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Contents

Guidelines for Authors

Aesthetic Medicine is a multidisciplinary Journal with the aim of informing readers about the most important developments in the field of Aesthetic Medicine.

Submission of manuscripts

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

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The title page should include:
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The length of the abstract should be no more than 250 words and should include the following hea- dings: Background, Aim, Methods, Results, Conclusions

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Up to six keywords should be listed and separated by a comma (please, verify keywords on MeSH).

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The manuscript should be organised in the following sections:
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· Results
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· Conflict of interest
· Reference list
· Legends (max 10)

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Acknowledgments

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

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

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AMA Manual of Style: A Guide for Authors and Editors. 10th ed. Oxford: Oxford UP.

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Example Article

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

In-Text Citation Example

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

References Section Example

References

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

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

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Via Monte Zebio, 28 - 00195 Rome
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Editorial

In modern years, aesthetics has become quite important in every aspect of everyday life: following the hundreds of journals, magazines, blogs and websites pointing their attention towards this interesting and fascinating topic, the request for aesthetic medicine has increased manifolds.

Aesthetic Medicine is a new field of medicine, in which different specialists share the aim of constructing and reconstructing the physical equilibrium of the individual. Treatment of physical aesthetic alterations and unaesthetic sequel of illnesses or injuries, together with the prevention of aging, are perhaps two of the most iconic areas of intervention for Aesthetic Medicine.

However, in order to prevent frailty in the elderly, a program of education is similarly important.

Furthermore, the line between health and beauty is extremely thin: psychosomatic disorders resulting from low self-esteem due to aesthetic reasons are frequent and can- not be ignored by a clinician.

It is therefore clear that there is no figure in the field of medicine which is not involved in Aesthetic Medicine: endocrinologists, gynecologists, angiologists, psychologists and psychiatrists, plastic surgeons, dermatologists, dieticians, physiotherapists, orthopedists, physical education instructors, massophysiotherapists, podologists, and rehabilitation therapists are just some of the specialists who are sooner or later going to have to answer their patients' needs for aesthetic interventions.

The involvement of all these specialists fits the description of health as defined by the WHO: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" for which, undeniably, a team of different physicians is required.

The number of patients requiring medical consultation for esthetic reasons is rapidly increasing: in order to be able to provide adequate feedback, medical and paramedical specialists should be trained and, more importantly, should be taught how to work together. Existing Societies of Aesthetic Medicine from different countries share the aim of creating such teams and provide constant updates to the literature: the creation of an international network of specialists from all around the world under the flag of Aesthetic Medicine represents a challenge, but at the same time it is the proof of the widespread interest in this topic.

The first issue of this Journal represents the results of the efforts of the many national Societies and of the Union Internationale de Medecine Esthetique, now together as one; it is our hope that in years to come this Journal might improve our knowledge in this field, and provide adequate scientific advancement in the field of Aesthetic Medicine.

Francesco Romanelli
MD Editor-in-chief
Associate Professor at "Sapienza" University of Rome

Editors' notes

Aesthetic Medicine, the booming medical activity

Aesthetic Medicine was born in France 40 years ago.
The French Society of Aesthetic Medicine was the first of its kind in the world, followed by Italy, Belgium and Spain. Starts were rather difficult as aesthetic procedures in those early years were only surgical.
At that time aesthetic doctors and cosmetic dermatologists had very few real medical procedures to offer to their patients for treating aesthetic problems on face and body.
At the beginning of the '80s, viable medical procedures started to emerge in Europe for aesthetic and cosmetic purposes. Mostly, at that time, they were imported from the United States: those included collagen injections for wrinkles (Zyderm by Dr. Stegman), and chemical peels (phenol by Dr. Baker, TCA by Dr. Oba- gi). But, subsequently, European research on Aesthetic Medicine gained momentum. Hyaluronic acid appeared on the market, as it was discovered that it could be used as a dermal filler for wrinkles. During the '90s, the use of lasers offered aesthetic doctors and cosmetic dermatologists new possibilities.
The "beam revolution" started with CO2 laser for facial resurfacing.
Today, CO2 resurfacing is not used as much anymore, because of the long and difficult postop. CO2 laser was replaced with the gentler Nd-YAG and Erbium lasers and more recently with non invasive photonic devices for facial rejuvenation, including IPL, US and radiofrequency. These new technologies allow today's aesthetic doctors and cosmetic dermatologists to offer their patients procedures with low risk of post- op complications. Then, Botulinum Toxin has "invaded" both sides of the Atlantic Ocean.
Today, Botox injections are the most popular treatment for facial expressive wrinkles.
Botox injections are now so common everywhere that many cosmetic surgeons have given up their bistouries for syringes. Last but not least, development in Aesthetic Medicine is shown by mesotherapy and adipolipolysis.
About lipolysis, new data and recent publications have explained that radiofrequency, ultrasounds and cryolyse could have positive action to dissolve fat and to improve some unaesthetic disorders like cellulite.
These non invasive procedures intend to replace the surgical liposculpture with success.
Nowadays, Aesthetic Medicine has the necessary tools to address all major disorders within the aesthetic field. After 40 years, Aesthetic Medicine is now active in 32 countries in the world (France, Italy, Spain, Belgium, Morocco, Poland, Russia, Switzerland, Kazakhstan, Algeria, Brazil, Argentina, Uruguay, Venezuela, Colombia, Chile, Mexico, U.S.A, Canada, South Korea, Ecuador, China, South Africa, Turkey, Ukraine, Georgia and recently Croatia, Portugal, India, Guatemala, Peru and Bolivia). All 32 national Societies are members of the Union Internationale de Médecine Esth tique (U.I.M.E.). Aesthetic Medicine is taught in 7 countries (France, Italy, Spain, Argentina, Mexico, Venezuela, Kazakhstan) in universities that deliver UIME's diplomas after 3 to 4 years of studies.

What is the future of Aesthetic Medicine?

In the last few decades, patients' desires to look and feel younge, have fueled Aesthetic Medicine and Cosmetic Dermatology: many different procedures have been developed to satisfy the demands.
As life-span have increased, patients today are not only asking about aesthetic procedures, they are also asking for a way to stay in good physical conditions in the last decades of their lives. As a direct result, Anti-Aging Medicine, which covers skin aging and general aging, has recently emerged and expanded very quickly. Anti-Aging Medicine can offer senior patients better nutrition, dietary supplementation with vitamins, minerals, antioxidants, and eventually hormone replacement therapy, but only when needed.
Today, and in the near future, both Aesthetic Medicine and Anti-Aging Medicine will offer to our patients, who now live longer, better wellness with aesthetic treatments for skin aging and anti-aging treatments for general aging. Aesthetic Medicine is booming, but all medical practitioners should be correctly trained, so its future will be bright.

Jean-Jacques Legrand
Former General Secretary and Honorary President of UIME

Aesthetic Medicine: a bioethic act

When in 1977 the Italian Society of Aesthetic Medicine published the first issue of the magazine “La Medicina Estetica” Carlo Alberto Bartoletti, the Founder, wrote an editorial in which traced the pathway of the discipline and of the Scientific Society, still valid and projected into the future.
Today from that Editorial Board arise an International Journal, which wants to be indexed, in order to give to the doctors practicing Aestehetic Medicine all around the world a solid basis of shared knowledge.
In the late ‘60s, what was called in Italy Aesthetic Medicine, moved its first steps thanks to “remise en forme and anti aging projects” imported from the experience the “Institutul de geriatrie Bucuresti”, directed by Dr. Ana Aslan.
For this reason,there is the bioethical imperative that the Discipline should be first prevention, then return to physiology and finally correction.
The worldwide diffusion and the efforts of Industries born on the wave of the phenomenon have often led to choose the fastest route to achieve and maintain the physical aspect in the myth of beauty at all costs, without considering that aesthetic is not synonymous of beauty, but it is a balance between body and mind, and the role of the doctor is to take care of the Person globally and not only focusing on the correction of “a badly accepted blemish”.
Faithful to the teaching of my Master had almost 50 years ago, this new journal will have the task of elevating the human resources, aligning and validating methodologies, but above all affirming the humanitas of the medical art in its purest sense to pursue the good and the graceful for the person who relies on it.

Fulvio Tomaselli, MD
Honorary President of the Italian Society of Aesthetic Medicine

Aesthetic Medicine needs science. All over the world

All Aesthetic Doctors know that science is the basis for safety. Safety is the most important issue in our discipline.
Unfortunately, Aesthetic Medicine is more often surrounded by marketing than by science, despite the hard work done by Scientific Societies all over the World. And, too often doctors working in this field are dealing with sellers that promote products with insufficient scientific studies.
However, they sell it anyway. I think that doctors must learn that the first thing to ask about a medical device is the scientific background regarding that product: patients treated, follow up period, adverse events and, most of all, publications.
With this new International Journal completely dedicated to Aesthetic Medicine, proposed by the Italian Society of Aesthetic Medicine, endorsed by UIME and shared by all the National Societies of Aesthetic Medicine belonging to UIME, World Aesthetic Medicine wants to stimulate scientific production in this discipline to increase safety and quality in aesthetic medical procedures.
Another important goal of the Journal is to catalyze the proposal of new protocols and guidelines in Aesthetic Medicine, with the consensus of the entire Aesthetic Medicine Scientific Community.
What this Journal should achieve in the near future is to improve the number and quality of scientific production in Aesthetic Medicine, in order to allow this discipline to grow in the field of evidence based medicine, not only in the rationale field.
I hope this can be the start of a new era for Aesthetic Medicine, with the commitment of all Scientific Societies all over the world.

Emanuele Bartoletti, MD
Managing Editor
President of the Italian Society of Aesthetic Medicine

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President: M. OUGHANEM

ARGENTINE SOCIETY OF AESTHETIC MEDICINE
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pinto@soarme.com - www.soarme.com
President: R. PINTO

BELGIAN SOCIETY OF AESTHETIC MEDICINE
Chaussée de Marche 390 - 5100 Jambes - Belgium
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1087 Roosevelt Crescent, North Vancouver, BC Canada V7P 1M4.
info@caam.ca - www.caam.ca
President: R. Van AARDT

CHILEAN ASSOCIATION OF AESTHETIC MEDICINE
Avda President Riesco 2955, apto 1102, Las Condes Santiago - Chile
info@sochme.cl - www.sochme.cl
President: G. MARZULLO

CHINA ACADEMY OF AESTHETIC MEDICINE
Department of Stomatology, General Hospital of PLA 28 Fuxing road, BEIJING 100853 - China
zhengxing@vip.163.com
President: LI SHIRONG

COLOMBIAN ASSOCIATION OF AESTHETIC MEDICINE
Calle 4 Sur, n. 43 a 195 - Oficina 141 - Bloque B - Medellin - Colombia
acicme@gmail.com - www.acicme.com.co
President: G. ARROYAVE ESTRADA

CROATIAN SOCIETY OF AESTHETIC MEDICINE
51414 Opatija, Croatia - Phone: 0038 5921707322
drbunar@gmail.com - www.huem.eu
President: E. BUNAR

ECUADORIAN SOCIETY OF AESTHETIC MEDICINE
Ave de los Shyris 344 y Eloy Alfaro, Edificio Parque Central, Oficina 609 - Quito - Ecuador
seem2008cg@gmail.com - www.seem.com.ec
President: V. TINOCO KIRBY

FRENCH SOCIETY OF AESTHETIC MEDICINE
154, rue Armand Silvestre - 92400 Courbevoie - France
jjlegrand-md@sfme.info - www.sfme.info
President: J.J. LEGRAND

GEORGIAN SOCIETY OF AESTHETIC MEDICINE
Irakli Abashidze str. 77, Tbilisi 0162 - Georgia
info@gsoam.ge
President: E. UGREKHELIDZE

ASSOCIATION OF AESTHETIC AND ANTIAGING MEDICINE OF GUATEMALA
6a Av. 9-18 Zona 10 Edif. Sixtino 2, Of. 405 ala 2, Guatemala Cd.
dr.rosalescarlos@gmail.com
President: C. A. ROSALES GONZÁLEZ

INDIAN SOCIETY OF AESTHETIC MEDICINE
E-52/Basement/ Greater Kailash-II, New Delhi-110048
dr.a.rana@gmail.com
President: A. RANA

ITALIAN SOCIETY OF AESTHETIC MEDICINE
Via Monte Zebio 28 - 00195 Rome - Italy
sime@lamedicinaestetica.it - www.lamedicinaestetica.it
President: E. BARTOLETTI

KAZAKHSTAN ASSOCIATION OF AESTHETIC MEDICINE AND PLASTIC SURGERY
139, Tulebaeva Str. – 480091 Almati, Medeouski
arugulnar@hotmail.com
President: G. ZHUMATOVA

KOREAN ACADEMY OF AESTHETIC MEDICINE
Han-Song B.D. 801, Myeong-dong, Jung-gu, Seoul - Korea
hanwooha@nate.com
President: WOOHA HAN

MEXICAN SCIENTIFIC SOCIETY OF AESTHETIC MEDICINE
Cincinnati 81-307 - Col. Noche Buena - Mexico D.F. 03720
bmillerkobisher@yahoo.com - www.facebook.com/Sociedad.Mexicana.Cientifica.Medicina.Estetica
President: J-B. MILLER KOBISHER

MOROCCAN SOCIETY OF AESTHETIC MEDICINE
19, place du 16 Novembre - 20250 Casablanca - Morocco
drbourra@hotmail.com - www.dermastic.asso.ma
President: A. BOURRA

SCIENTIFIC ASSOCIATION OF AESTHETIC MEDICINE OF PERU
Av. Jose Pardo 1801, Miraflores Lima - Peru
info@asocime.com.pe - www.asocime.com.pe
President : I. OGATA

POLISH SOCIETY OF AESTHETIC AND ANTI-AGING MEDICINE OF POLISH MEDICAL SOCIETY
Ujazdowskie 22, 00-478 Warszawa - Poland
psme@psme.waw.pl - www.ptmeiaa.pl
President: A. IGNACIUK

PORTUGUESE SOCIETY OF AESTHETIC AND ANTI-AGING MEDICINE
Rua Maria Vitoria Bourbon Bobone, Lote 21, N°41, Apto. 201 P-3030-502 Coimbra
joao.vale@spme.pt - www.spme.pt
President: J.P. VALE

RUSSIAN NATIONAL AESTHETIC MEDICINE SOCIETY
12/3 Fotievoi Street, Pol. n.3 - of.512 - 119333 Mosca - Russia
o.panova@rs-am.ru
President: O. PANOVA

AESTHETIC AND ANTI AGING MEDICINE SOCIETY OF SOUTH AFRICA
PO Box 26716, Monumentpark, Pretoria, Gauteng, South Africa, 0105
cobus@drcobus.co.za - www.aestheticdoctors.co.za - info@aestheticdoctors.co.za
President : J. VAN NIEKERK

SPANISH SOCIETY OF AESTHETIC MEDICINE
Ronda General Mitre, 210
08006 Barcelona - Spain
secretaria@seme.org - www.seme.org
President: P. VEGA

SWISS SOCIETY OF AESTHETIC MEDICINE
La Clinique - avenue de Collonge, 43 - CH - 1820 Territet - Montreux
s.lehuu@laclinique.ch - www.ssme.ch
President: S. LE-HUU

SOCIETY OF AESTHETIC MEDICINE IN TURKEY
Rumeli Caddesi Durak Apt N° 2, D.7 - Nisantasi, Istanbul
subasihasanm@superonline.com - www.estetiktipdernegi.org.tr
President: H. SUBASI

UKRAINIAN SOCIETY OF AESTHETIC MEDICINE
Bunina Street, 10 Odessa 65026 - Ukraine
office@virtus.ua - usam.org.ua
President: V. TSEPKOLENKO

AESTHETIC MEDICINE SOCIETY OF URUGUAY
Ave. Sarmiento, 2470 - 11300 Montevideo - Uruguay
alberto@drelbaum.com - www.sume.com.uy
President: A. ELBAUM

AMERICAN ACADEMY OF AESTHETIC MEDICINE
24671 La Vida Drive - Laguna Niguel, Ca 92677 - USA
mdelune@aol.com - www.aaamed.org
President: M. DELUNE

AESTHETIC MEDICINE SOCIETY OF VENEZUELA
Av. Sucre de Los Dos Caminos, entre 4ta y 5ta transversal,
Res. Centro Parque Boyacà, Edificio Centro, Piso 20, Off. 201 1070 Caracas - Venezuela
fuceme@gmail.com - www.fuceme.org - www.sociveme.org
President: V. GARCIA GUEVARA

aesthetic medicine

Original Article

AFLAX MLT®: a new medical treatment, effective and powerful to treat skin flaccidity

Graciela Melamed

MD, GMC Clinic, Buenos Aires - Argentina

Abstract

Introduction: cutaneous flaccidity is a complex problem that involves intrinsic and extrinsic factors. Many treatments and procedures have been developed to improve it, but the results obtained so far have not been truly satisfactory, thus, the development of new minimally invasive products that can recover the mechanical properties of the skin and offer natural results continues. The objective of this study was to evaluate the efficacy and safety of a new treatment, AFLAX MLT®, minimally invasive that acts at different levels of the skin.

Methods: prospective, study was carried out in women between 29 and 62 years old with abdominal flaccidness, who received three AFLAX MLT® treatment sessions. Each session consisted in the administration of two injectable vials (one at superficial subcutaneous level and another one intradermal) and a cream that was applied topically, in the last place. All treatments were performed by the same researcher. The firmness and flexibility of the skin were evaluated by cutometry, and pain as well as patient/physician satisfaction were evaluated by self-assessment scales.

Results: 39 patients with a mean age of 45.80 (10.09) were treated. The differences between pre- and post-treatment measurements were statistically significant for all the variables, achieving an improvement of skin flaccidity at 30 days after the third session of 22.91% for R0, 16.82% for R2, 14.40% for R5 and 20.73 for R7.

Conclusion: the results obtained with the new AFLAX MLT® multilevel therapy were well tolerated and rated very satisfactorily by patients. It showed an improvement of the mechanical properties of the skin, with a significant increase in the firmness as well as the elasticity of the treated area.

Keywords

Flaccidity, abdomen, aging

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Correspondence

Graciela Melamed, MD

GMC Clinic, Buenos Aires – Argentina
E-mail: gramelamed@gmail.com

Introduction

Flaccidity is closely related to age. Currently, the fight against the passage of time and its impact on the body results in a continuous i+d race for products and procedures aimed at mitigating the visible signs of aging. Cutaneous flaccidity is a complex problem that involves intrinsic and extrinsic factors. The loss of volume, excess of skin pigmentation and the low or irregular reflectance of light are among the intrinsic factors[1]. On the other hand, the most relevant extrinsic factor is sun exposure, also known as photo-aging.

One of the first events in skin aging is flaccidity. For example in the face, a descent of the middle and lower thirds occur. Flaccidity can also be seen in other areas of the body, such as the abdomen or brachial area. In this dynamic process, aging, as well as soft tissue and bone structures are involved[1]. Not only is there a decrease in collagen, skin thinning and fat loss lead to flaccidity[2,3]. In addition, there is a subtle interaction between bone resorption, fat atrophy, the thinning of collagen and elastic fibers[1], and an evident decrease in cell turnover. All these factors together added to the effect of gravity on the loose tissue, ultimately conduct to the formation of folds, wrinkles and the fine lines[4].

Very frequently, the correction of these aging signs has been approached with surgical techniques and other invasive rejuvenation procedures, such as sutures[5], or other suspension systems, like threads. But these invasive procedures are not the desired choice for many patients.

Skin rejuvenation therapies should be oriented towards the mitigation of the damage and the restoration of the original structure of the tissues, in order to recover their mechanical properties. Procedures should be as minimally invasive, safe and effective as possible, and deliver natural and more lasting, focusing on the needs of each patient individually[4].

The objective of this study was to evaluate the safety and efficacy of AFLAX MLT®, a new multilevel, minimally invasive treatment to recover the elasticity and firmness of the skin.

Materials and methods

Study design

Prospective, non-randomized, single-center study, carried out on women, at the GMC Clinic center in Buenos Aires (Argentina), during February 2018.

The study was conducted in accordance with the principles established in the current revised version of the Declaration of Helsinki, with Good Clinical Practice (BPC).

Inclusion criteria: Women from 29 to 62 years old, with signs of abdominal flaccidity.

Exclusion criteria: i) systemic pathologies, ii) under daily medication, and iii) have received any aesthetic treatment one month before or less of the first session.

Study protocol

Patients were consecutively recruited.

Patients received 3 treatment sessions with AFLAX MLT® in the abdomen, over a month, according to the product specifications. A follow-up visit was made 30 days after the third treatment. The treatment consisted of the administration of three products, two of them injectable and a third topical:

- Vial 1: injectable for subcutaneous action. Assets specially designed to act in depth, nourish and protect the tissues that offer trophic support and provide structural basis for the upper layers. Active principles: glycine, proline, lysine, leucine, alanin, hialuronic acid, decapeptide-4, oligopeptide-24, lipoic acid, thiamin, cyanocobalamin, adenine.
- Vial 2: intradermal injectable product specifically designed to act where proteins such as collagen, fibrin or elastin are synthesized. Improves skin mechanical properties. Active principles: centroxifenoxine, ascorbic acid, sodium lactate, copper gluconate, zinc gluconate, condroitin sulphate, tripeptide-6.
- Vial 3: cosmetic topical product. This cream on the most superficial layers of the skin (epidermis) producing a tensor effect, immediate and lasting. Active principles: glutapeptide, cafesilane C2, celutrat, raffermine, sesaflash, lecithin.

Aflax MLT® protocol must be administered by a physician.

Procedures prior to treatment

Before starting the treatment, skin mechanical properties were evaluated with a cutometer /MPA 580, Courage + Khazaka Electronic GmbH, Cologne, Germany). The Cutometer® measures the elasticity of the skin by means of pressure (suction) that deforms the skin. The resistance of the skin to the negative pressure is related to the firmness and its ability to return to the initial position. All parameters are shown as curves in real time during the measurement. This device allows the obtainment of information about the elastic and mechanical properties of the skin and to quantify objectively its efficiency[6-7]. Measurements were taken at a pressure of 450 mbar, through a 2 mm probe hole. Cutometry parameters were: suction 2 seconds (on), 10 repetitions and 2 seconds between suction (off).

Treatment protocol

The treatment protocol included 3 sessions of AFLAX MLT® multilevel therapy in the abdomen, in a period of 1 month. Each session lasted approximately 20 minutes and was performed by the same physician and in the same facilities. Every session, included the application of the 3 AFLAX MLT® products (vial 1, vial 2 and cream): i) vial 1 was injected at a depth of 5-6 mm through a slow, retrograde, fan technique, with a 27G / 40mm needle; ii) vial 2 was injected intradermally (3 mm), with a 30G1/2 needle: iii) and vial 3 was applied topically in the consultation. The patient was given the tube of cream for a home-based application during the following 10 days, in the same area and once a day, until the next session.

Post treatment evaluation

After each treatment, pain was assessed with a visual analog scale (VAS), classifying it from 0 to 10 (0: no pain and 10: maximum pain that the patient was able to imagine).

30 days after the third therapeutic session, patient and

physician satisfaction was evaluated, using a subjective 1 to 5 scale (1: not satisfied, 2: I am not sure, 3: a little bit satisfied, 4: satisfied and 5: very satisfied).
30 days after the third therapeutic session cutometry was performed again. R0, R2, R5 and R7 variables were re-evaluated with the Cutometer®MPA 580.
At each treatment and follow-up visit, any adverse effects and its characteristics were recorded.

Evaluation of the data

Analyzed variables were: age, patient and researcher satisfaction (outcome), pain and cutometry variables (R0, R2, R5 and R7):

- **R0**: Parameter that shows the maximum amplitude of the curve and represents the passive response of the skin to force (firmness).
- **R2**: represents the gross elasticity, which is the resistance versus return capacity
- **R5**: represents the net elasticity: elastic portion of the curve
- **R7**: Assesses the portion of the elastic curve compared to the complete curve. The closer is to 1 (100%), the more elastic the curve.

Side effects were recorded at every visit.

Statistical analysis

Unless otherwise indicated, quantitative variables are described as the mean followed by the standard deviation (SD) between brackets, while categorical variables are described as a percentage. Statistical analysis included appropriate measures for statistical significance (Student's paired two-sample t test) using the standard cutoff for significance of P<0.05 via Microsoft Excel.

Results

The study included 39 female patients, with an average age of 45.80 (10.09).

Skin characteristics

Before treatment, the mean results of skin cutometry were: R0 = 0.28 (0.05) mm, R2 = 0.65 (0.09) mm, R5 = 0.42 (0.07) mm and R7 = 0.33 (0.04) mm. After 30 days of the third treatment, the results were: R0 = 0.34 (0.05) mm, R2 = 0.76 (0.07) mm, R5 = 0.48 (0.07) mm and R7 = 0.33 (0.04) mm. The differences between the pre- and post-treatment values were statistically significant for all variables R0 p <0.0001, R2 p <0.0001, R5 p = 0.0003 and R7 p <0.0001 (*Figure 1*).
The percentages of improvement of the characteristics of the skin at 30 days after the third treatment were: 22.91% for R0, 16.82% for R2, 14.40% for R5 and 20.73% for R7.
R0: Parameter that shows the maximum amplitude of the curve and represents the passive response of the skin to force (firmness). **R2**: represents the gross elasticity, which is the resistance versus return capacity. **R5**: represents the net elasticity: elastic portion of the curve. **R7**: Assesses the portion of the elastic curve compared to the complete curve. The closer is to 1 (100%), the more elastic the curve.

Subjective evaluation

The subjective evaluation of the treatment by the patients, 30 days after the third treatment with AFLAX MLT® was: 35.90% 5 points "very satisfied", 53.85% 4 points "satisfied", 10.26% 3 points "a little satisfied", 0% 2 "I'm not sure", 0% 1 "not satisfied".
The subjective evaluation of the treatment by the researcher, 30 days after the third treatment with AFLAX MLT® was: 28.21% 5 "very satisfied", 53.85% 4 "satisfied", 12.82% 3 "a little satisfied", 5.13% 2 "I'm not sure", 0% 1 "not satisfied".

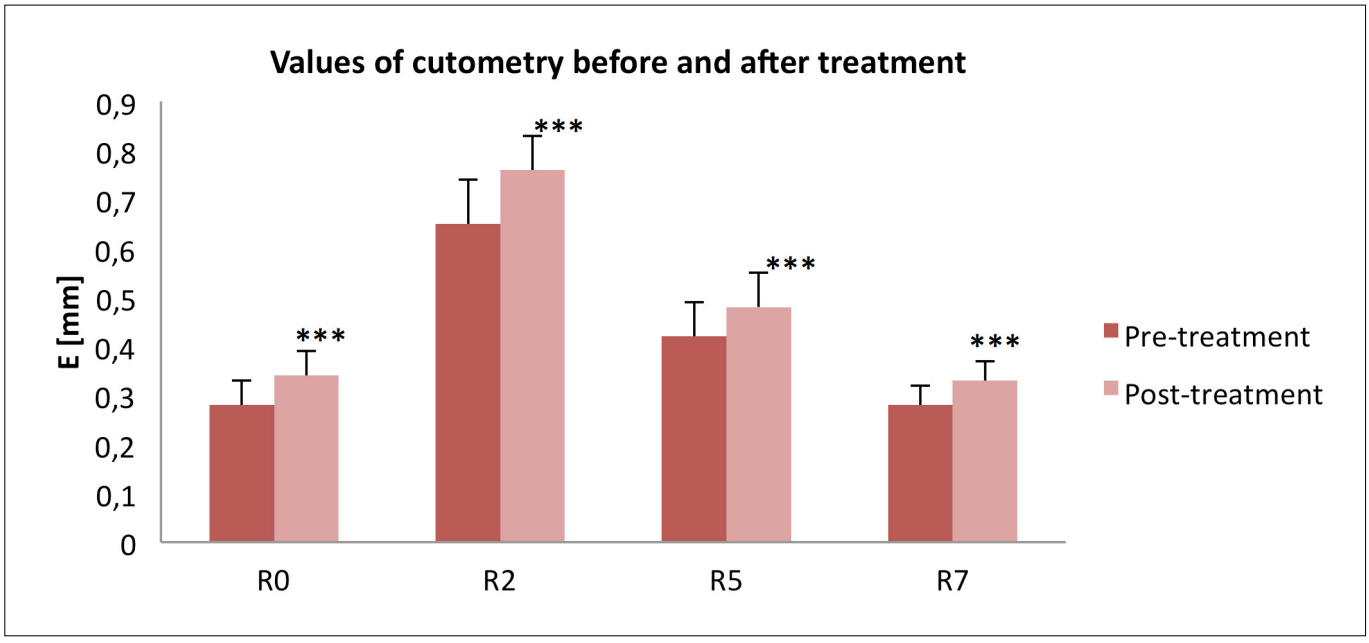

Figure 1 *- Mean result of cutometry parameters obtained before treatment and 30 days after the third session.*

The average of the subjective assessment by the patients included in the study was 4.26 ± 0.64 and 4.05 ± 0.79 by the researcher. The differences between the two assessments were not statistically significant (p = 0.2010).

Pain assessment

The average value of pain assessment by the patients after the application of each product of AFLAX MLT® treatment, by a VAS scale: was: 2.33 ± 1.44 for vial 1; 2.77 ± 1.51 for vial 2 and 0.03 ± 0.16 for cream. The differences between vial 1 and vial 2, both administered by injection with 27G and 30G1/2 needle respectively, were not statistically significant (*Table 1*)

Safety data

The only adverse effects observed were the usual mild inflammatory signs after a puncture. All resolved within few days.

Discussion

The results of the study show that AFLAX MLT® multilevel therapy improves the mechanical properties of the skin, significantly increasing firmness and elasticity. Both the patients and the researcher evaluated positively the results. The treatment was well tolerated by the patients, without observing adverse effects. AFLAX MLT® multi-level treatment is designed for each product to act at the proper level and help replenish the original structure of the tissue that has deteriorated over time. Each product contains different actives and its action targets a specific depth of the skin.

This approach is based on the multi-factorial physiopathology of flaccidity. The results obtained are good and patients´ appearance is natural. This treatment is indicated when the first symptoms of skin aging appear, so that it could delay the onset of the visible signs of flaccidity and restore the damage. These statements can be made after reviewing the results of the cutometry, a validated technique that analyzes the mechanical behavior of the skin and thus, the repercussion of age-related changes and photo-aging. R parameters recorded an important increment in skin firmness compared to the basal values. Other treatments, such as injected conditioned autologous serum, have also reported an improvement in skin characteristics, but the results have not been as good as the ones reported in this study, with AFLAX MLT®. Increments of 10.38% in R0, 16.59% in R2, 11.21% in R5 and 16.16% in R7 were reported[8]. Other techniques such as non-invasive treatment with ultrasound, have also reported the amelioration of the mechanical properties of the skin. A study assessed the improvement of normal skin after the application of ultrasound, obtaining an improvement in firmness (R = 0) of 15.95%, and 5.52% in the elastic component (R2)[9].

Conclusions

The multi-level treatment AFLAX MLT® offers a minimally invasive option, with no important side effects and with significant results that improve the mechanical characteristics of the skin in a natural way. However, more studies would be needed with a greater number of patients, in which men were included and with longer follow-up. Likewise, the duration of the treatment effect should be evaluated and assessed to see if it is possible to improve the result by administering a greater number of sessions and analyze whether it offers the same benefits in other areas of the body.

Conflict of interests

None.

	vial 1		vial 2		cream	
Scale score VAS	patients	%	patients	%	patients	%
0	3	7.69	0	0.00	38	97.44
1	9	23.08	9	23.08	1	2.56
2	12	30.77	9	23,08	0	0.00
3	6	15.38	12	30.77	0	0.00
4	5	12.82	3	7.69	0	0.00
5	4	10.26	4	10.26	0	0.00
6	0	0.00	1	2.56	0	0.00
7	0	0.00	1	2.56	0	0.00
8-9-10	0	0.00	0	0	0	0.00

Table 1 *- Patients' pain assessment after the application of each product.*

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aesthetic medicine

Original Article

Results of practical application of fibroblasts in treating age-related skin changes. An open, prospective, non-randomized study

Anna Tsepkolenko[1], Aleksandr Litus[2], Vladimir Tsepkolenko[3]

[1]Dermatologist at Institute Virtus, postgraduate student of the dermatovenerology department at P.L. Shupik National Academy of Postgraduate Education
[2]MD, PhD., Professor, head of the dermatovenerology department at P.L. Shupik National Academy of Postgraduate Education
[3]MD PhD., Professor, director of Institute Virtus, professor of the dermatovenerology department at P.L. Shupik National Academy of Postgraduate Education

Abstract

Growth factors and inflammatory cytokines of platelet origin effectively stimulate proliferative and synthetic ability of fibroblasts thus justifying their use for increasing the efficiency of cell therapy in correcting aging skin involutionary changes.

Objective: present the results of practical application of neofibrolifting method based on the ability of growth factors and cytokines to stimulate the functional activity of connective tissue and immune cells with the following autologous dermal fibroblasts transplantation.

Methods: the research work included 60 women of different age who turned to the Institute of Plastic Surgery and Cosmetology "Virtus." Platelet-rich plasma was processed using automatic centrifuge Harvest Smart PReP2 (USA). The material for achieving and culturing dermal fibroblasts was harvested using punch-bioptate from the postauricular area. The research employed the method of ultrasound dermoscanning using «DUB - Digital Ultraschall Bildsystem-tpm» device and DUB- SkinScan ver. 3.2 software (Germany). Multi Skin Test Center® MC 1000 (Courage+Khazaka electronic GmbH, Germany) system was applied for moisture tests and its evaporation. The blood flow was determined by Doppler scanning ("Minimax-Doppler-K" device St. Petersburg, Russia).

Results: involutionary skin changes development with ageing is defined by progressively decreased epidermal, dermal thickness, acoustic skin density, its hydration, increased transepidermal loss of water and slow blood flow rate.

As a result of the application of the developed neofibrolifting approach with transplantation of dermal autofibroblasts into skin, conditioned by administration of platelet-rich plasma in all age groups of female patients we observed obvious correction of involutionary facial skin changes in the course of the twelve months of the conducted research.

Conclusion: anti-ageing neofibrolifting is based on the administration of selectively chosen young fibroblasts taken from the culture and implanted into the area enriched with growth factors and inflammatory PRP-cytokines. This method represents an effective way of correcting aging skin involutionary changes.

Keywords

Skin, aging changes, rejuvenation, autologous dermal fibroblasts, PRP, neofibrolifting

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Correspondence

Vladimir Tsepkolenko, MD PhD.

Institute Virtus: Sudostroitelnaya 1, Odessa, Ukraine.
Phone: +380503164088

Introduction

As it is known the leading and prompting role of involutionary skin changes genesis is caused by abnormal microcirculation based on endothelial and immune dysfunction as well as structural and functional alterations in intercellular matrix (ICM), represented by the consequences of mainly quantitative and functional interruptions in systemic interaction of connective tissue and immune cells [1-4].

Along with that, objective characteristics of involutionary skin changes with well-known clinical signs can be achieved using instrumental skin assessment to make it more specific.

Nowadays, autofibroblasts have proven their efficiency in correcting facial contour, various folds, wrinkles, and atrophic scarring. Satisfactory clinical effect was observed after three transplantation procedures and lasted for some months[5-6]. It is convenient that the biopsy can be repeated many times, cells can be obtained at early passages with the possibility of cryobanking until the next time application. Safety and efficiency of dermal fibroblasts autotransplantation have been proven by the results of many multi-central randomized placebo-controlled double-blind clinical studies[7]. Until now, the most well-known and officially recognized technology of dermal autofibroblasts application was developed in the USA, LAVIV (azficel-T) by Fibrocell Science company. In 2011, FDA (Food and Drug Administration) authorized Fibrocell Science with the right to use LAVIV (azficel-T) for nasolabial folds correction[7].

However, despite the quite convincing results of fibroblasts autotransplantation, the obtained effect is not always satisfactory neither regarding the clinical manifestations nor the duration of action. Therefore, currently, new approaches are being developed to the method, sometimes combining it with transplantation of cells with different tissue origin.

A new way of using platelets properties in the course of their co-transplantation with fibroblasts is currently being developed. However, there has yet to be presented convincing evidence of such an approach's effectiveness in cosmetology at this point. Nowadays platelet functions have demonstrated a fundamentally new, unexpected side. As it turned out, the platelets actively participate in inducing inflammation, necessary to prompt the immune reflex, renewal, and formation of immunological response via the cells of native and adaptive immunity (containing TLR-2, TLR-4, TLR-7 i TLR-9)[8]. They produce lots of growth factors as well as other biologically active substances. According to the available data, platelet granules contain 827 proteins[9] and their secretion provides cross-coupling of platelets, immune and stromal cells.

It has been shown that fibroblasts stimulated by cytokines respond with the synthesis of collagen and non-collagen proteins[10]. Administration of platelets or their products prior to dermal fibroblasts leads to the limited, moderate inflammation. It may create the conditions for adequate influence upon the transplanted fibroblasts of inflammatory cytokines which in their turn, provide a positive selection of young cells and stimulate their activity. In this way an increase of cellular efficiency of autofibroblasts can be achieved, transplanted following the platelets, and therefore, we can expect an increased number of young skin fibroblasts because of their high remodeling activity.

In the view of the above said and considering the main function of fibroblasts, at the heart of the method of involutionary changes correction development called neofibrolifting lies the idea of autotransplantation of exactly these cells. Based on the information regarding the fibroblasts properties in *ex vivo* cultures as well as currently known powerful stimulatory action, we designed the method which implies prearrangement of moderate and positive inflammation using the platelet-based product. As a result we influence fibroblasts and inflammatory immune system cells with the following transplantation of autofibroblasts in the initially prepared area.

Objective

Throughout this article we would like to present the results of practical use of neofibroblifting method, which is based on stimulation of connective tissue and immune cells by means of growth factors and cytokines followed by administration of autologous dermal fibroblasts.

Materials and methods

Characteristics of the study: open, prospective, non-randomized study

Study population

The study involved female patients who turned to the Institute of Plastic Surgery "Virtus" for cosmetological assistance, with concerns regarding the process of involutionary skin changes. They were divided into 4 age groups: 25-35 y.o. (n=13), 36-45 y.o. (n=16), 46-55 y.o. (n=18), 56 and older (n=13).

Inclusion criteria

Prior to participation in the research program all patients were examined by a dermatologist, physician, surgeon, endocrinologist and clinical immunologist.

Exclusion criteria

In cases of existing pathology that required treatment, patients received necessary recommendations and were excluded from the program of involutionary skin changes correction.

Protocol used

The material for obtaining and culturing dermal fibroblasts was obtained from the postauricular area punch-bioptate using the 3.5 mm punch-needles. Following the mechanical morcellization, the achieved tissue fragments were transferred to the Petri dish into the warm (37,0±0,5°C) growth medium DMEM/F12 with L-glutamin (CTS™ GlutaMAX™-I Supplement, Gibco), 1% non-essential aminoacids (MEM Non-Essential Amino Acids Solution, 100×, Gibco), 9 nmol main fibroblasts growth factor (FGF-Basic (AA 1-155) Recombinant Human Protein, Gibco), 15% fetal bovine serum (Fetal

Bovine Serum, Gibco) and 0.5% antibiotics (Penicillin-Streptomycin, Gibco). Then the dishes with the material were placed into CO2-incubator. The culture medium was changed every 3-4 days.

Plasma rich platelets (PRP) were extracted out of 20 ml of the patients' whole venous blood. For that purpose, a Harvest Smart PReP2 centrifuge (USA) was used. For structural skin changes evaluation an Ultrasound dermal scanning method by means of mobile high-frequency US device «DUB - Digital Ultraschall Bildsystem-tpm» with Software DUB-SkinScan ver.3.2 (Germany) was used. Epidermal hydration level was evaluated using corneometry, based on the measurement of electric capacity of dielectric medium. Examination of the epidermal barrier function was carried out by measuring skin surface moisture evaporation, transepidermal water loss (TEWL).

The studies employed the diagnostic system Multi Skin Test Center® MC 1000 (Courage+Khazaka electronic GmbH, Germany). For blood flow testing an ultrasound Doppler scanning (device "Minnimax-Dopler-K", St.Pete, Russia) was used. Blood flow rate in microcirculatory bloodstream was measured using the sensor with emission frequency of 25 mHz. Additionally, volumetric blood flow rate skin control, forehead and mental area was performed (Qas in ml/sec/cm).

For the interpretation of the results the critical value of significance level was considered 0.05.

The obtained results were processed using the variational statistics methods and Excell (MS Office XP). As a means of descriptive statistics for quantitative measure, the mean (M) value with standard deviation (±SD) was used as well as the Student parametric statistics (t).

Treatment method

Neofibrolifting technique was performed the following way: PRP was administered intradermally at the amount of 14 ml. After 2 weeks, the same area was treated with intradermal transplantation of 60 mln autofibroblasts. Bioptates harvesting for the research was performed prior to the treatment, 2 weeks after PRP administration and then 2 weeks afterwards, on the 6th and 12 months after the fibroblasts autotransplantation.

On certain dates, clinical lab and instrumental exams were performed.

Results

As shown in *tables 1-7*, neofibrolifting resulted in the essential improvement of structural and functional skin parameters (*Table 1*).

Table 2 shows that the dermal thickness essentially increased in the youngest group as a result of PRP action and remained thick up to six months after the administration of fibroblasts, having normalized after twelve months. Such an easy enhancement might be the evidence of the so-called reserve of regeneration mechanisms at a relatively young age. In three other older groups, a considerable increase of dermal thickness took place just six months after autotransplantation and continued increasing up to the twelfth month following the treatment.

Table 3, shows the acoustic skin density also increases as a result of neofibrolifting. In two young groups this result took place after six and twelve months following the fibroblasts administration, while in other older groups the skin acoustic density increased already after the PRP administration and remained increased up to the end of the studies and even grew thicker in the 2nd and 3rd groups after twelve months.

Age groups	Epidermal thickness, mkm (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	Fibroblasts	6 months	12 months
25-35 y.o.	103,3±5,2	100,8±4,1	112,1±4,2***	106,4±7,2	101,9±5,5
36-45 y.o.	93,8±4,5	94,2±4,4	97,9±3,8*	97,3±6,4	94,8±4,2
46-55 y.o.	90,2±7,1	97,5±4,4**	98,7±4,9***	99,3±7,0**	99,6±3,3***
56 y.o. and older	88,3±5,1	86,2±4,8	89,8±4,4*	89,4±6,4	88,2±5,0
* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment					

Table 1 *- Epidermis thickness in patients of different age groups in treatment dynamics.*

Age groups	Dermal thickness, mKm (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	Fibroblasts	6 months	12 months
25-35 y.o.	1805±48	1910±48***	1951±38***	1912±36***	1807±39
36-45 y.o.	1583±48	1580±47	1599±52	1656±37***	1688±37***
46-55 y.o.	1543±53	1534±40	1559±35	1614±42***	1645±40***
56 y.o. and older	1486±46	1491±39	1515±38	1558±42***	1612±40***
* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment					

Table 2 *- Dermal thickness in female patients from different age groups in treatment dynamics.*

Age groups	Acoustic skin density, conditional units (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	Fibroblasts	6 months	12 months
25-35 y.o.	106,4±6,8	105,3±4,6	107,9±4,4	112,1±7,8*	115,7±8,2**
36-45 y.o.	99,8±5,2	100,3±4,4	102,9±4,3	107,1±6,0**	114,8±5,7***
46-55 y.o.	92,7±9,1	99,4±4,8*	101,3±4,2**	109,0±6,1***	116,8±5,3***
56 y.o. and older	89,8±7,6	96,5±4,8**	98,2±4,3***	101,5±6,1***	104,3±5,7***
* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment					

Table 3 *- Acoustic skin density in female patients in different age groups in treatment dynamics.*

Analyzing the changes of corneometric and vaparometric values in female patients' skin of different age groups in the dynamics of fibrolifting treatment (*Tables 4 and 5*), it was discovered that the level of skin hydration in all studied groups increased following the treatment, while TEWL gradually decreased.

We can observe pronounced tendency of increasing corneometric indicators after PRP administration in all the studied groups, while considerable increase was shown only in group 3. After fibroblasts administration skin hydration became considerably high in all groups, however the high and level in 12 months was recorded only in the 2nd and 3rd groups.

TEWL indicators influenced by neofibrolifting dropped considerably after 6-12 months following autofibroblasts implantation, except for the older group of patients, where the changes after 12 months period seemed uncertain (*Tables 6 and 7*). In patients of 56 years of age and older, the increased VBF in the forehead area was observed just after PRP administration; proved stimulation in the cheek area was registered after fibroblasts autotransplantation.

Age groups	Corneometry indicators, Od (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	fibroblasts	6 months	12 months
25-35 y.o.	72,0±26,2	74,2±25,7	94,1±30,9*	93,0±26,6*	72,1±23,9
36-45 y.o	60,1±20,9	70,2±24,3	78,2±25,7*	80,8±23,1*	78,3±25,9*
46-55 y.o	49,5±16,3	64,3±22,3*	68,4±22,5*	65,7±18,8*	66,4±22,0*
56 y.o and older	42,3±12,0	48,0±16,6	56,2±18,5*	57,5±16,4**	52,9±17,5

* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment

Table 4 *- Corneometry indicators in female patients of different age groups in treatment dynamics.*

Age groups	TEWL indicators, g/year/m^2 (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	fibroblasts	6 months	12 months
25-35 y.o	11,3±2,1	11,4±4,0	10,9±3,6	9,3±2,7*	8,8±2,4**
36-45 y.o	12,2±4,3	12,3±4,3	10,4±3,5	9,5±2,8**	8,4±2,3***
46-55 y.o	16,0±5,4	14,2±5,0	13,4±4,5	12,4±3,6**	12,5±3,5**
56 y.o and older	19,8±5,8	19,0±6,7	17,3±5,8	15,4±4,5*	16,0±4,4

* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment

Table 5 *- TEWL indicators in patients of different age groups in treatment dynamics.*

Age groups	Volumetric blood flow rate, mkl/sec/cm^3 (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	fibroblasts	six months	twelve months
25-35 y.o.	80,1±64,3	90,2±58,6	103,8±61,5	115,1±95,0	127,3±78,2
36-45 y.o.	79,4±39,1	95,6±53,1	96,5±39,1	128,6±67,1*	138,8±55,9**
46-55 y.o.	62,6±41,9	95,9±67,1	115,7±75,5*	121,7±92,2*	109,3±81,0
56 y.o and older	24,1±30,7	85,7±81,0*	98,0±92,2**	101,4±81,0**	98,9±89,4**

* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment

Table 6 *- Dermal volumetric blood flow rate in the forehead area in patients of different age groups in treatment dynamics.*

Age groups	Volumetric blood flow rate, mkl/sek/cm^3 (M±SD)				
	Before treatment	During the treatment after administration of		After treatment	
		PRP	fibroblasts	6 months	12 months
25-35 y.o.	100,4±44,7	102,7±53,1	129,1±64,3	142,3±69,8	147,9±47,5**
36-45 y.o.	71,4±50,3	81,4±47,5	123,2±61,5*	136,7±50,3**	126,4±75,4*
46-55 y.o.	48,8±41,9	75,2±75,4	123,8±89,4**	125,4±100,6*	120,7±86,6**
56 y.o. and older	31,1±39,1	62,1±50,3	126,4±81,0***	129,4±89,4***	115,4±78,2***

* p<0,05, ** p<0,01, *** p<0,001 – comparison to the indicators before treatment

Table 7 *- Volumetric blood flow rate in the cheek area dermis in patients of different age groups in treatment dynamics.*

Discussion

Involutionary skin changes process was determined by progressively decreased epidermal, dermal thickness, acoustic skin density, its hydration, increased transepidermal loss of water (TWEL) and slow blood flow rate, in the forehead and cheek area that possibly is a proving evidence of the influence of microcirculation disorder that leads to structural and functional skin disorganization. Our studies proved that after the administration of the fibroblasts the epidermal thickness clearly increased in all age groups, while in group 46-55 y.o., it had a demonstratively positive and considerable reaction to the PRP administration (*Table 1*). In the 1st, 2nd and 4th groups the effect was achieved following autofibroblast administration. Positive effect of the procedure related to the epidermal thickness was observed after six and twelve months only in the 46-55 y.o. age group. Increased skin acoustic density as a result of neofibrolifting influence can be explained by the enhanced synthesis of collagen fibers, which represents the key elements, that reflect ultrasound waves in the organized state [Jasaitiene D et al, 2011]. Therefore, according to the structural and functional indicators skin conditions were substantially improved based on such indicators as epidermal and dermal thickness, acoustic density, corneometric and evaporimetric data practically in all age groups, most frequently following the fibroblast administration. The achieved effect lasted for 6-12 months in most cases after autotransplantation It can be assumed that positive skin changes in the process of neofibrolifting treatment can basically be explained by the considerable stimulating therapeutic effect on the volumetric blood flow rate (*Tables 6 and 7*). As it is demonstrated in the presented tables, the volumetric blood flow (VBF) in the course of neofibrolifting increased in the forehead and cheek area. However, in the 1st and the youngest group of patients (25-35 y.o.) the increase in the forehead area was observed only in terms of pronounced tendency and it was only in the cheek area that the increased blood flow was real at the end of observation period. In the group of patients of 36-45 y.o., VBF increased considerably in the forehead area for six months following the fibroblasts treatment and lasted for twelve months. Increased VBF in the cheek area in this group took place immediately after fibroblasts administration and as well lasted until the end of observation. In the group of 46-55 y.o., the

real increase of VBF in both areas took place immediately after autotransplantation and lasted for twelve months of observation, however in the forehead area the increased indicators during the observation period had only pronounced tendency nature.
It is important to note that VBF stimulation at the level of pronounced tendency in both areas in all groups of patients was registered just after PRP administration. Such an obvious consistency even despite the large range of measured values, allows one to assume that PRP administration practically always promotes those necessary fundamental changes that provide further development of transplanted autofibroblasts effect.
Therefore, as a result of the neofibrolifting treatment we can observe pronounced stimulation of age-related structural and functional skin indicators such as: epidermal and dermal thickness, acoustic density, hydration of epidermis and TEWL, as well as VBF in forehead and cheek areas.
The obtained results indicate that aging skin goes through serious structural and functional changes that involve both epidermis and dermis. They have complex and complicated nature and result in the abnormalities of different levels of regulatory mechanisms. That is why dermal fibroblasts stop receiving enough metabolic microcirculatory support, and are negatively influenced by endothelial dysfunction, which is largely developed by immunologic mechanisms. Apparently, understanding the immunopathology process of skin aging mechanism and its influence over the development of involutionary changes has become the key issue in the aging skin regeneration approaches.

Conclusion

1. As a result of neofibrolifting, VBF rate essentially increases under the influence of fibroblast autotransplantation. PRP administration can strongly influence indicators mainly in the forehead area and only in the group of patients at the age of 56 and older. However, in all cases, obvious regenerative tendency can be observed.
2. All structural and functional aging skin indicators can be largely normalized by using neofibrolifting. PRP administration in some cases could lead to positive results, however, the “complete” neofibrolifting, that is PRP combined with autofibroblasts led to the promotion of regeneration and normalization of functional and structural indicators. Most studies which demonstrated a regeneration of aging skin were observed over the whole period following the treatment of twelve months.

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Conflict of interests

The Authors declare no conflict of interests or funding.

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aesthetic medicine

Original Article

Cryolipolysis with active vacuum technology and simultaneous stimulation of the microcirculation in body reharmonization: comparative study on 40 patients divided into 2 cohorts

Fabrizio Melfa[1], Daniela Gaetana Caruso[2], Michela Maggi[3]

[1]MD, MSc, Lecturer at the University of Pavia, Pavia, Italy, and Founder of the Mediaging Program, Palermo/Milano/Catania, Italy
[2]MD, Aesthetic physician in private practice, Mediaging program, Catania, Italy
[3]Medical engineer, laser and technical equipment expert

ORCID: https://orcid.org/0000-0002-1009-0527

Abstract

Background: cellulite is a common syndrome. Many studies have examined whether cellulitis should even be considered a disease. The nature of cellulite is linked to different physical and hormonal factors as well as to lifestyle and is characterized by the presence of localized adiposity and weight increase.
Aim: we aimed to measure the clinical and scientific value of cryolipolysis treatment combined with bioactive currents. We studied both the effectiveness of cryogenesis on adipose tissue and the action of 50-Hz current pulses on tonicity.
Methods: enrolled patients were evaluated with an anthropo-plicometric examination, ultrasonography, blood tests, and photographs and divided into two groups: one group maintained a low-calorie balanced diet and the other group combined the same diet with cryolipolysis treatment. The cryolipolysis device used in the study had an active no-inertial vacuum technology for the maintenance and integrity of the vascular system, suffering if subjected to cryogenesis and aspiration. Bioactive currents preserved the functionality of the cells and tissue oxygenation. Results were obtained at baseline and at 8 weeks after treatment delivery. We call this specific device cryoliposculpt.
Results: we enrolled 40 patients (mean age, 43 years), 20 patients in each group. Average decreases in treated adiposity and cellulite with accompanying improvement in dermoepidermal tissues were greater in the group treated with a low-calorie balanced diet plus cryolipolysis than in the diet only group.
Conclusions: cryolipolysis combined with bioactive currents produced measurable improvements at 8-week follow-up, even after only one treatment session. The ability to manage the controlled food program, by patients submitted to cryoliposculpt than others was better.

Keywords

Cryoliposculpt, cryolipolysis, cellulite, adipose tissue

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Correspondence

Fabrizio Melfa, MD, MSc

Mediaging Program
Address: Via M. D'Azeglio, 27/c - 90141 Palermo, Italy
E-mail: dottormelfa@gmail.com

Introduction

Cellulite is a very common syndrome, universally characterized by the accumulation of localized adiposity and increased body weight[1,2]. The condition is so prevalent (especially in women) that many studies have sought to determine whether it is a pathologic occurrence or should even be considered a chronic disease precisely because it is so common. Although it is very difficult to define a condition that is not considered pathologic, if a condition affects quality of life, it becomes pathologic. Scientific research tells us that although the genesis of so-called cellulitis is linked to causal, hormonal, genetic, circulatory, and lymphatic factors, it also depends on the subject's lifestyle.

In the last few years, different modalities have become available for the noninvasive reduction of adipose tissue, including radiofrequency and low-energy laser procedures, high intensity focused ultrasonography, and cryolipolysis[3].

In March 2018, an American Society of Plastic Surgeons Report showed a rise in body shaping and non-invasive procedures; the statistics also reveal Americans are turning to new and innovative ways to shape their bodies, as minimally invasive cosmetic procedures have increased nearly 200% since 2000. More people are choosing to shape different parts of their bodies using ultrasound, radio frequency, infrared light, vacuum massage and injectable medication to reduce fat cells. Non-invasive procedures to eliminate fat and tighten the skin are gaining popularity, with the fastest growing procedure - cellulite treatments - up nearly 20% over last year 2017[4].

The term *cryolipolysis* refers to the gradual and noninvasive cooling of adipose tissue to induce a process called *lipolysis*, or the breakdown of lipids.

Among these technologies, cryolipolysis has been studied most often, both in in vitro animal models and in randomized controlled trials involving humans[5,6].

Scientific studies have shown that under conditions of prolonged exposure to temperatures close to freezing, fat cells are more vulnerable to the effects of cold than surrounding tissues are[7].

Other scientific articles have demonstrated that exposure to cold induces the apoptosis of fat cells and the production of cytokines and other mediators of inflammation that gradually eliminate the cells involved[8]. In the weeks after treatment, macrophages steadily digest the fat cells exposed to cooling, thus reducing the thickness of the treated adipose layer. The lipids derived from the cells are slowly released and transported by the lymphatic system for processing and elimination, as happens with fats derived from food.

Although inflammatory reactions and the in situ recall of cells responsible for the elimination of particles are triggered by cryolipolysis, the therapy does not alter blood chemistry values. This finding indicates that the technology is noninvasive compared with other techniques[9].

The low rate of adverse effects associated with cryolipolysis is, in fact, the main reason doctorsand patients prefer this technology over others[7].

The first target of a body remodeling treatment is certainly to guarantee the best result, one that is tangible, lasting, and maximally safe in terms of collateral risks[10] and ineffective outcomes. In this study, we combined the destruction of adipose cells with the simultaneous emission of modulated currents (50-Hz pulses) to sculpt the dermal-epidermal profile (cutaneous), while improving the elasticity of the skin and preserving uninvolved tissues. The use of cold temperatures combined with a vacuum exploits the principles of cryogenesis and cryocyanogenesis, which act on areas with excess fat, facilitating its disposal. As stated previously, after treatment, an apoptotic process is triggered in the adipocytes, which leads to a natural, physiological death. The cells of the immune system determine the natural disposal of damaged adipocytes[1].

Our approach to this retrospective study was to demonstrate the irrefutable and certain validity of cryoliposculpt treatment through the analysis of data and presentation of the results.

Materials and Methods

A total of 40 patients were involved in our retrospective study, divided into two cohorts. Inclusion criteria included an age between 20 and 66 years, presence of localized adiposity and so-called Cellulite (PEFS - Edematofibrosclerotic Panniculopathy), in diet treatment by weight loss with personalized diet. Exclusion criteria: patients in pregnancy / lactation, renal / hepatic insufficiency, previous cardiac pathologies and / or in pharmacological treatment.

For this study, recruitment of patients was ultimately based on choice of anatomic area and thickness of the fat layer and recognition that cryolipolysis is not recommended for everyone (ie, it is indicated for localized adiposity rather than for obese patients and is most suitable for "body sculpture"). All subjects were evaluated after undergoing a medical examination, an anthropoplicometric examination, ultrasonography of the panniculus adiposus, and blood tests. Patients were assigned to one of two groups: patients who followed a balanced low-calorie diet only or patients who followed a balanced low-calorie diet and underwent a body rehabilitation protocol with cryolipolysis combined with bioactive currents in different areas (Cryoliposculpt).

Every 15 days the weight was checked and the measures of waist, hip, abdominal line, buttocks circumference, thigh root and thigh median were evaluated. Photographs were taken before and after the evaluation period because it has been shown that cryoliposculpt also induces action on fibroblasts over time[11]. The evaluations of our retrospective and observational study were conducted at T0 (baseline) and at T1 (ie at 8 weeks from the beginning of the therapeutic program) as inspected by other studies in the literature[7]. All the raw data collected, of the anthropometric measurements already specified, have been elaborated and produced using statistically relevant graphs.

The cryolipolysis device used in this study is called Cryoliposculpt. It has unique technical characteristics that guarantee the efficacy and safety of the treatment while preserving cellular structures and their functionality. The applicator generates aspiration through an active vacuum, which sucks the treated area inside a cavity, where it comes into contact with two

cooling elements. These cooling elements reduce the temperature by 8°C to 10°C. A contact sensor constantly monitors the surface temperature of the skin to ensure safety and efficacy throughout the treatment (*Figure 1*). The active non-inertial vacuum, which is continuous and customizable (with respect to the mechanical resistance of the tissues), preserves local microcirculation.
In addition to an inertial vacuum, the device allows delivery of a cycle of modulated microcurrents emitted in succession (spikes of current at 50 Hz) in a random way that does not induce adaptation in the cells. The microcurrents act on the extracellular interstitium, the microcirculation, and the remodeling and orientation of the collagen fibers without inducing a joule heating in contact with the tissues[12].

During treatment, the applicators were positioned on the area of the body where the patient hoped to reduce fat. An inverse thermal shock was applied to the underlying adipose tissue, cooling it to freezing, while avoiding other tissues. Although the tissues were under a negative pressure of about 30 mm Hg for 50 minutes during standard treatment, the constant mobilization of the tissue ensured there was no vascular damage or atrophy of the microcirculation; thus, no post-treatment massage was necessary[13] (*Figure 2*).
The other Cryolipolysis machines on the market cause the formation of the "stick of butter" and, therefore, to avoid problems are matched as a result of the treatment or manual massages[14] or shock waves to accelerate the process of 'restitutio ad integrum' of the treated tissues[15].

Figure 1 *- Cryoliposculpt treatment with 4 hand pieces.*

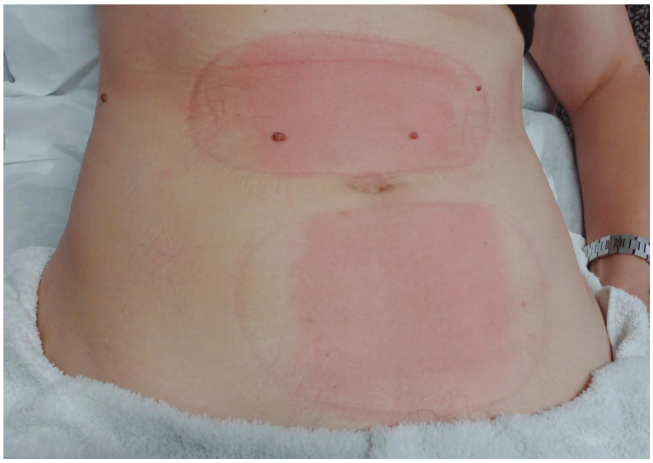

Figure 2 *- Patient abdomen immediately after treatment with cryoliposculpt.*

Results

We enrolled a total of 40 patients with localized fat and cellulite (average age, 43 years). Of these, 20 patients were treated with a personalized balanced low-calorie diet and cryoliposculpt and 20 patients followed only a personalized balanced diet. After measuring the previously indicated areas (waist, hips, abdominal line, buttocks, thigh root and thigh median) at T0 and T1, in this retrospective study we observed in the cohort that performed both the diet and the cryoliposculpt, better results compared to the cohort that only performed the diet. All 40 patients performed a similar personalized diet. We observed that the cohort patients who did both the diet and the cryoliposculpt, were much more adherent and precise in following the dietary indications achieving better weight loss results. From the measurements measured at T0 and T1, in the areas already specified, we observed a quantitative improvement in localized fat deposits and treated cellulite (*Figure 3*). In patients treated with cryoliposculpt, we observed a marked improvement in the dermoepidermal tonicity of the treated areas. We verified with these patients the results, using a verbal questionnaire concerning the result obtained on a scale from 0 to 3 (0 = null result, 1 = discrete, 2 = good, 3 = excellent), which confirmed our observation. These observations were also confirmed by the photographic documentation carried out at T0 and T1, with frontal, rear, right lateral and left lateral views, using a standardized grid for the position of the feet. The evaluation of the photos was made by us

doctors and by the patients themselves. *Figure 3* shows the average measurements reported between T0 and T1 (ie, 8 weeks from the beginning of the therapeutic path), the period necessary to determine real results of the treatment[7]. We managed to reduce the average waist circumference by 3.65 cm with combined cryolipolysis and diet versus a 1.65-cm reduction with diet alone, a greater than twofold difference between the groups. The most striking and significant result was evident in the side area, with an average reduction of 4.55 cm in the combined cryolipolysis and diet group compared with 0.275 cm with diet alone, an approximately 16-fold difference between the groups. In the abdominal area, average reductions were approximately 6 cm and 1.7 cm, respectively. In the buttocks, average reductions were 7.9 cm and 1.4 cm, respectively. In the thighs, reductions of 3.35 and 2.625 cm were observed in the cryoliposculpt and diet group compared with reductions of 1.05 cm and 1.275 cm in the diet only group (*Figure 4 and Figure 5*). We therefore deduce that a therapeutic treatment program that includes cryoliposculpt and a balanced and controlled diet facilitated reductions in circumference in different areas of the body that were approximately 4 times greater than those produced by diet alone.

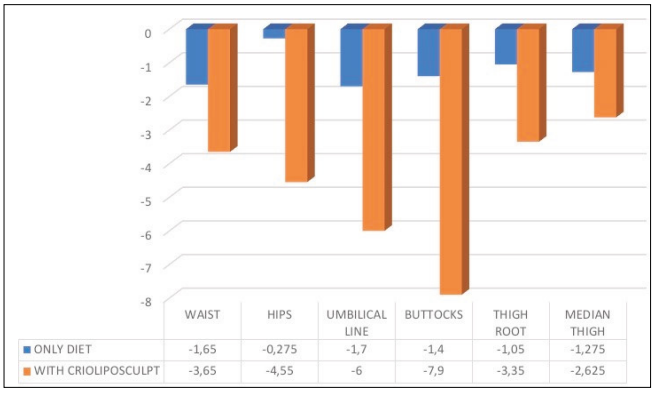

Figure 3 *- Average reductions (in centimeters) of different anatomic areas between patients who were treated with a low-calorie diet alone and patients who were treated with cryoliposculpt in addition to the diet.*

PATIENTS TREATED ONLY WITH THE DIET

PATIENTS	T0						T1						weight loss	DIFFERENCE T0 - T1					
	waist T0	hips T0	umbilical T0	buttocks T0	Thigh root T0	median thigh T0	waist T1	hips T1	umbilical T1	buttocks T1	Thigh root T1	median thigh T1		waist	hips	umbilical line	buttocks	thigh root	median thigh
	cm	cm	cm	cm	cm	cm	cm	cm	cm	cm	cm	1	Kg	CM	CM	CM	CM	CM	CM
P1	71	90	79,5	96,5	59,5	55	70,5	90	76	94	59	55	1,8	-0,5	0	-3,5	-2,5	-0,5	0
P2	111	116	110,5	110	68	63	110	117	111,5	110	66,5	62	1,6	-1	1	1	0	-1,5	-1
P3	95,5	101	98,5	103	62,5	56	89	99	96,5	99,5	57,5	53	3,3	-6,5	-2	-2	-3,5	-5	-3
P4	99,5	100	101	101	59	55	95	90	98	98	58	54	2,6	-4,5	-10	-3	-3	-1	-1
P5	79	64,5	83	90	54	49,5	72,5	86,5	77	87	51	48	3,4	-6,5	22	-6	-3	-3	-1,5
P6	96	100	100	99	59	49	90,5	98	93,5	91,5	55	47	4,8	-5,5	-2	-6,5	-7,5	-4	-2
P7	87	87	92,5				83	85	87				3	-4	-2	-5,5	0	0	0
P8	87	94	95				93	98,5	101				-0,8	6	4,5	6	0	0	0
P9	84	92	90	91			87	92	90	88			0	3	0	0	-3	0	0
P10	71	91,5	81,5	91	57	51	65,5	88	75	88,5	55	50	3,1	-5,5	-3,5	-6,5	-2,5	-2	-1
P11	82,5	92,5	85	93,5	57,5	51	80	89,5	83	93,5	55	50	3,7	-2,5	-3	-2	0	-2,5	-1
P12	88	101	89	95	50	53	89	99	88	95	51	42	0,5	1	-2	-1	0	1	-11
P13	81	98	89	85	53	46	82	98	91	96	53	45	-2	1	0	2	11	0	-1
P14	70	89	81	95	55	49	68	88	79,5	93	53,5	48	2,9	-2	-1	-1,5	-2	-1,5	-1
P15	61	77	66,5	85	51	45	62	78,5	68,5	85,5	54	47,5	0,7	1	1,5	2	0,5	3	2,5
P16	97	118	108	127	73	61	97,5	118	106	126	74	61	0,7	0,5	0	-2	-1	1	0
P17	97	116	98	119	68	59	97	115	100	120	69,5	59	1,6	0	-1	2	1	1,5	0
P18	78	98,5	90	98,5	56	50	76	94,5	88	95	55,5	48,5	7	-2	-4	-2	-3,5	-0,5	-1,5
P19	83	95,5	91	103	61	48	80,5	95	89	99	58	47	3,1	-2,5	-0,5	-2	-4	-3	-1
P20	80	101,5	90,5	101	59	49	77,5	98	87	96	56	47	2,7	-2,5	-3,5	-3,5	-5	-3	-2
													2,185	MEDIUM	-1,65	-0,275	-1,7	-1,4	-1,05	-1,275
													2,02	STANDARD DEVIATION	3,27	5,95	3,23	3,62	1,99	2,55

Figure 4 *- Raw data and statistical evaluations of the cohort of patients treated only with the diet.*

PATIENTS TREATED WITH DIET AND CRYOLILYSIS

PATIENTS	T0						T1						weight loss	DIFFERENCE T0 - T1					
	waist T0	hips T0	umbilical T0	buttocks T0	Thigh root T0	median thigh T0	waist T1	hips T1	umbilical T1	buttocks T1	Thigh root T1	median thigh T1		waist	hips	umbilical line	buttocks	thigh root	median thigh
	cm	cm	cm	cm	cm	cm	cm	cm	cm	cm	cm	cm	Kg	CM	CM	CM	CM	CM	CM
P1	65	82	71	90	55	51,5	59	76	60	81	48	46	5,7	-6	-6	-11	-9	-7	-5,5
P2	68,5	93	80,5	100	62	55	64	86	72	93	57,5	52	4	-4,5	-7	-8,5	-7	-4,5	-3
P3	70	96	79	96	58	54	63	85	68	37,5	53,5	50	5,7	-7	-11	-11	-58,5	-4,5	-4
P4	64	85,5	77	96	57,5	49,5	56,5	75	58,5	82,5	48,5	43	8,6	-7,5	-10,5	-18,5	-13,5	-9	-6,5
P5	69	80	76	84	52	47	62,5	77	67,5	79	47,5	45	2,4	-6,5	-3	-8,5	-5	-4,5	-2
P6	81	94	88	91	53	50	75	90	83	87	50	46	4,4	-6	-4	-5	-4	-3	-4
P7	89	104	98	97,5	62	57	84	102	92	91	56	53,5	4,2	-5	-2	-6	-6,5	-6	-3,5
P8	71	94	86	93,5	59	52	69,5	92,5	82,5	91	55	50	1,2	-1,5	-1,5	-3,5	-2,5	-4	-2
P9	86,5	105,5	93	112	65	56	81	101	87	108	60	52	4,7	-5,5	-4,5	-6	-4	-5	-4
P10	64	85	71	85	49	47	65,5	79,5	71,5	84	50	46	-0,4	1,5	-5,5	0,5	-1	1	-1
P11	76	98	92	94	58	50	75	97	90	93	57	49	1,9	-1	-1	-2	-1	-1	-1
P12	79	95	88	90	54	44	79	96	88	87	53	43	1	0	1	0	-3	-1	-1
P13	79	97	86	94	57	48	75,5	89	78,5	87	53	44,5	5,1	-3,5	-8	-7,5	-7	-4	-3,5
P14	90	97	101				84	92	94				11,7	-6	-5	-7	0	0	0
P15	71,5	90,5	80	95,5	57	52	66	80,5	70	83,5	51	46	6	-5,5	-10	-10	-12	-6	-6
P16	78	90	83	98	60,5	51,5	78	89	82	92	58	50	1,7	0	-1	-1	-6	-2,5	-1,5
P17	80	90	86				79	90	84				4,3	-1	0	-2	0	0	0
P18	66	81	74	89	53	47	63	77	68	83	49	44	2,5	-3	-4	-6	-6	-4	-3
P19	80	95	88	86	53	47	76	92	85	84	51	46	2,8	-4	-3	-3	-2	-2	-1
P20	74	96	81	100	53	41	73	91	77	90	53	41	2	-1	-5	-4	-10	0	0
													3,975	MEDIUM	-3,65	-4,55	-6	-7,9	-3,35	-2,625
													2,79	STANDARD DEVIATION	2,71	3,45	4,55	12,51	2,65	1,99

Figure 5 *- Raw data and statistical evaluations of the cohort of patients treated with diet and cryolipolysis.*

Discussion and Conclusions

The results of the present study suggest an important role of cryoliposculpt in the so-called cellulite, as association of cryolipolysis and active microcurrents for the improvement of the tone and texture of the treated tissue.

This new technique was shown to be a good and safe alternative to invasive treatments of adipose tissue[16], even if it remains the gold standard.

Overall, the study demonstrated a reduction in different anatomic areas that was approximately four times greater than that obtained with diet alone.

The safety of all results obtained and efficacy of treatments, in a protocol tested worldwide, lets convalited non-invasive alternatives to body remodeling.

No adverse collateral effects were shown. Damage to and destruction of adipose cells was achieved without adverse effects to nearby tissues and vascular vessels while preserving all cellular functions of the treated tissues that were under mechanical stress and thermal shock inverted. Nerves and bones were also unaffected, and no changes were observed in the main organs of the body[17].

Gradual improvements over time in the thickness of adipose tissues, illustrating the concept of systemic body remodeling, induced physiological - but nontraumatic - reactions in the body.

Overall, we observed greater improvements in areas with a large quantity of adipose tissue; in addition, the biological inflammatory process removed adipocytes over time and reduced the adipose layer.

Thus, adipose tissue freezing offers a potential new option for many people by remodeling the body without any invasive side effects[18].

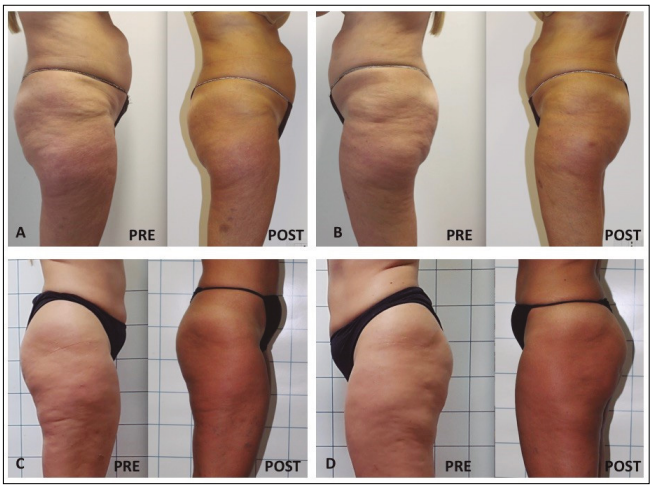

Figure 6 *- (A, B, C, D) – Pre and Post two months after treatment with Crioliposculpt and diet.*

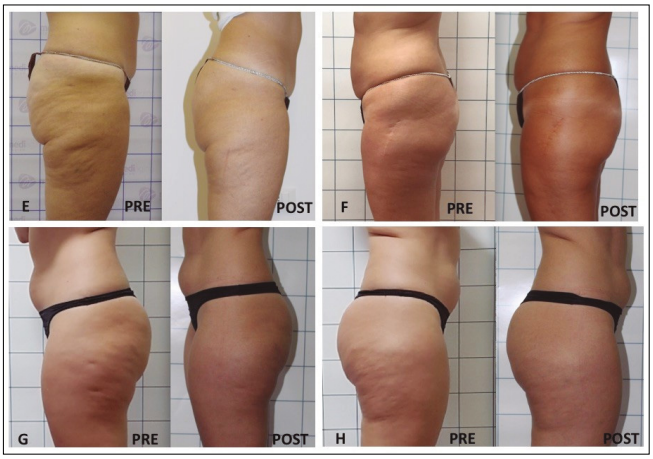

Figure 7 *- (E, F, G, H) – Pre and Post two months after treatment with Crioliposculpt and diet.*

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Conflict of Interest

The authors declare that they have no conflict of interest.

Disclosures

Michela Maggi, she is Biotec scientific consultant and was responsible for training in southern Europe Lumenis

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aesthetic medicine

Review

Dercum's disease or Adiposis Dolorosa: a complex condition still awaiting full definition

Paola Palumbo[1], Benedetta Cinque[2], Francesca Lombardi[3], Lucia Romano[4], Corinna Genovesi[5], Gino Orsini[6], Pietro Leocata[7], Maria Grazia Cifone[8], Maurizio Giuliani[9]

[1]PhD, Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito - 67100 L'Aquila, Italy.
E-mail: paola.palumbo@univaq.it

[2]PhD, Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito - 67100 L'Aquila, Italy.
E-mail: benedetta.cinque@univaq.it

[3]PhD, Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito - 67100 L'Aquila, Italy.
E-mail: francesca.lombardi@univaq.it

[4]MD, Plastic and Reconstructive Surgery Unit, Casa di Cura Di Lorenzo, 67051 Avezzano, L'Aquila - Italy.
E-mail: lucia.romano@graduate.univaq.it

[5]MD, Plastic and Reconstructive Surgery Unit, Casa di Cura Di Lorenzo, 67051 Avezzano, L'Aquila - Italy.
E-mail: corinnagenovesi@gmail.com

[6]MD, Plastic and Reconstructive Surgery Unit, Casa di Cura Di Lorenzo, 67051 Avezzano, L'Aquila - Italy.
E-mail: gino_orsini@libero.it

[7]MD, Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito - 67100 L'Aquila, Italy.
E-mail: pietro.leocata@univaq.it

[8]MD, Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito - 67100 L'Aquila, Italy.
E-mail: cifone@univaq.it

[9]MD, Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito - 67100 L'Aquila, Italy; Plastic and Reconstructive Surgery Unit, Casa di Cura Di Lorenzo, 67051 Avezzano, L'Aquila - Italy. E-mail: maurizio.giuliani@univaq.it

Short title: Dercum's Disease or Adiposis Dolorosa

Abstract

Dercum's disease (DD), also called adiposis dolorosa (AD), is known as a rare, chronic and progressive disorder characterized by multiple, subcutaneous painful adipose tissue masses. DD mainly occurs in overweight or obese adults, mostly post-menopausal women. Pain, which can be severe and often debilitating, is frequently, but not always, associated with generalized weakness and mental disturbances. Other associated symptoms are also recorded but are not common in all cases diagnosed as DD. To date, the etiology remains indefinite and the basis of the pain is not yet clear. Thus, DD is mainly described for its symptoms rather than for the pathophysiological process. In sporadic cases, the condition has been reported to be inherited as an autosomal dominant trait. To date, treatment is still symptomatic and includes liposuction or surgery for the most painful fatty masses and analgesics to control pain. Nonetheless, the symptoms are often uninfluenced by conventional pain therapy. In the present review, we have retraced the most significant historical steps of research and study on DD, mostly highlighting the difficulties in defining pathophysiology, diagnosis and treatment which are mainly due to the wide variability of the findings and clinical signs in the cases described in the literature. The extremely complex picture that emerges should strongly stimulate to develop scientific studies aimed at identifying the etiologic factors of this devastating pathology that, with high probability, is not always recognized and, too often, neglected.

Keywords

Dercum's disease, adiposis dolorosa

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Correspondence

Maurizio Giuliani, MD

Department of Life, Health and Environmental Sciences, University of L'Aquila - Building Delta 6, Coppito. L'Aquila, Italy
Phone: +390862434934
E-mail: maurizio.giuliani@univaq.it

Historical notes

Adiposis dolorosa (AD) was first described in 1892 by the physician, philosopher, neurologist, scientist, Francis Xavier Dercum[1-4], from a case in the Philadelphia Hospital[5]. In this original paper, Dercum described 3 cases of the disease with the gross pathological findings of 2 cases, both of which showed abnormal thyroid glands, thus leading the neurologist to believe that the disease was a clinical entity on the basis of a "*disthiroydia*". This article was preceded by a case report by Dercum himself in 1888[6], as a 51 year-old woman of Irish heritage with severe pain and enlarged subcutaneous adipose tissue on her arms and back.

He wrote: "*Evidently the disease is not simple obesity. If so, how are we to dispose of the nervous elements present? Equally plain is it that we have not myxoedema to deal with. All of these cases lack the peculiar physiognomy, the spade-like hands, the infiltrated skin, the peculiar slowing of speech, and the host of other symptoms found in myxoedema. It would seem then, that we have here to deal with a connective tissue dystrophy, a fatty metamorphosis of various stages of completeness, occurring in separate regions, or at best unevenly distributed and associated with symptoms suggestive of an irregular and fugitive irritation of nerve-trunks - possibly a neuritis... Inasmuch as fatty swelling and pain are the most prominent features of the disease, I propose for it the name Adiposis Dolorosa*".

Dercum regarded the disease as a clinical entity and named it adiposis dolorosa (AD) because of its most characteristic symptom, painful fat.

In 1899 White[7] described an interesting case of AD as follows: "*My patient shrieks when she is gripped...my patient can hardly walk,...My patient goes out of her mind temporarily. Headache is a common symptom.*

Herpes, hematemesis, epistaxis, early menopause, slight pigmentation of the skin, atrophy of the muscles of the hand, and reaction of degeneration of them have all been described as occasional symptoms.

...In my case administration of thyroid did no good....She has been in several hospitals but all with no benefit".

The first clinical classification system for AD (also named Dercum's Disease, DD) was developed in 1900 by Giudiceandrea[8] as follows:

I. Nodular type.

A form with painful lipomas, most commonly on the arms or the legs or on the back or thorax. Sometimes the lipomas occur on multiple locations and occasionally the lipomas form a confluent mass.

The nodules are variable in size and painful on palpation.

II. Diffuse type.

A form with diffusely painful adipose tissue. The pain is symmetric.

III. Mixed type.

A form with diffusely painful adipose tissue and with painful nodular masses.

This classification was then revised in 1901 by Roux and Vitaut[9] which proposed four cardinal symptoms of DD, used as diagnostic criteria for several years[10-17]:

1. *Multiple, painful, fatty masses*
2. *Generalised obesity*
3. *Weakness and susceptibility to fatigue (asthenia)*
4. *Psychiatric manifestations, including emotional instability, depression, epilepsy, confusion, and dementia.*

What was reported by Burr in 1900[18], was then confirmed in 1902 by Dercum[19] who described two other cases of AD and considered the most interesting histological finding to be interstitial inflammation of the nerves in the adipose tissue of the painful sites. In the same year, Dercum and MacCarthy[20] published a case of AD with complete autopsy findings, the main pathological lesion being an "adenocarcinoma" of the pituitary body, while the thyroid appeared regular. Next, several cases were described, many of which showed abnormalities of the pituitary gland[21-24]. DD was also defined as a disorder of the "haemolymph" system by Dercum and McCarthy themselves[20] and "*a general disease of the lymphatic system*" by Mills[25], suggesting that dysfunction in the hemovascular and/or lymphatic systems may contribute to the development of lipomas. As early as 1910, Stern[26] noted that neuropsychiatric disturbances and asthenia did not accompany every case. Cushing in 1912[27] first questioned the rationale of calling the disease a clinical entity, stating that, in his opinion, many cases reported as AD, "*are actually examples of disturbed metabolism secondary to disease of the ductless glands*". In his later articles, Dercum appeared to be of the same opinion. In sections from DD adipose tissue increased levels of connective tissue were described by Myers in 1923[28]. In 1924 Purves-Stewart[29] classified the disease among the thropho-neuroses, probably due to disturbed activity of the thyroid and the posterior lobe of the pituitary body. Winkelman and Eckel in 1925[30] reported that the disease could be considered as a polyglandular disorder with a consequent altered fat metabolism. In the first decades of the 1900s several further cases of AD were described[31-39]. Moreover, Foot et al in 1926[23] described a case of AD with necropsy: "*The body is that of an extraordinarily adipose negress. …The necropsy findings coincide very accurately with those in undoubted cases of AD. The very definite lesions in practically all the endocrine glands are striking: pituitary sclerosis and hyperplasia, with a tumor; sclerosis and changes in the colloid content of the thyroid; persistent and well preserved thymic rests; adenoma of both suprarenals, with hyperplasia; ovarian sclerosis and atrophy; and definite, though slight, changes in the pancreas. Besides these, we see changes in the cranial bones, with exostoses and definite cerebral atrophy, with some generalized thickening of the dura. …. It is justifiable, however, to ascribe the pathologic findings in this case to a profound disturbance in the endocrine system, probably arising as a result of one of the lesions found in the hypophysis cerebri*". At the same time, Labbé and Boulin[40] reported a case of AD with psychic and nervous disorders which they could not attribute *to any one thing which could at the same time cause obesity.* These Authors questioned whether the weakness and susceptibility to fatigue and psychiatric manifestations should be classified as cardinal symptoms.

They argued that obesity per se can induce asthenia, and that it is unclear whether mental disturbances should be included as cardinal symptoms. Gram in 1930[41] described a high incidence of obesity with tender subcutaneous infiltrations, "*deforming arthritis*" of the knee, and arterial hypertension in women around and after the climacteric age. Newburgh in 1931[42] pointed out that painful areas of fat could disappear just by

regulating diet. According to Wilson[43] the disease could be considered as "*really a syndrome of symptoms in obese people*" and "*AD could not be a clinical entity since there have been no findings consistent in all the cases reported in literature*". He considered more reasonable to assume that the condition is one of either simple obesity or lipomatosis associated with neurosis or neurasthenia, and that the pathological conditions that had been found in these cases that have come to autopsy were incidental. A report by Boller in 1934[44] showed that intralesional injections of procaine relieved pain in six cases. Kling in 19374[5] reported on 112 cases of juxta-articular AD, their significance and relation to DD and osteoarthritis. Since then, four cases of juxta-articular DD in association with seropositive rheumatoid arthritis were reported[46,47]. Furthermore, Kling[45] came up with the theory that adipose tissue deposits around the knees might interfere by pressure on the joint with the blood supply and resulted in the development of painful osteoarthritis. In 1952 Steiger et al[48] expressed their doubts on the pluriglandular involvement in DD. Hovesen in 1953[11] reported the inflammatory signs in the DD adipose tissue, i.e. infiltration of leukocytes and plasma cells. The painful lipomas could appear in any location and, even if several adipose tissue diseases may present similarly, the pain of DD is specifically associated with fatty nodules[49-52]. The absence of pain of the adipose masses should indeed distinguish DD from Cushing syndrome, multiple symmetric lipomatosis, familiar multiple lipomatosis and lipedema as well as cutaneous malignant metastases[53-56].

In 2005 DD was unrelated with malignancy by Wortham and Tomlinson[52]. Gastrointestinal symptoms were also found to be associated in some DD patients[57,58] as well as metabolic complications including obesity, diabetes, hypertension, dyslipidemia, and nonalcoholic fatty liver disease[58,59].

Hereditary factors in DD have been reported by some Authors[53,60,61]; however, most reported cases of familiar occurrence of the condition was considered to be sporadic[62]. DD has been suggested to be an expression of familial multiple lipomas, which is an autosomal dominant disease characterized by multiple asymptomatic lipomas[63]. This observation was derived by studying the family patterns of 2 siblings with DD; findings suggested that the disease segregates in an autosomal dominant fashion with variable phenotypic expressivity, ranging from totally asymptomatic to extremely painful lipomas. Mutational analysis excluded the 8344A→G mitochondrial mutation seen in other patients with multiple lipomas[62,63]. The A→G transition at position 8344 in the tRNAlys gene of mitochondrial DNA has been described in the syndrome myoclonic epilepsy and ragged-red fibers (MERRF). The presence of multiple lipomas resembling those of multiple symmetrical lipomatosis had been described in some members of pedigrees with MERRF harboring the 8344 tRNA mutation[64]. An inflammatory etiology has been proposed for DD[65-67]. However, laboratory markers for inflammation markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were reported by some authors as normal in most patients[12,47,57-59,67-76]. On the other hand, a few studies revealed elevated levels of CRP and ESR, even if some patients were also affected by an autoimmune disease[58,75,77]. Commonly, markers for autoimmune disease, such as autoantibodies, are negative in DD[77-79]. A review of the histopathologic findings of DD showed no consistent histologic abnormality in the adipose tissue that might distinguish these tumors from common sporadic lipomas[80]. The involvement of hormones and neuropeptides as well as a low level chronic inflammation and vascular factors was discussed by Hansson et al in 2011[81]. In theory, the sudden appearance of the disease together with the incidence of a slight increase in the number of inflammatory cells in the fat pointed toward the disease being, in part, an immune defense reaction[76,82]. Herbst et al in 2009[83] reported that inflammation and excess collagen may contribute to lower relative resting energy expenditure in patients with AD. The authors observed significantly higher IL-6 as well as mononuclear giant cell levels in AD compared with control adipose tissue. The study on adipokines indicated that there was no difference in the levels of tumor necrosis factor (TNF)-α, leptin, adiponectin, plasminogen activator inhibitor-1, interleukin (IL)-1β, IL-8, IL-10, macrophage inflammatory protein (MIP)-1α, and monocyte chemotactic protein (MCP) compared to controls[83]. Nonetheless, significantly lower MIP-1β expression and a trend toward higher levels of IL-13 (interleukin-13) were reported. In addition, lower levels of fractalkine, also known as chemokine (C-X3-C motif) ligand 1, were seen. The authors concluded that the lowered fractalkine levels were logical, since with prolonged release of fractalkine as seen in neuropathic pain, the receptors to which fractalkine binds are upregulated. This suggests that there is shift from fractalkine release to receptor-bound fractalkine. The lower levels of fractalkine found in DD could thus suggest that the substance is receptor-bound. When receptors are occupied by fractalkine, pain and resistance to opioid analgesia are promoted.

Rasmusssen et al[84] discovered an abnormal lymphatic phenotype in three patients with the disease compared with four female controls using near-infrared fluorescence (NIRF) lymphatic imaging. The lymphatics in the participants with DD were intact and dilated but could not readily clear lymph when compared with lymphatics in four control patients. Further NIRF imaging revealed masses of fluorescent tissue within the painful nodules, suggesting a lymphovascular etiology. Kawale et al[85] presented a DD patient with painful thickening of the scalp in bilateral parieto-occipital areas and vertex for more than a year. The pain in the scalp caused headaches and disturbed sleep and daily activities. CT and MRI revealed diffuse thickening of the scalp tissue, but no evidence for other anomalies. Tsang et al[86] noted a case of DD that caused weight loss failure after Roux-en-Y gastric bypass. Eighteen months after the operation the patient was unable to lose weight, despite adherence to behavioral and dietary guidance. Endoscopy performed 15 months after the operation excluded that any complications had occurred. Dercum patients often report that their obesity is refractory to diet and exercise intervention. Nonetheless, this has never been studied.

Hao et al (2018)[87] have recently described an interesting case of a 39-year old man with trauma induced DD. The

authors in their report highlighted the rare nature of painful adipose deposits and the diagnostic challenges. On histopathology, the fat deposition in DD was notable for mature adult fatty tissue and sometimes, a number of blood vessels suggesting an angiolipoma.

According to some reports, ultrasonography and magnetic resonance imaging (MRI) may aid in the diagnosis of DD[74,88,89]. In the study by Tins et al[88] on 13 patients with DD, lesions of the condition were found to be markedly hyperechoic on ultrasound, superficial in location, and distinct from characteristic lipomas. Further, when validated on more than 6000 MRIs, they appeared as ill-defined, nodular, "blush-like" subcutaneous fat on unenhanced MRI with a decreased T1-weighted signal. No case of DD was without these features in the study, and the authors concluded that these findings, along with multiple subcutaneous fatty lesions, is "very suggestive and possibly pathognomonic" for the condition. In regards to the pain treatment in DD, some improvement was reported after systemic or intralesional treatment with corticosteroids[47,80,90,91], whereas others experienced worsening of the pain[92]. According to Taniguchi et al[93], the alterations of fat metabolism induced by corticosteroid excess could play a role in the development of this syndrome. An earlier study suggested that a defect in the synthesis of monounsaturated fatty acids may play a role in its development[12]. Further studies are needed to support this hypothesis and to identify a specific biochemical defect. Dalziel[94] suggested that the autonomous nervous system mediates pain in DD. Vasoconstrictor response could be normalized by lidocaine infusion that is thought to decrease the local or central sympathetic vasoconstrictor tone. Nonetheless, any substantial evidence of nervous system dysfunction has never been found in DD and is hence merely a theory.

Gonciarz et al[95] reported in 1997 that interferon (INF)-alfa-2b induced long-term relief of pain in 2 patients with AD and chronic hepatitis C. The analgesic effect of IFN therapy occurred 3 weeks after treatment for 6 months. Whether the mechanism of pain relief with IFN is related to its antiviral effect, to the production of endogenous substances, or to the interference of INF with cytokines involved in cutaneous hyperalgesias, i.e. interleukin 1 and tumor necrosis factor-alpha, remains still undefined. Two DD case reports have described pain relief with daily intake of mexiletine, an antiarrhythmic[70,96]. Traditional analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), had been thought to have a poor effect, with the pain in DD often refractory to analgesics and to non-steroidal anti-inflammatory drugs (NSAIDs)[44,46,68,77-79,91-100]. However, in their extensive article published in 2007, Herbst and Asare-Bediako concluded that 89% achieved relief when treated with an NSAID, as did 97% when treated with an opiate[58]. In the same year, Singal et al[101] reported improvement of a DD patient on infliximab, with and without methotrexate. In 2008, Desai et al[102] reported on successful treatment with a lidocaine (5%) patch, and Lange et al[69] on one with pregabalin associated to manual lymphatic drainage. Metformin was used with success for AD associated pain by Labuzek et al[103]. It was hypothesized that the drug could favorably alter the cytokine profile, impacting on tumor necrosis factor, interleukin–1, and leptin[104,105]. The pilot study of Herbst and Rutledge[105] suggested that rapid cycling hypobaric pressure might reduce pain in patients with DD. Nonpharmacological approaches for DD may be used as adjuncts to pharmacologic treatments. Some of these include acupuncture, cognitive behavioral therapy, hypnosis, and biofeedback[68,106]. Several liposuction treated patients were reported by Hansson et al in 2011[107]. According to Dalziel the mechanism behind pain relief following liposuction was nerve plexus destruction within the adipose tissue[94]. However, Hansson et al retained unlikely that direct nerve destruction alone explained the pain reduction seen following liposuction[107,108]. Liposuction is regarded as a supportive treatment for DD. Any skeletal pain is not affected. A significant initial reduction of pain and an improved quality of life is seen but these effects decrease over time[109].

Dercum's disease still looking for clear and definitive answers

In an extensive review published in 2012 based on literature data and studies concerning 111 DD patients[81,107,108], Hansson et al[56] described the classification, symptoms and diagnosis, as well as, the epidemiology, etiology, genetic counselling, treatment and prognosis of the disease. They discussed which symptoms were cardinal and which were associated and promoted a "minimal definition" of AD which including the following signs:

- *Most often generalized overweight or obesity*
- *Chronically painful adipose tissue (>3 months)*

These authors also suggested the following classification system:

- *Type I: Generalized diffuse form; generalized, widespread painful adipose tissue in the absence of discreet lipomas*
- *Type II: Generalized nodular form; widespread painful adipose tissue with concomitant intense pain in and around multiple discreet lipomas*
- *Type III: Localized nodular form; pain in and around multiple discreet lipomas*
- *Type IV: Juxta-articular form; discreet deposits of excess fat in specific locations, including the medial aspect of the knee, the hips, and, rarely, the upper arm.*

Hanssen et al[56], by retracing many cases described in the literature, analyzed the consistency between the clinical signs reported and the minimum criteria for the diagnosis of DD. With the exception of a few cases[110], according to the authors most of the analyzed literature cases[67,72,85,104,111-114], were not fully consistent with the minimal diagnostic criteria.

Since the original description of DD, in addition to the painful nodular fatty deposits (which are often unaffected by weight loss), the clinical spectrum has changed to include to various degrees other components of DD[58] i.e. general obesity, easy fatigability and weakness (asthenia), and a wide variety of unexplained emotional disturbances, such as depression, confusion, and dementia. This observation is why DD has been proposed to be relabeled as "Dercum syndrome"[80]. DD has been classified by the World Health Organization (WHO) as a distinct entity and listed as a rare disease by the Orphanet[115] and by the National Organization

for Rare Disorders (NORD)[116]. According to the latter "*Dercum Disease is a rare disorder in which there are fatty deposits which apply pressure to the nerves, resulting in weakness and pain. Various areas of the body may swell for no apparent reason. The swelling may disappear without treatment, leaving hardened tissue or pendulous skin folds*". Steiner et al[70] referred to DD as a frequently overlooked disease and considered its assignment to the neuropathic pain syndromes to be justified. Traditional management of DD relying on weight reduction and surgical excision of particularly troublesome lesions has been largely unsatisfactory. Even at the present time, no known drug can change the course of the disease, and available treatments are only symptomatic. Originally, Dercum[5] attributed the disease to an endocrine dysfunction, as he found atrophy of the thyroid gland. Similarly, Waldorp proposed that the disease is caused by hypophyseal dysfunction[24]. However, endocrine involvement was ruled out as early as in 1952[48]. In addition, more actual approaches have not revealed any endocrine abnormalities[12,16,59,80,117]. So, an endocrine dysfunction as the etiology of DD has little support in the modern literature.

Moreover, there are no uniform findings pointing to an inflammatory etiology in DD.

In conclusion, the findings on DD pathophysiology are still inconclusive and the clinical significance of some reports is unclear.

Based on literature data and personal experience, the perception is that this complex condition, which often takes on the contours of a real syndrome, is much more frequent than one might think. Specific research aimed at defining its pathophysiological aspects could undoubtedly allow better clinical results and therefore a strong effort by the scientific community is warranted to make the diagnosis more accurate and develop targeted therapies against such complex pathological condition which, despite being devastating for patients, is not always recognized and, too often, either underestimated or even neglected.

Conflict of interest disclosure

The authors declare no conflicts of interest.

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aesthetic medicine

Case Report

Clinical and aesthetic results after medical treatment of subeyelid nodular basal cell carcinoma

Vincenzo Di Blasio[1], Angelo Forgione[1], Antonio Di Lucrezia[1], Dario Dorato[2]

[1]MD, Emergency Service - PSAUT Maria delle Grazie - ASL BN1- Benevento
[2]MD, General Secretariat - Italian Society of Aesthetic Medicine - Rome

Abstract

Basal Cell Carcinoma is the most common skin cancer worldwide. Currently, the best treatment method is surgical removal, but there are cases in which surgery is not feasible and alternative methods must be used. Imiquimod, a potent immune-modulator recently introduced, was effective in the topical treatment of several skin diseases of viral and neoplastic origin, with promising results.

This study aims, firstly, to evaluate Imiquimod's effectiveness in the treatment of subeyelid Nodular Basal Cell Carcinoma; secondly, to evaluate the aesthetic and functional results, in an area of the face where surgery is not always indicated.

A 95 year old women, who for two years had a Nodular-BCC, was treated with topical application of 5% Imiquimod cream, with the following protocol: 3 applications a week for a duration of 7 weeks. After the end of treatment, a monthly follow-up was performed for the first six months, then quarterly, in the next six months; subsequent monitoring was done every six months.

The method we used, was fully effective, leading to complete disappearance of the tumor, with no evidence of recurrence at 36 months. There were good functional results, without any static or dynamic alteration of the eyelid function. Aesthetic results appeared excellent, without scar, discoloration or atrophy, and without other types of damage.

This method appears fully effective and easily achievable, with excellent aesthetic and functional results. The method could become the first choice for this particular site and it could also find broad indication in other delicate areas of the face.

Keywords

Basal Cell Carcinoma, nodular basal cell carcinoma, imiquimod

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Correspondence

Vincenzo Di Blasio, MD

Emergency Service - PSUT Maria delle Grazie - ASL BN1 - Benevento
Phone: + 39 0824 812203 - Fax: +39 0824 812233
E-mail: vince.dibla@gmail.com

Introduction

Basal Cell Carcinoma (BCC) is the most common skin cancer worldwide, with an incidence of 146-422 cases/year/100,000 persons in the US, depending on latitude[1]. It is more frequent in men and in elderly, but its incidence amongst people younger than 40 is increasing, particularly in women[1]. The main cause is the exposure to UV rays of the sun (intermittent intense, rather than cumulative)[1,2,3], which is why it is more common in equatorial regions, in the most sun-exposed areas of skin and in fair skin types (tendency to burn, rather than tan)[1,3]. The sites most affected are the photo-exposed areas and in 90% of cases it is localized to the head, preferring cheeks, nasolabial folds, forehead and eyelids[1]. The periocular region is interested in 20% of cases[4]. Regarding the clinical features of BCC, six overall subtypes have been identified, of which three are more frequent and three are quite rare, but more aggressive (high risk). Nodular Basal Cell Carcinoma is the most common subtype (50-79%) of all basal cell carcinomas[1] (*Table 1*). Basal Cell Carcinoma may be treated with different therapeutic procedures, even with high rates of healing1, but the surgical removal of the tumor remains the preferred method, due to its greater therapeutic efficacy[1,5]. Despite surgical treatment being the best method, there are cases in which surgery is not feasible and alternative methods must be used[6,7]. Over time, several alternative topical therapies have been utilized, some of which are now obsolete, others are rarely used, and others, more recent, appear promising[1,2,5,7,8] (*Table 2*). Imiquimod (IMQ), an immune-modulator recently introduced, was effective in the medical treatment of certain skin diseases of viral and neoplastic origin[7]. Currently, many studies are underway in order to evaluate its effectiveness in several skin diseases and neoplasms, while the preliminary results are already very promising[1,7,8]. Objectives of this study are: first, to evaluate Imiquimod effectiveness in the treatment of subeyelid Nodular Basal Cell Carcinoma; second, to evaluate its ease and safety in delicate areas of the face; third, to evaluate the aesthetic and functional results, in an area of the face where surgery is not always indicated, because of possible permanent sequelae.

Case Report

A 95 year old woman, with fair skin, light brown hair and blue eyes (Fitzpatrick skin-type 3), for two years had a Nodular Basal Cell Carcinoma in the left subeyelid region. From six months the lesion ulcerated (rodent ulcer), with a crater-like appearance and hardened edges (*Figure 1*). The patient was treated with topical application of 5% Imiquimod cream with the following protocol: 3 applications a week (Mon-Wed-Fri) for a duration of 7 weeks. The cream was applied in the morning, by covering with a thin layer across the neoplasm, including an annular area of healthy skin around the lesion, for a width of 2 mm. The cream was left to act for 8 hours, and then it was washed with warm water and mild detergent. Care was taken to anamnestic and clinical evaluation, also with photographic documentation, at the start of each week, before applying the cream. After finishing the course of therapy, a monthly follow-up was performed for the first six months; then quarterly, in the next six months; subsequent monitoring was done every six months.

Subtypes	*Incidence*
Three main clinical subtypes:	
Nodular Basal Cell Carcinoma	50-79%
Superficial Basal Cell Carcinoma	10-15%
Morpheaform (Sclerosing) BCC	5-10%
Other rare subtypes:	
Infiltrative BCC	
Micronodular BCC	
Basosquamous Carcinoma (Metatypical)	

Table 1 *- Basal Cell Carcinoma: Clinical features.*

Method	*Notes*
Intralesional Injections	*obsolete and painful*
Cryosurgery	*discolored scar, recurrence*
Radiation Therapy	*dermatitis, atrophy, fibrosis*
5-Fluorouracil, topic	*approved, but rarely used*
Laser Therapy	*controversial, but promising*
Photodynamic Therapy	*not approved, but promising*
Imiquimod, 5% topic	*recent, approved, promising*

Table 2 *- BCC: Alternative topical therapies.*

Results

In the first two weeks, the treatment produced a progressive erythema, which affected the tumor, the upper portion of the cheek and the lower eyelid. In the next week, it established a growing edema, with a mild serous oozing and some crusts. Meanwhile, in the upper cheek, growing itching appeared, and sometimes burning with desquamation. From the fourth week a progressive regression of the tumor was observed, while intense erythema persisted associated with edema. At the end of treatment the tumor had disappeared; the residual edema resolved within two weeks, while the erythema showed a progressive reduction and disappeared altogether during the third month (*Figure 2*). In the following controls we never observed redness or swelling, discolored or atrophic outcomes, and we did not find any other sign of aesthetic damage. At 36 months, there was no evidence of tumor recurrence and no functional impairment of the involved eyelid; cheeks and eyelids were perfectly symmetrical, with excellent aesthetic results and high satisfaction of the patient (*Figure 3*).

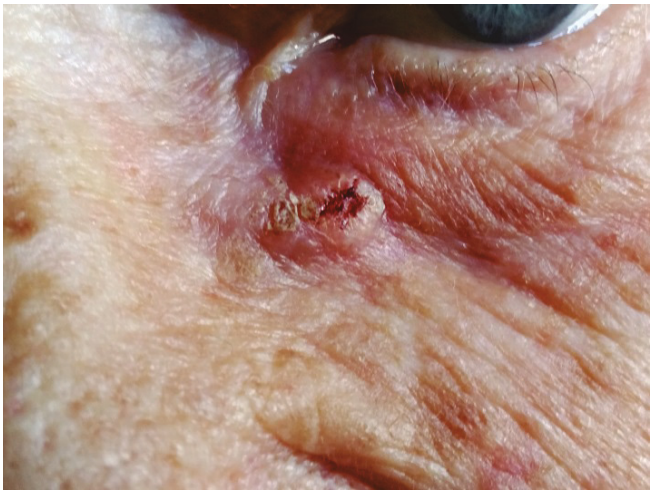

Figure 1 *- Nodular-BCC in the left subeyelid region.*

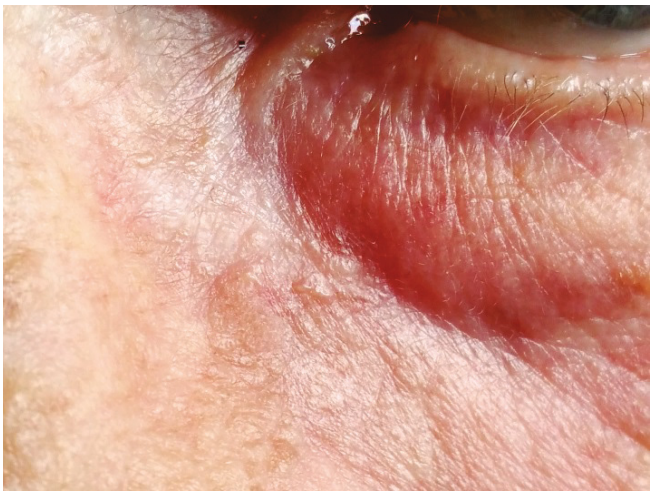

Figure 2 *- Result after the end of treatment.*

Discussion

Surgical removal is the best treatment method for all Basal Cell Carcinoma, due to its greater therapeutic efficacy[1]. Currently, three main surgical techniques may be used, all of which are effective in high percentage of cases[1,2,9] (*Table 3*). Electrodesiccation and Curettage is effective in 95.1% of cases, but it may exit in discolored scar[1]; Standard Surgical Excision is effective in 95.2% of cases, but it may give unacceptable aesthetic and functional outcomes[1,3,10]. Mohs Micrographic Surgery, a tissue sparing method, gives the best results, with efficacy in 98.6% of cases[1,3,4]; however, this technique is not always feasible, for the frequent lack of specific infrastructures[3]. Despite surgical removal remaining the best therapeutic method for Basal Cell Carcinoma, there are cases in which surgery is not possible[2,4]. There is no indication for surgery in cases of large or multiple lesions, in difficult anatomical sites, and in high surgical risk patients (elderly, comorbidity, anticoagulants); in other cases there is a consistent risk of unacceptable aesthetic and functional outcome or the patient refuses surgery[4,5,8]. Moreover, as in the case we observed, the tumor also may involve a part of the lower eyelid, exposing to the risk of functional damage in case of surgical removal, with possible ectropion, as well as unpredictable cosmetic damage[4]. When surgery is not feasible, there are several alternative topical therapies[1,2] (*Table 2*), of which Imiquimod 5% topic cream, is the most recent and the most promising, because it was effective in the medical treatment of several skin diseases of viral and neoplastic origin[7].

At present, Imiquimod is approved by the FDA only for the treatment of Anogenital Warts, Actinic Keratosis and Superficial-BCC[3,7,11]. Consequently, the use of IMQ in the Nodular subtype of BCC, currently, must be considered off label. However, as some recent studies show, it may also be effective in the Nodular-BCC[4,5,9], as in other skin tumors[1,6,8,10].

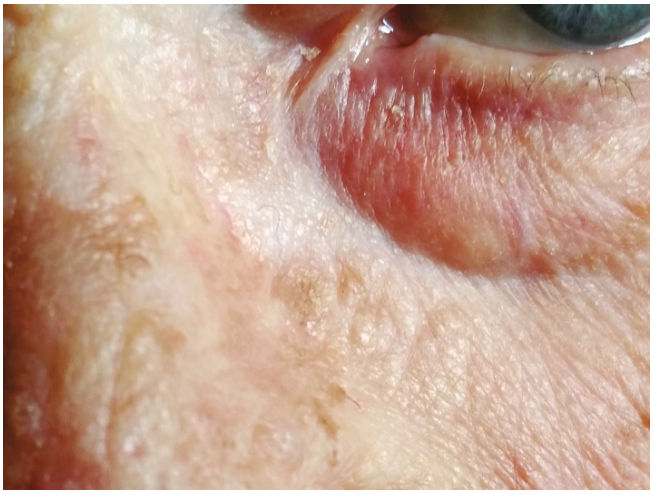

Figure 3 *- 36 months follow-up: no tumor recurrence.*

Technique	*Efficacy*
Electrodesiccation and Curettage	95.1%
Standard Surgical Excision	95.2%
Mohs Micrographic Surgery	98.6%

Table 3 *- Basal Cell Carcinoma: Surgical options.*

Imiquimod acts as a potent immune response modifier: it has, firstly, a direct action, with induction of apoptosis in tumor cell lines, by up-regulating pro-apoptotic proteins[8]; secondly, an indirect action, by release of modulatory cytokines (ILs, IFNa-g) which increase the cytotoxic T-cells and natural Killer-cells[7,8,11]. The main advantages are: high effectiveness with low costs, easy home use, and useful alternative for subjects who cannot be treated surgically[7,10]. The local side effects of IMQ are, generally, modest and tolerable, consisting of: erythema, edema, itching, burning, erosion, scabbing, crusting[1,2,3]. The systemic adverse effects are very rare and may consist of: flu-like symptoms, nausea, headache, myalgia, fatigue and fever[5]. For the use of Imiquimod, a standardized protocol does not exist3. The most used application is provided 5 times a week, for 6 weeks[3,5,8,9]; but there are other protocols with application 2-7 times a week, for 4-12 weeks[2,4,5,10,11,12]. The effectiveness of the treatment varies from 78,4 to 93,4%, in relation to different variables, and in some works success rates up to 100% have been reported[4,5,10,11]. The method we used, with topical application of 5% Imiquimod cream, 3 times a week for 7 weeks, was fully effective, leading to the complete disappearance of the tumor, with no evidence of recurrence at 36 months (*Figure 3*). Also from a functional point of view, there were good results, as no static or dynamic alteration of the eyelid function was observed, which can happen with surgical treatment[4]. Technically, the method was easy to play; the procedure was done at home, without the need for hospitalization. The treatment was well tolerated, with erythema, edema, crusting, and only a mild itching or, sometimes, a burning sensation. In addition, the method did not require anesthesia, removal of tissue, suture, reconstruction or other surgical traumatism. With regard to aesthetic aspects, there was no scar, no discoloration, no atrophy or fibrosis, and no other type of cosmetic damage. Cheeks and eyelids appeared perfectly symmetrical, without any anatomical alteration to the lower left eyelid. The hypo-pigmented area, under the medial canthus, appearing in *figure 3*, was not caused by this treatment, because it was pre-existing, as seen in *figure 1*, and was due to photo-chrono-aging, like other discolorations of the face.

Conclusions

Effectiveness: Imiquimod shows full effectiveness also in the Nodular-BCC, with complete disappearance of the tumor and no recurrence at 36 months.
Easy and safe: home treatment may be done, without need for hospitalization; IMQ use is easy and safe in difficult sites and in certain patients, without need for anesthesia, tissue removal, sutures or reconstruction.
Aesthetic results: IMQ gives excellent aesthetic results, as well as functional, without scar, discoloration or atrophy, and without functional damage.
This recent therapeutic method appears fully effective and easily achievable. The procedure could become the first choice for this particular site and could also find broad indication in other delicate areas of the face.

Conflict of interest

The authors declare that they have no conflicts of interest, and have not received any contribution for this publication.

Legends

BCC	Basal Cell Carcinoma
N-BCC	Nodular Basal Cell Carcinoma
IMQ	Imiquimod
FDA	Food and Drug Administration

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Courses and Congresses

2018

7 - 8 September - Paris (France)
39th National Congress SFME
French Society of Aesthetic Medicine
Palais des Congrès de Paris
President: J.J. Legrand
Email: congres@sfme.info
Web: www.sfme.info

27 - 30 September - Warsaw (Poland)
XVIII International Congress of Aesthetic and Anti-Aging Medicine
Poland Society of Aesthetic and Anti-Aging Medicine - PTMEiAA
Hilton Warsaw Hotel and Convention Center - Warsaw
President: A. Ignaciuk
Web: www.icaam.pl

26 - 27 October - Toronto (Canada)
CAAM 15th Annual Conference
Canadian Association of Aesthetic Medicine
Hilton Toronto / Markham Suites Conference Centre
President: R. Van Aardt
Web: www.caam.ca/annual-conference

9 - 10 November - Santiago (Chile)
XII Chilean Congress of Aesthetic Medicine
Chilean Association of Aesthetic Medicine
Hotel International - Las Condes, Santiago - Chile
President: G. Marzullo
Email: ecco@eccochile.cl
Web: www.sochme.cl/congesomedicinaestetica

9 - 11 November - Miami (Florida - USA)
15th Annual AAAM Congress
American Academy of Aesthetic Medecine
JW Marriott, Miami
President: M. Delune
Email: delegate@aaamed.org
Web: www.aaamed.org

7 - 9 December - Cascais, Lisbona (Portugal)
3rd National Congress of Aesthetic Medicine
Portuguese Society of Aesthetic Medicine
Hotel The Otaivos, Cascais
Presidente: J.P. Vale
Email: congressonacional@spme.pt
Web: www.spme2018.com

2019

21-23 February - Malaga (Spain)
34th National Congress SEME
Spanish Society of Aesthetic Medicine
Palacio de Ferias y Congresos
President: P. Vega
Email: seme2019@pacifico-meetings.com
Web: www.seme2019.org

9 - 10 March - Seoul (Korea)
22th World Congress of Aesthetic Medicine - UIME
Organised by: Korean Academy of Aesthetic Medicine
Coex, Seoul
President: Wooha Han
E-mail: with@thewithin.co.kr
Web: http://ons.thewithin.kr/register/2019_24/intro.html

26 - 27 April - Brussels (Belgium)
Congress SBME - BVEG 2019
Belgian Society of Aesthetic Medicine
Radisson Blu Royal Hotel
President: J. Hebrant
Web: www.radissonblu.com

17 - 19 May - Rome (Italy)
40th SIME Congress
Italian Society of Aesthetic Medicine
Rome Cavalieri Congress Center
President: E. Bartoletti
E-mail: congresso@lamedicinaestetica.it
Web: www.lamedicinaestetica.it

14 - 15 June - Basel (switzerland)
16th Congress of the Swiss Society of Aesthetic Medicine
7th Congress of the Swiss Society of Aesthetic Surgery
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President: S. Le Huu
Email: info@ssme.ch
Web: www.ssme.ch

13 - 14 September - Paris (France)
40th National Congress SFME
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Palais des Congrès de Paris
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Website: www.sfme.info

2020

15 - 17 October - Quito (Ecuador)
XIII Pan American Congress of Aesthetic Medicine - UIME
Organised by: Ecuatorian Society of Aesthetic Medicine
President: V. Tinoco Kirby
Email: medesteticapanam2020@gmail.com
Web: www.seem.com.ec

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