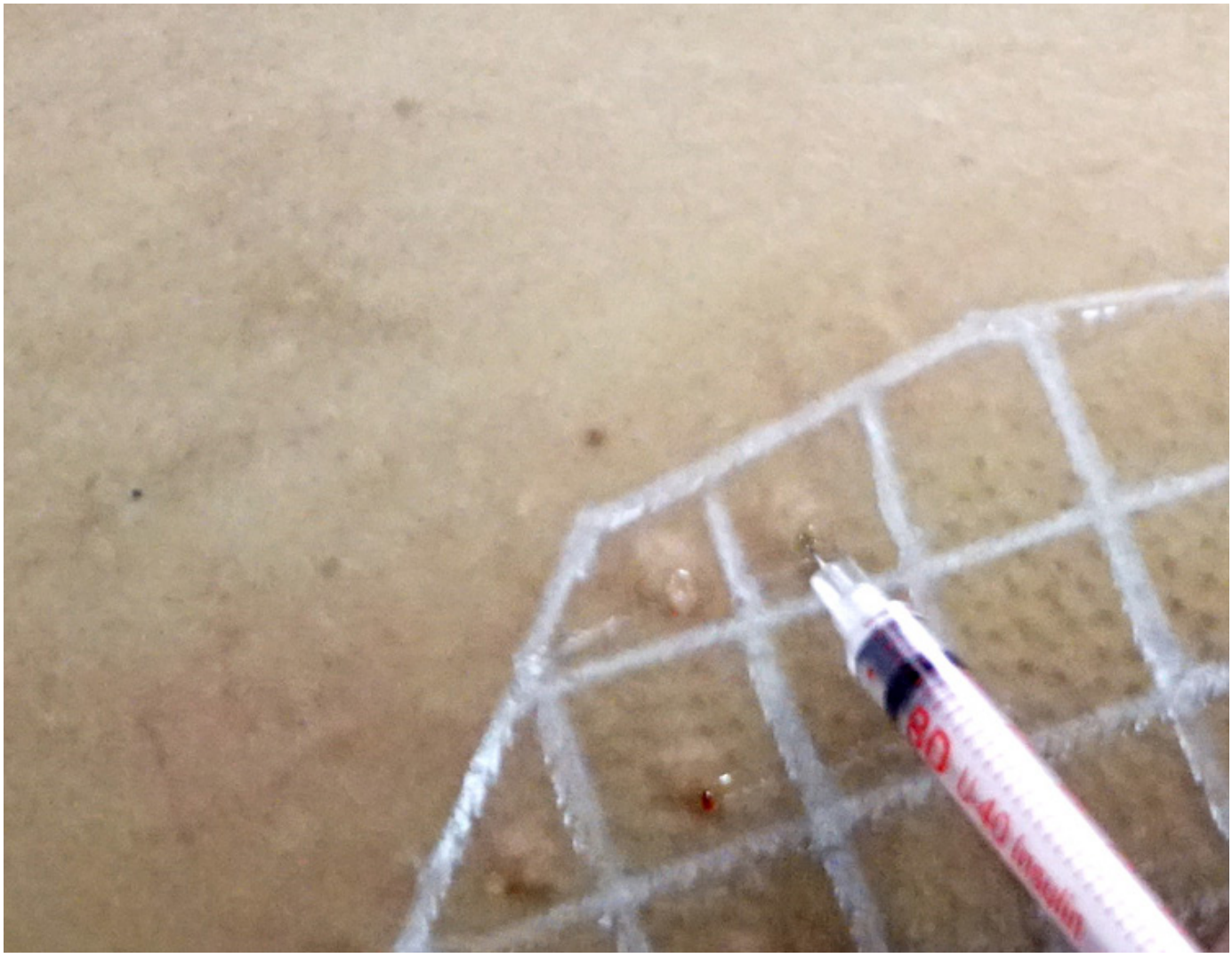

Fig. 2. *Intradermal injections of microbotox.*

The patient followed up in 4 weeks (Fig. 3). The pruritis has subsided without any medication. Upon examination, the erythema had reduced and there were no more scratch marks.

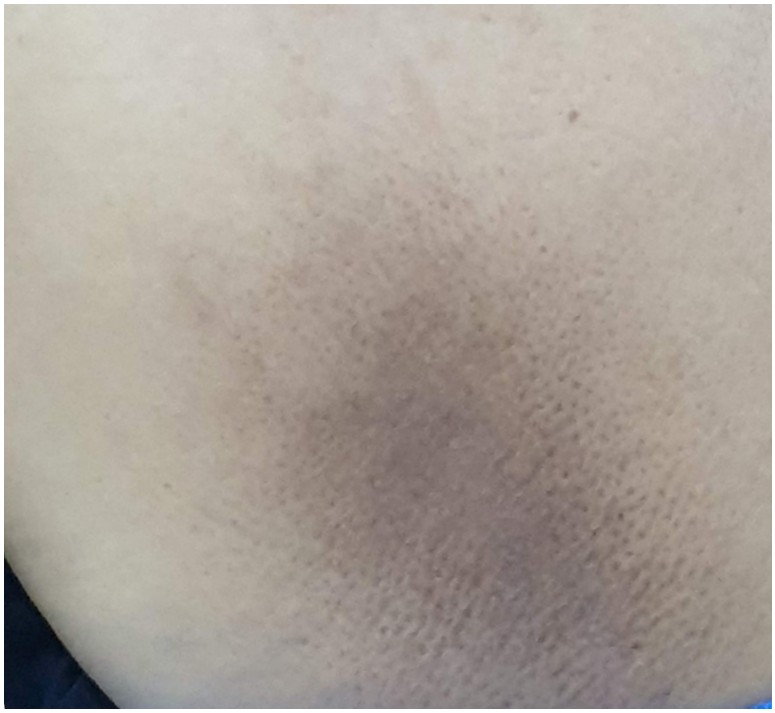

Fig. 3. *At 4 weeks follow up.*

The patient followed up at 4 months and 6 months, her itching had not recurred, and her patch was no longer lichenified. The skin felt smooth and the hyperpigmentation though present had reduced. At 8 month follow up, the patch was lighter, it still felt smooth, but the patient complained of occasional itch once in 4 to 5 days (Fig. 4).

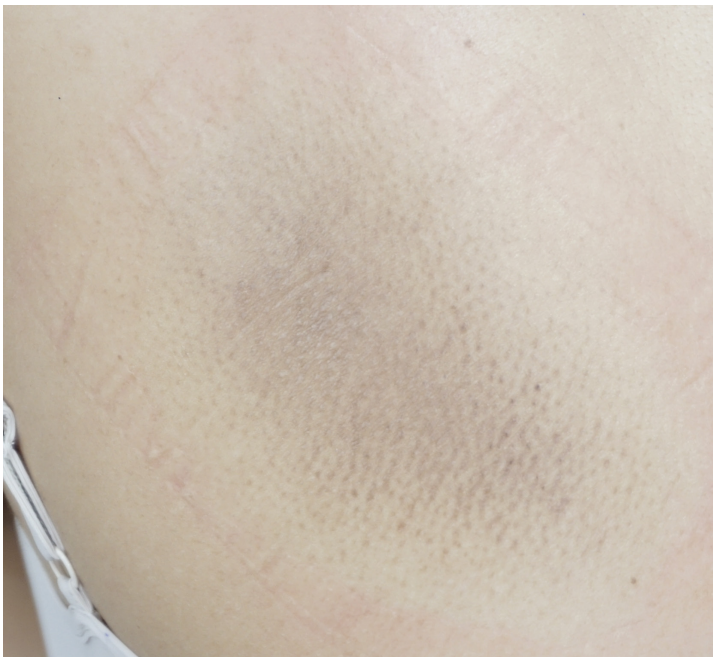

Fig. 4. At 8 months follow up.

Discussion

The cause of Notalgia paresthetica is not really known. While some say it is genetic, others say it could be due to a nerve root impingement (5) . In one study, skin biopsy of the affected area showed an increase in the density of intradermal nerves (6).

Topical capsaicin is the most commonly used agent, but it often results in burning, pain and tingling (7). Other topical treatments include tacrolimus, lidocaine, prilocaine, and a combination amitriptyline and ketamine cream (1). Topical and intralesional corticosteroids have been tried with no outcome (8). Oral antihistamines, gabapentin, oxcarbazepine, and amitriptyline are also prescribed (9).

Narrow-band UVB (NB-UVB) radiation, transcutaneous electrical muscle stimulation (EMS), Transcutaneous electrical nerve stimulation (TENS) , physiotherapy, paravertebral block, surgical decompression, and acupuncture are other therapies tried in NP but none of them have proven to be a cure (10-16).

Weinfeld, treated 2 patients of NP with intradermal botulinum toxin. She used a 3-mL dilution with preserved (0.9%) saline and injected 4 U of botulinum toxin type A superficially into the dermis, 2 cm apart for a total of 16 units in her first patient The patient remained symptom free at an 18 month follow up and her hyperpigmentation had completely resolved.

The second patient was treated with 24 units of botulinum toxin intradermally and was symptom free until 3 months following which she had intermittent pruritis. She was reinjected with 48 units of botulinum toxin after 18 months and became symptom free within a week. The hyperpigmentation on her back decreased in size and colour but was still evident 1 month after the second treatment (17).

Perez et al injected 5 patients of NP with up to 50 units onabotulinum toxin in a manner similar to Weinfeld and found no improvement in hyperpigmentation. There was improvement in pruritis in 3 patients for 1 month and increase in pruritis in 2 patients (18).

Wallengren et al injected six patients with intradermal onabotulinum toxin in the dose range of 18-100 u depending upon the size of the patch. Five out of six patients had reduced itching after a week. There was an average 28% decrease in pruritus at 6 week follow up in all five patients. One patient was symptom free, and another patient had 45% reduction in pruritis at 18 month follow up (19).

In a randomized, placebo-controlled, double blind controlled study in 20 patients with NP, Maari et al did not find any improvement in pruritis or hyperpigmentation upon injecting onabotulinum toxin intradermally. The patients had received 0.1 mL (50 U/mL) incobotulinum toxin A for every 1 to 2 cm2 of hyperpigmented area with a maximum dose of 200 U (20). There were no adverse effects reported in any of the studies except the temporary increase in pruritis in 2 patients.

Botulinum toxin type A is a purified protein that cleaves SNAP-25 and inhibits acetylcholine release at the neuromuscular junction (21). This causes chemical denervation resulting in paresis of muscle. The rationale for the use of Botulinum toxin against itch is the discovery that acetylcholine mediates itch in atopic dermatitis

(22), and the fact that botulinum toxin inhibits the release of acetylcholine from presynaptic vesicles. Botulinum toxin inhibits the release of substance P from cultured embryonic dorsal root ganglion neurons (23, 24). It reduces the release of calcitonin gene-related peptide from cultured trigeminal ganglia neurons (25). It also suppresses the release of glutamate and noradrenaline, all of which are involved in pruritis (21). In this case, diluted doses of onabotulinum toxin given as intradermal injections were tolerated better and had a wider dilution effect. The patient was symptom free during the 8 month follow up. The author proposes that even if one must repeat the doses once in 6 to 8 months, this technique relieves the patient of the relentless itching and is a modality worth considering. Since the lichenification has improved and the skin become smoother, skin lightening methods such as the use of Q switched Nd Yag laser could be tried after relief of symptoms with microbotox which the author chooses to perform on this patient and observe.

Conclusion

There are very few reports of using botulinum toxin for Notalgia Parasthetica. More studies would be encouraging and help the patients get relief from this condition which could actually play havoc in a person's daily life with embarrassing situations where one would want to scratch the back with anything they could get hold of.

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Does an ideal filler exist?

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key words: *acid hyaluronic filler, complications, infection, bruising, malar oedema, vascular complications*

Abstract

Introduction: Aesthetic procedures of skin regeneration and treatments are finding more and more use in daily practice. Today's trend leans towards non-invasive procedures compared to the number of these procedures performed in the previous years. The correct application of hyaluronic acid filler by trained doctors is accompanied by a small number or no complications at all. Purpose of this paper: To emphasize the importance of qualification in hyaluronic acid (Filler) injection procedures. To acknowledge and understand the possible complications and re-emphasize the ways of managing them after the application of hyaluronic acid. Materials and Methods: Patients treated with hyaluronic acid injections (Fillers) who developed complications after the procedure. The selected sample in this referral bases on the material and experience from our clinical cases encountered in the daily practice of 15 years. Results: Complications after hyaluronic acid injections are classified as immediate complications and delayed complications. The number of complications immediately after the procedure is larger compared to the number of complications that develop later and includes pain, edema, discomfort, hematoma, infections, nodules, vascular-necrosis compression, blindness. The number of delayed complications is smaller and includes infections, granulomas, filler migration. Conclusions: Every injection procedure (Filler) contains the possibility of

developing complications. Therefore, we can't say that an ideal filler does exist. Hyaluronic acid injection procedures are safe and effective procedures if applied by trained medical personnel. Having strong knowledge of anatomy and acquiring updated information on this sub-specialty, especially on the treatment of complications, is a necessity for the medical staff that performs these procedures. Aesthetic medicine is the bridge between medicine and art and should be entrusted to experts.

Introduction

Dermal fillers injections are among of the most performed procedures in the aesthetic dermatology practice. These procedures are increasing very fast during the last years. They are commonly known as tissue fillers, wrinkle fillers or injectable implants and are mostly used for filling of folds and replacement of soft tissue volume loss due to diseases or skin ageing. (1) Applying a dermal filler is generally well tolerated and safe, but occasionally they can develop complications. Of course, during the last years, the number of complications reported is increasing. Doctors must be aware for these complications that can be mild but medical emergency as a hypersensitive reaction. When performed by a medical doctor with deep knowledges of anatomy and good training the majority of these complication can be avoided. The recognition of early signs and symptoms prompts a correct treatment at early stages, avoiding the development of possible immediate or delayed complications.

Classification of dermal fillers

According to the literature, there are more than 160 filler products made from 50 different manufactures available worldwide. (2) The most common classification of dermal fillers is based on their longevity into temporary, semi-permanent and permanent fillers. According to one classification fillers are divided into biodegradable and nonbiodegradable (1, 2).

Biodegradable fillers – temporary or semi-permanent fillers (absorbable fillers)

Biodegradable fillers contain components of the derma (polysaccharide) that gradually degrade and are absorbed by the body (3). They fill the gaps between the wrinkles, increasing the hydration of the skin. These fillers are enzymatically degraded or desegregating from the mimic facial movements and absorbed. This process directly determines the duration of the treatment, diving them into temporary or semi-permanent, which also varies according to the patient's lifestyle (exposure to sunlight or solar tanning bed, smoking, drinking alcohol, stress) (4).

Some examples of biodegradable fillers are collagen, hyaluronic acid (HA, calcium

hydroxyapatite (CaHa) and poly-L-lactic acid (PLLA).

Collagen was the first injectable filler approved by the US Food and Drug Administration (FDA) (2). It makes up 70% to 80% of the dermis, which is gradually lost and becomes fragmented with age. It is less viscous and sometimes is more useful in the correction of fine lines and wrinkles because it is less likely to produce irregularities when injected superficially. The use of collagen is replaced with HA fillers.

HA is a polysaccharide with hydrophilic properties (a glycosaminoglycan disaccharide composed of an alternating and repeating unit of D-glucuronic acid and N-acetyl-D-glucosamine) which is a natural component of extracellular matrix (5). HA and its derivatives are considered to be the most popular dermal fillers due to their hydroscopic properties, biocompatibility, and reversibility.

Non-biodegradable fillers – permanent fillers. (non-absorbable fillers)

Nonbiodegradable fillers acts as foreign agents, which generate a reaction defined as chronic granulomatous reaction, that subsequently stimulates collagen deposition (3). Injected in the deep derma, they offer a longer effect that lasts about 2 years. Therefore, the patients do not require periodically refilling. However, they are prone to developing long-lasting complications that presents a challenge in their management. Some examples of nonbiodegradable fillers include polymethylmethacrylate (PMMA), polyalkylimide and silicone (1).

Complications

Even though dermal fillers that are used today are generally safe, complication can occur. They are commonly a result of 3 main actors:

(I) Medical Doctor (the injector and injection techniques)

(II) The product used as a dermal filler

(III) The patient itself (Table I).

Table I. *Factors that determine the occurrence of complications.*

Medical Doctor Strong knowledge on anatomy and technique Adequate training Adequate environment: good lighting, proper tools
Product A certified and approved filler The usage of right filler according to the indication
Patient Medical history and preexisting conditions Allergies, Active infections at the site, Inflammatory skin disorders, Neuromuscular disorders, Pregnancy and Lactation, Medication (anti-platelets and anticoagulants)

We have divided the complications of dermal fillers into three main categories: immediate, early and delayed, depending on the time of their appearance regarding the beginning of the procedure (Table II). Another way to divide these complications is temporarily and permanent complications. The larger part of possible side effects is mild and transient, but in the everyday practice and literature, cases of irreversible functional and aesthetic deficits have been reported (2).

Table II. *Filler complications regarding the time of onset.*

Immediate-onset Events (up to 14 sec post-procedure)
Injection site reactions: erythema, oedema, pain, ecchymosis (Allergy, Inflammation)
Early-onset Events (day to weeks post-procedure)
Infections
Type I Hypersensitivity reactions
Non-inflammatory nodules/ irregularities
Skin discoloration
Tyndall effect
Vascular occlusion/Emboli
Late-onset Events (weeks to years post procedure)
Malar oedema
Permanent discoloration
Type IV Hypersensitivity reactions
Infection (mycobacterial, biofilm related)
Inflammatory nodules and foreign body granulomas
Migration of filler material

Injection site reaction

Injection site reactions such as erythema, oedema, pain, discomfort, or ecchymosis usually have immediate onset, up to seconds after the procedure because of the local trauma. This side effects are mild, and they tend to persist for a short time, respectively erythema up to a few

hours and oedema up to a couple of days to a week (2). Their short longevity is explained with the superficial placement of the filler material (6). Pain is a common side effect; however, it can be minimized with several techniques such as using small needle gauge or topical anesthetic agents prior of the injection, cold ice compresses before and after the procedure and any NSAIDs immediately after. Bruising and ecchymosis is also considered a common complication. It is a result of extravasation of blood from the perforated dermal vessels or their rupture, either from the needle or the pressure caused from the filler material (7). Ecchymosis are commonly located in lower eyelids, upper third nasolabial fold, the upper lip, the lateral edge of the lower lip, and perioral rhytids and they appear immediately after the injection and gradually resolve within 5 to 10 days (7). Bruising can be either more present in a person that is using anticoagulant therapy and can be minimize if you can advise the patient to stop this medication a few days before the procedure, and the techniques low injections and using a blunt cannula can minimize this side effect. The other advice for your patient is to camouflage correctly and to use a medical make up to cover it perfectly during the first days. Erythema on the side of injection is usually mild and transit complication and can be minimize by applying a corticosteroid cream on the side for few days.

Adequate environment, a professional and good lighting during the procedure, a comfortable medical chair, an adequate necessary space are factors that influence in the possibility of happening some side effects during and after the filler procedure (Fig. 1)

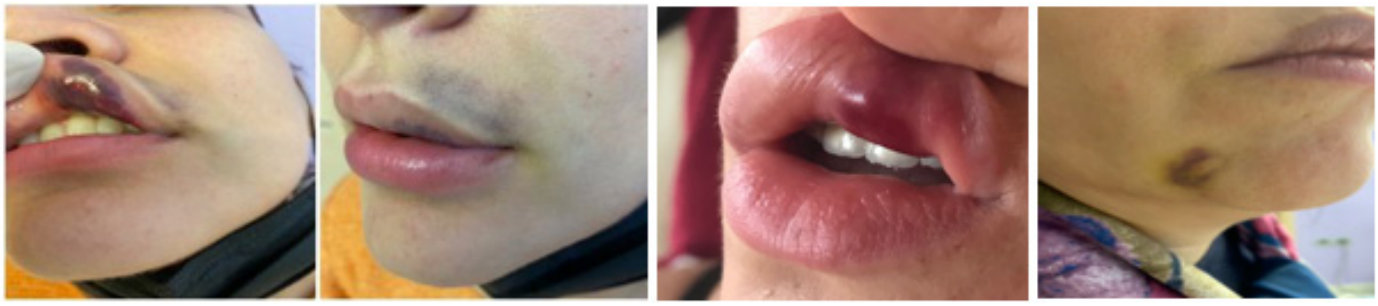

Fig. 1. *Bruising and Hematoma.*

Injection

Different infections (viral, bacterial and fungal) are noticed after the filler injection procedure due to the fact that the skin barrier is disrupted and the aseptic rules during the procedure are not to the demand. However, under favourable circumstances such as lack of appropriate preparation of the skin and adequate precaution, they can occur as the skin surface integrity breaches. The most common pathogens include staphylococcus, streptococcus, mycobacteria, viruses, yeasts and polymicrobial species. This complication can be noticed either a day after

(Herpes simplex), few days after but either a long period after the injection.

Referring our experience and as documented in literature, Herpes simplex infections are more often complications and can be triggered by lip filler augmentation or treating the fine smokers' lines in upper lips area. Therefore, a prophylactic antiviral therapy should always be considered prior procedure in those patients with a history of recurrent Herpes simplex outbreaks (2). Oral acyclovir should be taken two or three days prior the procedure and 1 day after for prophylactic reason. In cases of reactivation take in consideration to treat it locally or orally depend in the severity. If a patient has an active lesion of Herpes simplex the day of the procedure never perform a filler injection. Other infections due to streptococcus or staphylococcus microorganism can lead to abscess formation and cellulitis. The treatment of these complications by oral antibiotics is a must and should be perform as soon as possible especially in the eyes cellulitis as an emergency in dermatology.

A delayed infection can be noticed due to Mycobacterium chelonae and mycobacterium abscesses especially if is injected a contaminated filler (19). To avoid this, it is necessary not just the aseptic measures of the field of injection but either to be careful or to choose a certified filler.

Biofilms are a bacterial community which is surrounded by a protective and adhesive matrix, made by their own excreted polymers. This gives them the ability to develop and survive, even against the treatment (13). During the puncture of the skin surface, biofilms that resides on the surface, can enter and cause a local infection, a systemic infection or a granulomatous reaction depending on the depth of their penetration (14). It is classified either as inflammatory nodules and the treatment alternatives are antibiotics and in some cases corticosteroids (Fig. 2).

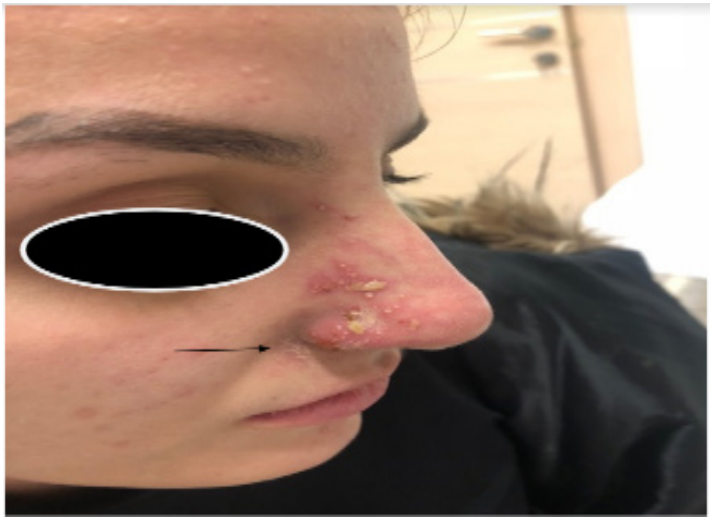

Fig. 2. *Infection.*

Hypersensitivity reactions (immediate or late - onset inflammatory adverse reactions)

The risk of developing hypersensitivity reactions must also be taken into consideration in every injection procedure. It may be triggered by the implantation of fillers, by the volume of the product injected or by the poor placement of the filler material. The temporary dermal fillers such as HA are more biocompatible and do not usually cause hypersensitivity reactions. Depending on the time of hypersensitivity reactions onset, it can be classified as acute (occur within minutes or hours after injections) and delayed (typically occur 48-72 h after injection but may be seen even several weeks or months post injection and can persist for months) (8). When the reaction is immediate, it is mediated by immunoglobulin E, describing a Type I Hypersensitivity with the typical signs such as erythema, pruritus, edema and rarely even anaphylaxis. These cases respond well to systemic corticosteroids and antihistamine (2). Always take in consideration the possibility of hypersensitivity due to lidocaine if you inject a filler with lidocaine and ask the patient prior the procedure.

Type IV hypersensitivity reaction appears later in time. It is manifested with erythema and oedema and is considered a delayed complication mediated by T-lymphocytes. The etiology of delayed of hypersensitivity to HA fillers is not completely understood (20), but triggering factors may be found like infections, trauma, vaccines, and different properties of the filler. (20, 21) Most of the late-onset adverse reactions are immune-mediated or inflammatory in nature. Most of them seem to have an immunological nature, on a background of genetic predisposition. These cases do not respond to antihistamines and often it is needed the removal of the allergen (9). Another possible complication to be aware is the hypersensitivity during the injection of hyaluronidase during the filler removal procedure. In this case you have to start immediately systemic corticosteroids.

Granulomatous reactions and nodules are rare late onset adverse reaction to HA fillers and much more frequent with permanent fillers. (20) A foreign body granuloma is clinically manifested as a nodus at the site of injection and appear after a period of time as a late complication. Always this complication needs a biopsy to be confirmed (18). Delayed reactions to HA fillers are treatable with systemic corticosteroids and hyaluronidase in case of lumps (21).

Non-inflammatory and inflammatory nodules

Nodules are another non-rare filler complication. Clinically they are prescribed as a bulge at the site of injection. It can appear early, within hours and days after filler application or after months or years (delayed nodules as a delayed complication). Based on the etiology there are divided into two categories: inflammatory and noninflammatory nodules.

Noninflammatory nodules are painless, non- erythematous and evident shortly after procedure. They arise from incorrect techniques, such as superficial placement, excess filler usage or incorrect product for the indication. In some cases, it can result due to migration of the product (21). Management include local massage at the side of injection or if it doesn't work, hyaluronidase injection(150IU/ml) is a treatment of choice for HA-filler. Performing the correct technique followed by local massage in the early post-procedure stage can prevent

noninflammatory nodules. It is important to choose the correct filler product for the correct indication and area (Fig. 3).

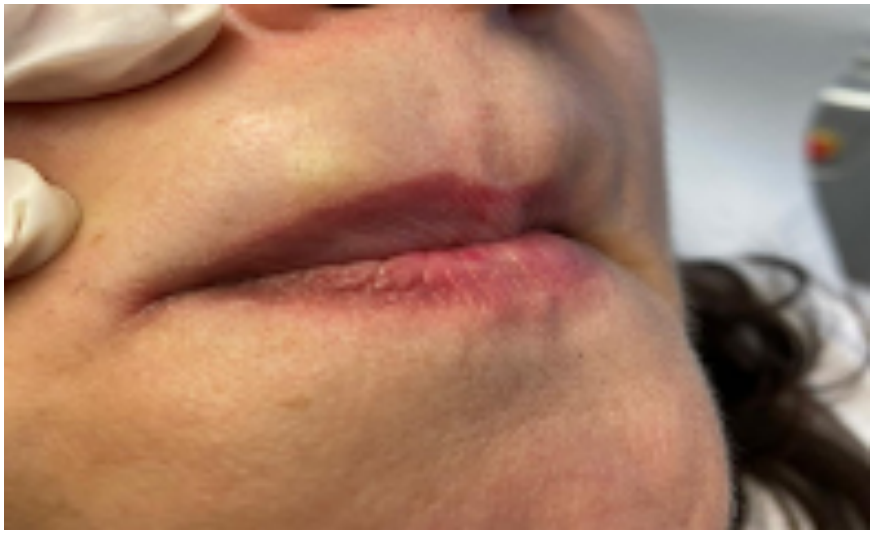

Fig. 3. *Non inflammatory nodus*.

Inflammatory nodules are painful, erythematous, and tender. They are either a result of an infection (Biofilms) or foreign body granulomas. Foreign body granuloma is a chronic inflammatory reaction of the body, which occurs as the immune system is not able to degrade or phagocytose this foreign material (16). This leads to the formation of multinucleated giant cells, which are characteristics of granulomas. Granulomas usually develop late, after the dermal filler injection as a delayed complication. The possibility of developing granulomas depends on the material used (usually it is seen in non-biodegradable fillers), large, injected volumes of the filler, the high molecular weight of the filler injected, infection or traumas at the site of dermal filler injection. (2, 17, 18)

Management typically includes local corticosteroids injection with hyaluronidase to the nodules and if it doesn't work a biofilm should be suspected. In these cases, a broad-spectrum antibiotic (quinolones or macrolides) should be use for a minimum of 4 weeks. The excision and a biopsy of granuloma can be a treatment of choice.

Skin discoloration

Skin discoloration as a late complication is in the form of hyperpigmentation post-inflammation or post-ecchymosis that are generally seen in patients with Fitzpatrick skin type IV-VI. Changes in the pigment can also happen when the material is placed superficially or with overcorrection (8).

Tyndall effect

It is an immediate complication presented as a 'bluish discoloration' of the skin and looks similar to an ecchymosis. As an inappropriate injection technique Tyndall effect happens when the filler is placed superficially and can cause scattering of blue light waves or the deposition of hemosiderin from intradermal bleeding. (13, 23) This discoloration usually dissolves within a couple of days or can persist for long period. Can be managed if you use a hyaluronidase first and re inject a filler a day of few days later.

Vascular occlusion/emboli

Vascular compromise is a rare complication but the most concerning possible complication of a dermal filler injection. This complication results are variable depending on the localization of the occlusion and the compromised vessel but always doctors should be aware to recognize this type of complication as soon as possible, to start aggressive treatment to avoid irreversible damages. If the occlusion happens locally, at the injection site, it will result in skin necrosis.

Localized vascular occlusion results from either direct intravascular injection or the compression of the vessels by the injected filler material (10). The patient usually complains immediate pain and acute changes of the skin color, which in cases of an arterial occlusion tends to be pallor and blanched, while in cases of a venous occlusion tends to be redder-more bluish. If the occlusion happens in distant to the injection site, it can result in blindness or cerebral ischemic events. The underlying mechanism is thought to be related to high pressure intra-arterial injection.

The accidental high injection pressure of the supratrochlear, supraorbital, angular and dorsal nasal arteries which are branches of the external carotid artery will result in a retrograde flow of the filler emboli into the ophthalmic artery (11). Once the physician stops the pressure on the plunger, the arterial pressure will push the filler emboli into the retinal circulation resulting in the loss of vision (12). In such events, vascular perfusion must be restored as soon as possible. The procedure must be stopped immediately (23). Inject hyaluronidase to the filler and meanwhile as emergency measures use of acetazolamide, sublingual nitroglycerine, and infusion of mannitol iv. These can be helpful to prevent blindness. An ophthalmologist or oculoplastic surgeon must be contacted urgently.

If the physician applies a greater force for a long time, the filler emboli can reach the internal carotid artery and then be propelled into the intracranial circulation resulting incerebral ischemic events (11). This complication is rare but is serious and life threatening. A doctor can avoid this complication by using the appropriate technique of injection and always aspirate before inject, inject low volume filler and not with high pressure, inject slowly and carefully, use less dense filler. In case of complication and change the color of the area when you inject, and pain stop the procedure immediately. Use hyaluronidase, hot compresses and massage the area. A paste with nitroglicerine 2% to the affected area can promote vasodilatation (Fig. 4).

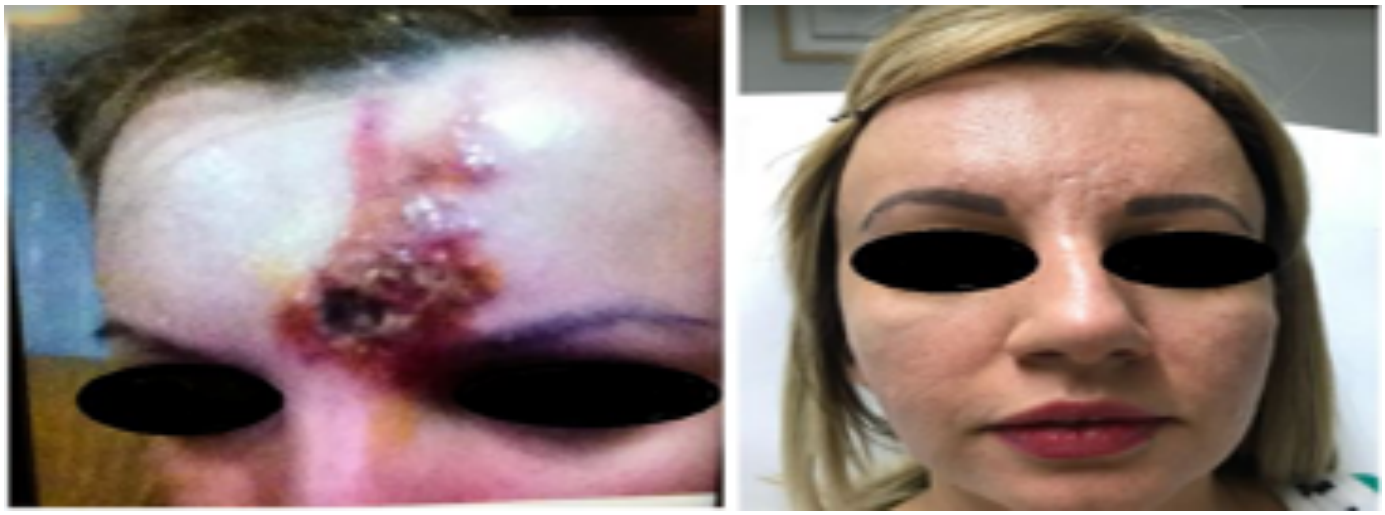

Fig. 4. *Vascular occlussin.*

Malar oedema

Malar oedema is a complication reaction that is formed in the infraorbital area and tear trough. It is caused from the pressure that the filler material causes to the local lymphatic drainage system in a patient that is predisposed to develop lymphatic drainage problems and the augmenting the barrier of the malar septum (23). It is recommended to use to this area products less hydrophytic and this can be associated with less possibilities for oedema, dyschromia. Malar oedema is a form of chronic oedema that should be taken inconsideration when inject to treat tear trough. It can persist for months and sometimes it can even become permanent if it does not respond to the treatment. Take in consideration to choose a filler that is less hydrophilic to treat this area, to inject it slowly and too deep, to use less product and retouch in another season to avoid this complication. The injection of hyaluronidase for this filler it could be a solution (Fig. 5).

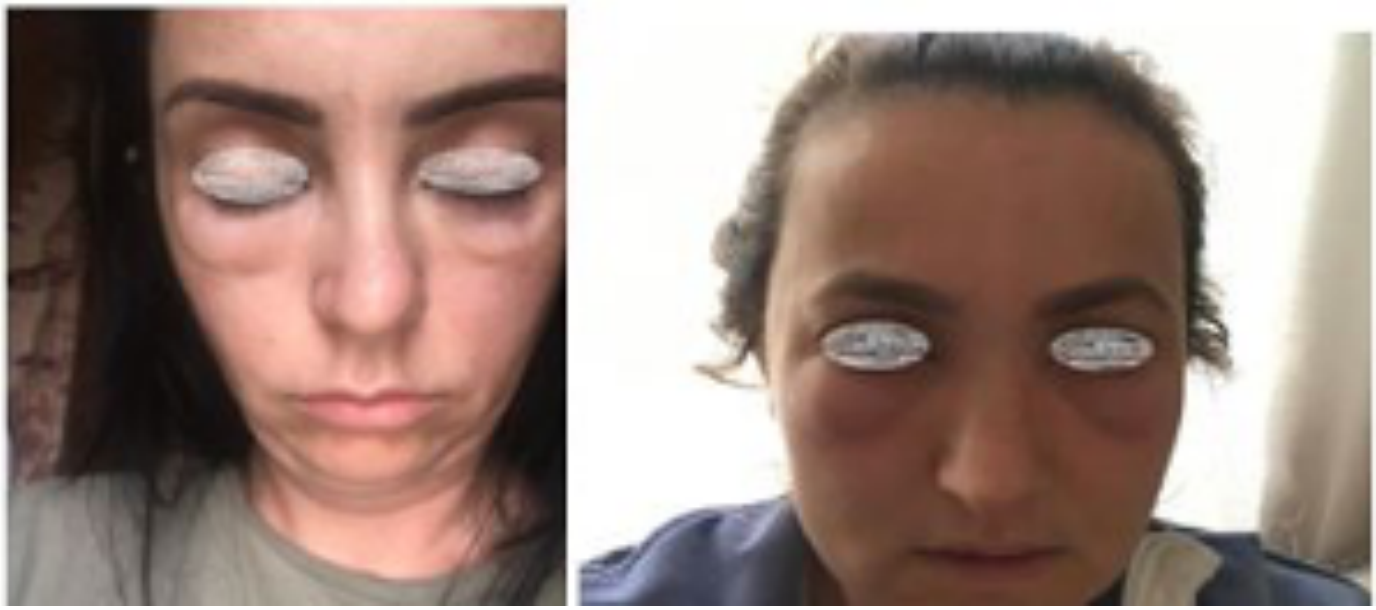

Fig. 5. *VMalar oedema.*

Migration of filler material

A migration of the filler material occurs when the filler is located remotely from the first injection site. Is a rare complication. It can occur at any given time up to several years after the procedure, for as long the dermal filler material (notably semi-permanent or permanent) is present. The reason of a possible migration of filler material, relies on the poor injection technique, high volume of the injected filler, pressure injected filler, overly massaging the area after the procedure, gravity or anti-gravity movements, induced pressure by additional filler placement, lymphatic spread and intravascular injection, or in some rare, documented cases, normal skin ageing (15). The only practical treatment is the removal of migrated filler (Fig. 6).

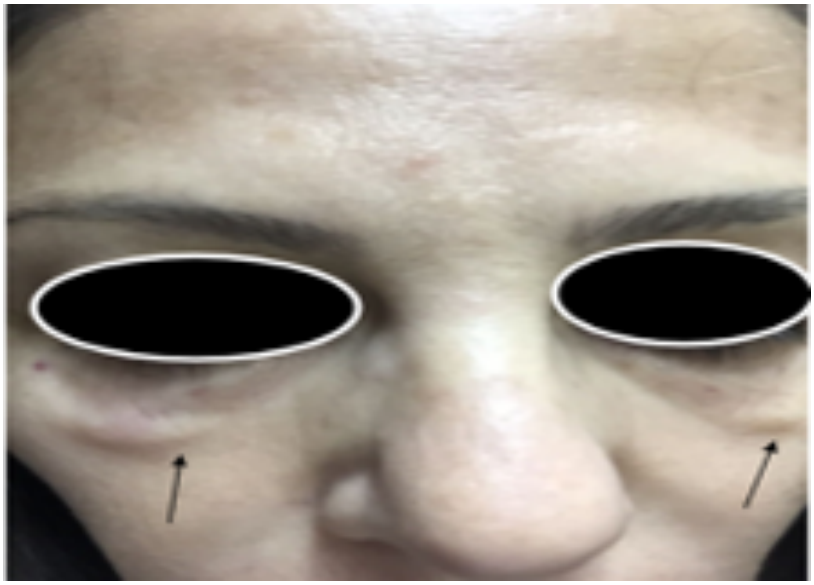

Fig. 6. *Filler migration.*

Conclusions

Hyaluronic acid injection procedures are safe and effective procedures if applied by trained medical personnel (23-30). Therefore, we cannot say that an ideal filler does exist. Every injection procedure (Filler) contains the possibility of developing complications. Having deep knowledge of anatomy and acquiring updated information on aesthetic medicine sub-specialty is a necessity for the medical staff that performs these procedures. Aesthetic medicine is the bridge between medicine and art and should been trusted to experts.

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