ENZYMES and Skin Science

The Cellulite Issue

Volume 01. May 2024

- Up to 98% of women can suffer from cellulite
- More than 40% of women report receiving embarrassing comments about their cellulite, having a profound negative psychosocial effects
- 78% feel the need to seek treatment
- Many non-surgical and surgical intervention give the opportunity to women to enhance their buttocks and improve their silhouette
- Pbserum is a novel recombinant enzyme technology with a synergistic effect enhancing its efficacy in addressing cellulite



- Several cases report show how recombinant enzymes High and Medium pbserum improve orange peel achieving excellent outcomes

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Content:

1. Cellulite: a synergistic approach **03**
Dr. Jorge López Berroa

2. The tissue dynamics happening below orange peel skin. **04**
Dr. Filis Demirgean

3. Analysing physiopathology, diagnosis and treatment: A case report **07**
Dr. Farah ElChaer

4. Therapeutical alternatives. the expert approach **10**
Dr. Oznur Goyce

5. Efficiency of recombinant enzymes from the pbserum medical line in cellulite treatment: Two cases report **13**
Dr. Joana Paola Bernedo Alcazar

6. The journey of patient Cecilia **17**
Dr Erick Santaella-Sosa

7. Psychological impact of orange peel skin **19**
Camino Olmedo

Enzymes
and Skin Science

Cellulite: a synergistic approach



Dr. Jorge López Berroa



In our Enzymes & Skin Science Editorial focused enzymatic treatments within the realm of aesthetic medicine, we proudly present "The Cellulite Issue". Here, we provide you with a unique opportunity to seek answers, insights, and guidance from leading professionals in the field of cellulite treatment and aesthetic medicine.

Cellulite, a concern that affects countless individuals worldwide, continues to challenge both patients and practitioners. With an array of treatment options and evolving research, navigating the landscape of cellulite management can be complex. That's where our panel of esteemed experts comes in.

We have gathered a team of experienced and knowledgeable specialists in the field of aesthetic medicine. They are ready to address your burning questions, demystify cellulite treatments, and offer expert advice tailored to your specific concerns.

Whether you are a Body specialized Plastic surgeon, Dermatologist or simply curious about the latest developments in cellulite management, this edition is your go—to resource.

Our experts bring years of clinical experience and a deep understanding of the science behind cellulite. They are here to provide you with evidence—based information, share their perspectives on emerging trends, and offer practical tips for achieving smoother, firmer skin.

> **"In our Enzymes & Skin Science Editorial focused enzymatic treatments within the realm of a esthetic medicine, we proudly present "The Cellulite Issue"**

Together, we'll embark on a journey to unravel the mysteries of cellulite and empower you with the knowledge to make informed decisions on treatment choice.

Welcome to "Enzymes & Skin Science" — your gateway to a deeper understanding of cellulite and the innovative approaches to tackle it. We look forward to assisting you on your path to radiant, cellulite—free skin.

As we move forward in our commitment to enhance the scientific evidence surrounding pbserum treatments, we express our deepest gratitude to the Global Enzymes Masters Ambassadors (GEMA) for their unwavering support and dedication. Their contributions are instrumental in shaping the future of aesthetic medicine and dermatology, ensuring that patients receive the most effective, evidence—based treatments available.

Through rigorous research, collaborative efforts, and the leadership of GEMA members, we aspire to elevate the standards of care in aesthetic medicine, offering patients safe, innovative, and scientifically validated solutions for their diverse see through care needs.

The tissue dynamics happening below orange peel skin



Dr. Filis Demirgean



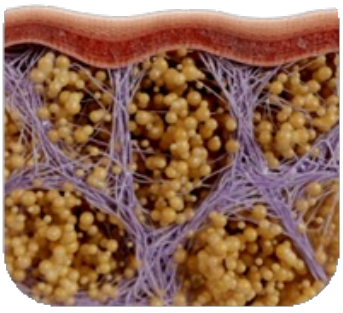
INTRODUCTION

Cellulite is a common skin condition characterized by dimpling of the skin, leading to an "orange peel" appearance affecting around 85% to 98% of postpubertal women[1]. It occurs mostly in areas with greater fat storage like the thighs and buttocks, and, to a lesser extent, the abdomen[2].

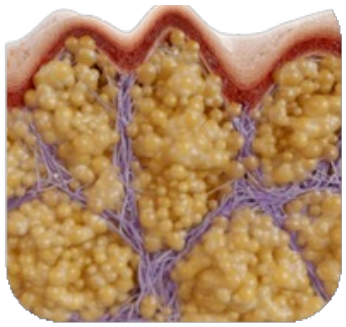
Cellulite is also called gynoid lipodystrophy, liposclerosis, or dermatofibrosclerosis[1]. Genetic, environmental, and hormonal factors have been implicated in the development of cellulite. Female gender and Caucasian race are more prone to develop it. Other factors involved are age, a sedentary lifestyle, alcohol consumption, and obesity; however, cellulite also occurs in lean women[3-5].

HISTOLOGY AND ETIOLOGY OF CELLULITE

At the microscopic level, there is a hypertrophy and dystrophy of the adipocyte structure, increased fibrosis of the interdigitating septae, and enlargement and thickening of the vascular endothelium leading to microangiopathy. Septal inflammation may be observed. Later stages show atrophy and dystrophy of the skin, extensive vascular damage, and appendage disturbances. Noticeably, there may be a blurring of the border between the skin and the underlying tissue. The etiopathogenesis of cellulite remains an enigma. Different pathophysiologic mechanisms have been proposed including structural, hormonal, vascular, and inflammatory[6-11].



Cellulite-free skin



Cellulite skin

The importance of treating cellulite. Association with systemic disease.

Cellulite is currently recognized as more than just an aesthetic issue; it also carries significant psychological implications. As our understanding of its causes expands, cellulite is now viewed as a systemic concern. Recent findings suggest a correlation between cellulite severity and susceptibility to systemic diseases. Shared pathological mechanisms suggest associations with insulin resistance, obesity, and increased cardiovascular risk. Hyperinsulinemia can accelerate lipodystrophy, while dystrophic adipose tissue may experience a loss of endocrine functionality[4].

TREATMENTS

Recent advancements in understanding cellulite have prompted the creation of new treatments addressing various causal factors in its development. However, there's a scarcity of scientific evidence to support the effectiveness of these treatments. Combining different therapeutic modalities is advised for more noticeable and longer-lasting results[9, 12].

Topical treatments

The main active ingredients found in topical formulations are xanthines (caffeine, aminophylline, and theophylline), retinoids, and a variety of botanical extracts. Possible mechanisms of action include enhancement of lipolysis, improved microcirculation, reduced inflammation, and increased neocollagenesis. A systematic review determined that the effectiveness of topical treatments was moderately significant. However, more robust studies are required to enhance our understanding of their efficacy.

Massage

LPG® Endermologie is a mechanical massage system approved by the US FDA for cellulite treatment. It employs positive pressure through dual rollers and negative pressure via aspiration on the skin and subcutaneous tissue. This method is believed to enhance lymphatic drainage and redistribute extracellular fluid. However, its effectiveness is not well-established. In clinical observation, any improvement in cellulite appearance resulting from massage are presumed to be temporary.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) employs electrical energy to induce mechanical disruption of tissues, resulting in a healing response characterized by collagen remodeling, neovascularization, and enhanced lymphatic drainage. Additionally, shockwaves attenuate fibrous septae and promote smoother skin in affected areas. A meta-analysis of 11 clinical trials concluded that ESWT improves the degree of cellulite. Nonetheless, data on long-term follow-up beyond one year are insufficient.

Radiofrequency

Radiofrequency (RF) waves are used to elevate the temperature of the dermis and subcutaneous tissue. This effect will promote dermal remodeling, targeted lipolysis, and enhanced microcirculation. Challenges associated with radiofrequency treatment encompass short-lived outcomes and the need for multiple sessions. RF devices come in various forms, depending on the electrode configuration (unipolar, monopolar, bipolar, tripolar, and multipolar) and integration with other modalities, such as vacuum suction, laser/light, or pulsed electromagnetic fields. Many RF devices have received FDA approval.

Subcision

The objective of subcision is to disrupt the connective tissue septae, promoting a better redistribution of tension and fat lobules, and inducing controlled tissue injury to stimulate collagen production. This procedure is advised specifically for cellulite with visible depressions, rather than those only apparent during muscle contraction. Subcision techniques may involve manual, vacuum-assisted, or laser-assisted methods.

Collagen biostimulators

Calcium hydroxyapatite (CaHA) and poly-L-lactic acid (PLLA) stand out as the predominant biostimulatory agents employed for skin tightening and lifting in the buttocks and thighs. While these substances have shown promising results for cellulite treatment, additional rigourous designed studies are required to comprehensively assess their efficacy and safety.

Collagenase clostridium histolyticum

Collagenase enzymes, extracted and purified from Clostridium histolyticum fermentation, received FDA approval in 2020 for treating moderate-to-severe cellulite in the buttocks of adult women. These enzymes target type I and III collagen, leading to the disruption of fibrous septae within cellulite. The mechanism of action involves enzymatic subcision and remodeling. Collagenase functions locally without systemic absorption. Both phase II and phase III studies have corroborated the efficacy of Collagenase for improving the appearance of buttock cellulite[13-17].

PBSERUM ACTION

Medium by pbserum is a recombinant enzyme technology, which comprises three enzymes: Lipase, Lyase and Collagenase. It has a synergistic effect enhancing its efficacy in addressing cellulite through enzymes with different mechanisms of action, capable of targeting different pathophysiological aspects that make up the cellulite tissue.



Lipase possesses the ability to specifically degrade triglyceride molecules into glycerol and free fatty acids. Lyase operates by hydrolyzing glycoproteins, thereby reducing the gel-like consistency in the extracellular matrix, and improving drainage. Collagenase in pbserum comprises G and H collagenases. It is a collagen-specific protease very effective to combat a fibrotic process as occurs in cellulite.

Medium by pbserum is the therapeutical alternative of choice to reduce fat deposits, double chin, and adipose predominant cellulite. It acts on the adipose component but the synergistic effect of the three enzymes can cover all aspects of cellulite physiopathology. Another alternative would be to use High when the fibrotic component is highly predominant, and the patient diagnosis is closer to a fibrosis than cellulite itself.

COMBINED PROTOCOL

After 10 years of experience, we have observed the best results in patients treated with combined therapies. In this way, we can target several mechanisms of action and end up improving the appearance of cellulite considerably. One of the favorite protocols is the combination of pbserum Medium and High (one vial of Medium to reduce the adipose component and one vial of High as a treatment for fibrotic areas) followed by RF on different sessions since heat can break down pbserum molecules and finally poli-lactic acid as a finishing touch. In each session, I begin with the application of enzymes to prepare the tissue, followed by the use of RF to enhance the effects achieved. Finally, I inject poli-lactic acid to complete the treatment. In this way, we manage to obtain the satisfaction of the patients and the result is maintained for at least 2 years.

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Analysing physiopathology, diagnosis and treatment: A case report.



Dr. Farah ElChaer



INTRODUCTION

Cellulite, characterized by dimpled and uneven skin texture, typically appears on the buttocks, thighs, and abdomen. It has a considerable impact on body image and self-esteem. Understanding the pathophysiology of cellulite is essential for developing effective treatment modalities.

FACTORS INVOLVED IN CELLULITE

Adipose Tissue Arrangement: The subcutaneous fat layer consists of discrete lobules separated by fibrous septae. In individuals with cellulite, these septae can become thicker and less pliable, leaning to the characteristic dimpling of the skin as fat herniates through weakened connective tissue.

Microcirculation and Lymphatics: Altered blood flow and impaired lymphatic drainage are thought to play a role in cellulite development. Reduced microcirculation may limit oxygen and nutrient supply to adipocytes, contributing to metabolic changes in the affected tissue.

Hormonal Factors: Hormones, particularly estrogen, influence the development and severity of cellulite. Estrogen promotes adipogenesis, alters connective tissue structure, and may contribute to water retention, all of which can exacerbate the appearance of cellulite. Other hormones like insulin, thyroid hormones, and catecholamines may also impact cellulite formation by affecting fat metabolism and tissue remodeling.

Genetic Factors: Genetics plays a role in an individual's susceptibility to cellulite. Some genes may predispose individuals to have a certain type of subcutaneous fat distribution and connective tissue structure that increases the likelihood of cellulite development.

Inflammatory Responses: Inflammation is emerging as an important factor in cellulite pathophysiology. Inflammatory mediators may contribute to fibrosis, collagen remodeling, and adipocyte dysfunction in affected areas.

USING RECOMBINANT ENZYMES TO TREAT CELLULITE

The use of recombinant pbserum enzymes for cellulite treatment is increasingly becoming the safest and most effective choice for enhancing the quality of patients' skin worldwide. Dermatologists, plastic surgeons, and aesthetic physicians are turning to this innovative approach to address cellulite-related concerns.

As we have said, cellulite results from adipose tissue hyperplasia, followed by inflammation, vascular compromise, edema, and fibrous tissue formation. Addressing each of these aspects is crucial for successful cellulite treatment. In this article, we delve into the combined synergy of lyase, collagenase, and lipase, targeting the primary components central to the cellulite challenge.

Lipase action:

Lipase possesses the ability to specifically degrade triglyceride molecules into glycerol and free fatty acids. When lipase interacts with adipocytes in the cellulite tissue, it can permeate the cell and fat droplet without

causing damage or side effects. In fact, lipase can substantially reduce fat volume without risking tissue necrosis. Topical application of lipase also diminishes skin sebum viscosity, thereby enhancing the quality of the hydrolipidic barrier.

The Role of Lyase:
Lyase's mechanism of action involves the hydrolysis of glycoproteins that increase the gel-like consistency within the extracellular matrix. This process effectively reduces edematous clusters, facilitating improved drainage. By addressing the initial stages of cellulite formation, Lyase acts as a key player in preventing its progression.

The Impact of Collagenase:
Collagenase, another essential component of the pbserum enzyme combination, targets the erratic collagen fibers responsible for the characteristic "orange peel" appearance of cellulite. By breaking down these fibers, Collagenase not only diminishes the visible signs of cellulite but also enhances the organization of dermal fibers, thereby increasing skin firmness.

In addition, we use pbserum High Molecular Weight Hyaluronic Acid which is proven to reduce fibrotic markers and be the nicest environment for pbserum enzymes so the product reaches the highest potency. It is a non-crossed linked hyaluronic acid which will not provide with volume or cause any complications.

The utilization of recombinant pbserum enzymes, featuring the powerful trio of Lipase, Lyase, and Collagenase, represents a groundbreaking approach in the treatment of cellulite. This innovative therapy tackles the multiple facets of cellulite formation, providing dermatologists, plastic surgeons, and aesthetic practitioners with a comprehensive and effective solution.

Its effect is done in a non-invasive manner, without pain or side effects. The patient can continue their normal life after the sessions, which becomes a great advantage. Furthermore, they may even begin to see results from the first session, thus motivating the patient right from the start.
As the demand for safer and more efficient cellulite treatments continues to rise, the combined synergistic action of these enzymes offers a promising avenue for improving patient outcomes, enhancing skin quality and, what is more, improving quality of life. Further research and clinical studies will undoubtedly shed more light on the full potential of pbserum enzymes in cellulite management, solidifying their place as a go-to option for patients seeking smoother, firmer and obviously mor beautiful skin.

CHANGING LIVES: THE CASE OF MARIA

The first step before treating a patient whose concern is cellulite and orange peel appearance on their lower body, is to mark the areas. Diagnosis is a key point to obtain good results. In Figure 1 we can see how our patient has marked the depression areas, the fibrotic plaques, and the adipose areas.

The patient is a 37-year-old woman in good health, without any pathologies or contra indications for the use of pbserum for Cellulite. She has previously undergone liposuction on her buttocks, which resulted in tissue alteration and the presence of Cellulite and fibrous plaques. The preferred treatment for tissue remodeling is the use of Medium by pbserum. Medium contains Lyase, Collagenase,

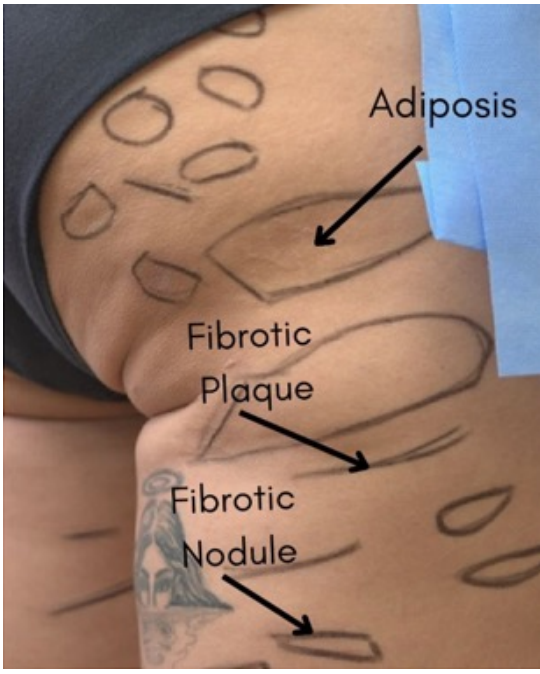


Figure 1. Details of marking for cellulite treatment using Medium pbserum

and a higher dose of Lipase with the aim of providing a comprehensive treatment for Cellulite and reducing unwanted volume.

Once the marking was complete, a 30G 13mm needle was used to apply pbserum Medium. Retrotracing from adipose tissue to superficial on the adipose areas and fanning on dimples and fibrotic plaques. One box per side were used and the patient received 3 sessions within one month and a half.

We could appreciate improvement already at the first session. Here we show pictures before starting the treatment and one month after the last session (Fig. 2 and 3). As we can see the appearance of adiposis, fibrotic plaques and nodules are diminished considerably giving a firmer and smoother skin.

As aesthetic medical doctor, I highlight the potential benefits of Medium by pbserum for cellulite treatment. Its ability to deliver improved patient

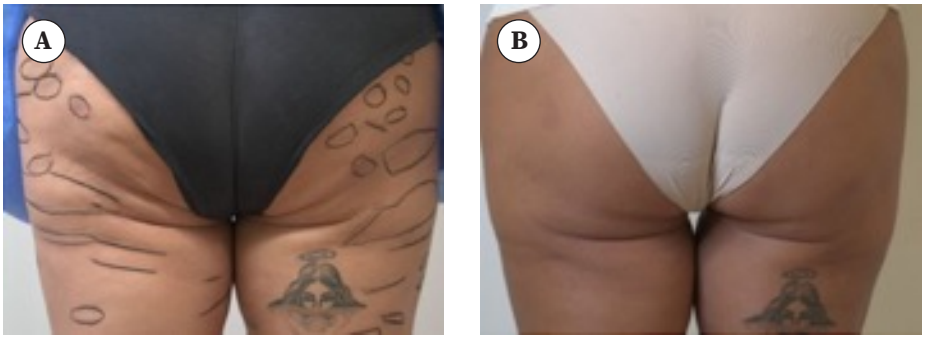


Figure 2. Pictures from the back angle: A) Before and B) after

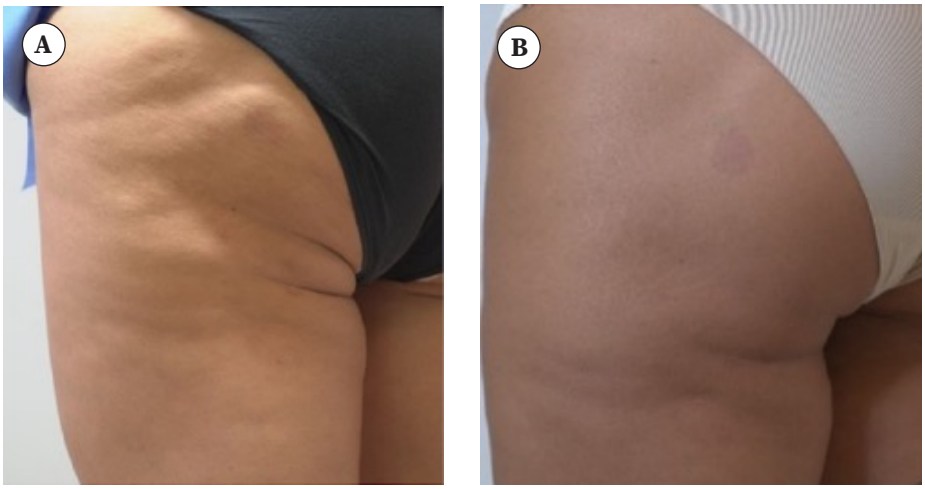


Figure 3. Pictures from a 45" Angle where we can see the quality of the skin. A) Before and B) After

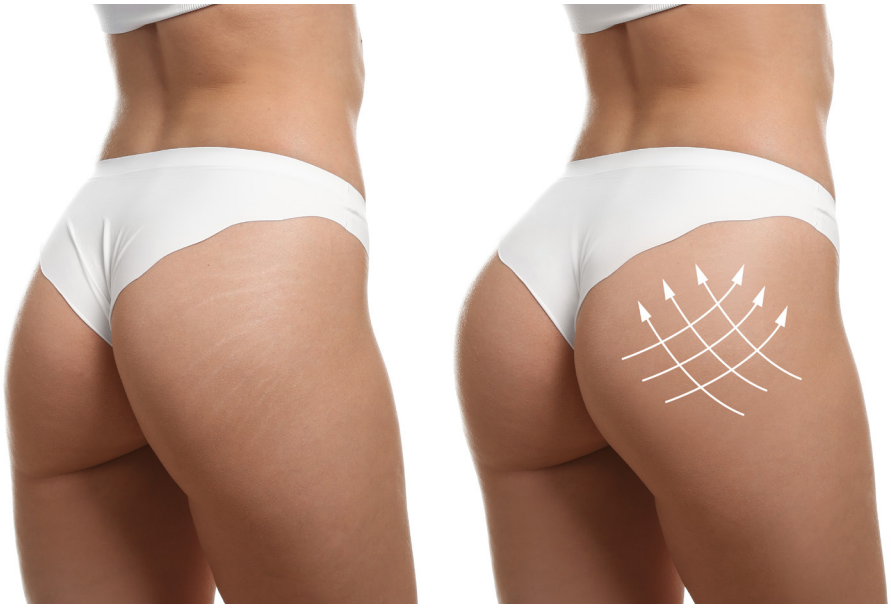
comfort and quicker, more visible results modes it a promising option in the field of aesthetic medicine. Further research and clinical studies are needed to validate these findings and explore the full potential of Medium in cellulite management.

"This treatment helped me feel much more confident going to the beach wearing shorter shirts and bathing suits. I was really concerned about these areas but now I am comfortable in my own skin." Was the testimonial of the patient.

Therapeutical alternatives. The expert approach.



Dr. Oznur Goyce



INTRODUCTION

In the realm of aesthetic medicine and plastic surgery, the quest for achieving an aesthetically pleasing silhouette has gained prominence.

One area of focus that has gained widespread attention is the enhancement of gluteal aesthetics in women. A shapely, well-proportioned derrière is not only a symbol of beauty but also a confidence booster. This article explores the array of treatments available in the field of aesthetic medicine and plastic surgery to improve the appearance of the buttocks in women.

NON-SURGICAL APPROACHES

Dermal fillers

Hyaluronic acid-based dermal fillers are a popular choice for non-surgical buttock enhancement. Injected strategically, they can add volume, improve contour, and create a lifted appearance.

Sculptra

This injectable stimulator promotes collagen production, resulting in gradual and natural-looking buttock enhancement. It is an excellent choice for those seeking subtler, long-lasting results.

Sculpsure

SculpSure is a system for contouring the buttocks, removing fat from its, using diode laser energy. During each 25-minute session, up to 24% of fat cells can be destroyed without surgery.

Thermage and radiofrequency

These non-invasive procedures tighten the skin and stimulate collagen production, which can improve the overall appearance of the buttocks by reducing sagging.

High-Intensity focused ultrasound (hifu)

HIFU technology targets deeper layers of skin and fat, providing a non-surgical lift and firmness to the buttocks.

Collagenase clostridium histolyticum

Several studies support the efficacy and safety of the use of collagenase to improve the appearance of the buttocks from the point of view of reducing the appearance of orange peel skin that occurs in a skin affected by cellulite.

SURGICAL INTERVENTIONS

Brazilian butt lift (bbl)

BBL is a popular surgical procedure that involves liposuction to remove excess fat from other parts of the body, which is then purified and injected into the buttocks for augmentation. It provides natural-looking results and enhances both volume and shape.

Butt implants

For patients seeking o more dramatic transformation, silicone buttocks implants can be surgically placed to add volume and create a fuller, rounder appearance.

Thread lifts

This minimally invasive procedure uses dissolvable threads to lift and shape the buttocks. It's on option for those with mild sagging or asymmetry.

ENZYMATIC SYNERGISTIC TREATMENT BY PBSERUM MEDICAL

The treatment alternative designed by pbserum medical combines four elements. High molecular weight hyaluronic acid (non-crossed linked) and the combination of three recombinant enzymes: Lyase, Collagenase and lipase.



IN RELATION TO A CASE

When facing a patient who suffers from a stage 2 of cellulite with a predominant component of fibrotic tissue, the treatment choice of High pbserum seems more suitable, since it contains a higher dosage of collagenase.

Case Presentation: Female patient, 38 years old, 174 cm in height and 57 kg in weight. She is an old fashion model and pays attention to her diet and exercises every day. She does not have any diseases and she is not using any medicine. She drinks alcohol every weekend. During the examination, it was determined that she had stage 2 fibrotic Cellulite, so the pbserum High presentation, which has a proportionally high amount of collagenase, was preferred.

Product used:

- 2 vials High pbserum
- 22 G 70 mm cannula for subcision
- 30 G 13 mm needle for retrograde injection

Steps of Application:

1. The patient was asked to tighten her muscles while standing and the fibrotic areas were circled using a white pen.

2. The patient was laid in the prone position. Skin antisepsis was applied to the application area.

3. 1 vial of 10 ml High pbserum was prepared for the right gluteal area. One vial of 10 ml High pbserum was prepared for the left gluteal area.

4. 3 ml of the prepared 10 ml solution was injected to the right side by subcision with a 22 g 7 cm cannula.

5. Using the remaining 7 ml solution, with a 30 g 13 mm needle tip, 0.2-0.5 cc of the product was used in each circled area until an intradermal papule was created, as a retrograde injection from a depth of 8-10 mm, depending on the depth of the fibrous areas.
The same application was made for the left side.

6. After the application, massage was performed for 5 minutes using sterile gloves.

Post-application recommendations:

1. A tolerable amount of redness and edema may occur after the application, and there should be no need for medication use.

2. After the application, it is recommended to drink plenty of water and stay away from carbohydrate-rich foods.

3. Massage should be started 48 hours after the application with pbserum Smooth Out Power.

4. It is recommended to take a shower after 48 hours.

5. Use of bath, sauna, and pool is not recommended for at least 5 days after the application.

Results:

The skin in the area improved considerably. The nodules and fibrotic plaques decreased, and the cellulite marks noticeably diminished. Now, the buttocks have a more curved, firmer appearance without irregularities (Figure 1).

COMBINATION APPROACHES

Many patients opt for a combination of treatments to achieve their desired results. For instance, combining liposuction with fat transfer (BBL) con sculpt the waist while enhancing the but-



Figure 1. 6 weeks after 1 session of 2 vials of High pbserum application.

tocks, delivering a more harmonious outcome. Other specialists resort to collagenase injections following liposuction to mitigate any minor deformations that may remain.

CONSIDERATIONS AND SAFETY

It's crucial to consult with a board-certified plastic surgeon or an experienced aesthetic medicine practitioner to determine the most suitable approach based on individual goals, body type, and medical history. Patient safety should always be the top priority, and a reputable practitioner will discuss the potential risks and benefits of each treatment.

CONCLUSION

With the advancement of aesthetic medicine and plastic surgery techniques, women have an array of options to enhance the appearance of their buttocks. Whether seeking non-surgical enhancements for subtle improvements or opting for surgical procedures to achieve more dramatic results, individuals can now tailor their gluteal aesthetics to their unique preferences.

As with any cosmetic procedure, informed decision-making is paramount. By consulting with qualified professionals and discussing treatment goals, women can embark on a journey to achieve the buttock aesthetics that boost their confidence and overall sense of beauty.

As far as pbserum treatment concerns, it is a safe alternative that improves functionality in patients concerned by edematous sclerotic paniculopathy. It is a global treatment that offers an improvement due to the synergy of its components. Adipose hypertrophy is reduced by Lipase, edematous component is resolved by Lyase and fibrotic septa and skin quality are treated with Collagenase. The final result is aesthetical and functional at the same time.

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Efficiency of recombinant enzymes from the pbserum medical line in cellulite treatment: Two Cases Report



Dr. Joana Paola Bernedo Alcazara

ABSTRACT

Cellulite is a common reason for consultation in aesthetic medicine and, although not described as a disease, it affects the self-esteem and quality of life of many patients. To date, there is no gold standard treatment for cellulite, and numerous technologies have been employed to improve its appearance in patients. It is important to note that up to 98% of the population suffer from cellulite. The review presented here briefly explores the etiology; pathophysiology, which is not fully elucidated; and treatment options for this multifactorial condition. Of particular note is the role of enzymes in managing cellulite, as all enzymatic components play an important role in treating this condition: Lipase reduces the triglyceride content of adipocytes and, therefore, the volume of the fat cell; collagenase helps to break down abnormal fibrous septa and stimulates collagen formation by fibroblasts; lyase has a draining and enzyme-diffusing effect; and high molecular weight HA has an anti-adherent effect and allows for better functioning of the extracellular matrix in the process of neo-collagenogenesis. Based on current knowledge of the pathophysiology of cellulite, this product works at all levels for the treatment of this condition, representing a significant milestone among current treatments. The cases presented here demonstrate how enzymes helped in the visual aspect of cellulite, where other technologies had failed, also improving self-esteem and quality of life.

INTRODUCTION

Cellulite impacts the self-esteem of many women and their quality of life. Studies have shown that cellulite affects the quality of life of patients by up to 84.6% of participants. Another study revealed that 70% of women who received treatment for cellulite had a positive impact on their lives. This emphasizes the importance of how it can affect self-esteem and the importance of treating it in clinical practice (1, 2). Cellulite is a multifactorial condition characterized by the presence of dimples in the skin, affecting up to 85-98% of women after puberty (3, 4). The etiology of cellulite depends on various predisposing factors (4), including genetics (5), age (6), ethnicity (6), dietary habits (7), sedentary lifestyle (7), smoking (8), and pregnancy (9). On the other hand, alterations in tissue structure also occur (7); certain body areas are more prone to develop cellulite, such as white fat versus brown fat (4). Other alterations that may predispose to cellulite include vascular (4) and hormonal changes (10). Recent proposals indicate that estrogens play an important role in cellulite genesis, as 17β-estradiol stimulates adipocyte replication and increases the response to anti-lipolytic alpha-2-adrenergic receptors. It has been theorized that there is an alteration in the dermal microvessels and an altered response of the precapillary arterioles. In addition, deposits of hyperpolymerized glycosaminoglycans (GAGs) occur in the walls of capillaries with bundles of collagen and elastic fibers; this excess GAG causes fluid retention in capillaries, adipocytes, and interlobular septa; in turn, edema causes vascular compression, hypoxia, and neoformation of capillaries, causing microhemorrhages

evident in histology. Kligman reports the presence of macrophages and lymphocytes in the fibrotic septum of biopsy areas with cellulite, which may be due to a low-grade chronic inflammation, resulting in dermal atrophy, thus demonstrating inflammation in patients with cellulite (11). Estrogens act through alpha and beta receptors stimulating fibroblasts in connective tissue, also activating metalloproteinases (MMP), which degrade collagen fibers supporting adipose tissue. Fibroblasts play an important role in the pathophysiology of cellulite, being responsible for maintaining tissue homeostasis (4, 11). In addition to an alpha-2-adrenergic response, which has an anti-lipolytic activity, the activation of these receptors promotes lipogenesis allowing hypertrophy and hyperplasia of adipocytes. The buttocks and thighs have a high concentration of alpha-2-adrenergic receptors compared to beta-adrenergic receptors, which have lipolytic activity, hence there is greater resistance to fat mobilization in certain body areas (9, 12). Understanding the etiology and pathophysiology of cellulite, its degree, and severity is vital to develop an effective treatment plan. There is a wide range of treatments available. Treatments are divided into three basic categories: pharmacological, non-pharmacological, and surgical treatments (4, 13). Among non-pharmacological treatments, we find dermal fillers (3), and recent advances in genetic engineering and molecular biology have allowed the synthesis of proteins including enzymes. Enzymes have significant activity in the pathophysiology of cellulite. Collagenase, widely used in wound healing, burns, keloids, cellulite, lipomas, Dupuytren's disease, and Peronie's disease, works to improve thick collagen fibers that cause cellulite dents or dimples (14-17). Proteos Biotech introduces HA 1.5 Low/Medium/High, a line of recombinant enzymes of high molecular weight, HA, lipase, collagenase, and lyase. Registered as injectable medical devices, these enzymes offer exciting possibilities in aesthetic medicine. These cases report demonstrate the therapeutic application of recombinant enzymes, highlighting their potential for safe and effective treatments of cellulite.

Cases Report

Case 1

A 65-year-old woman, with no relevant medical history, underwent liposuction 15 years ago with fat transfer to the buttock area and multiple cellulite treatments (radiofrequency, carboxytherapy and manual massages) for years without seeing satisfactory improvement. The patient took no medication, did not smoke, did not have a healthy diet, and did not exercise regularly. She came to our clinic seeking to improve the appearance of her cellulite, stating that the appearance of her cellulite greatly affects her self-esteem, to the extent that she has not worn a swimsuit in many years. On examination, grade III cellulite was observed according to the Doris Hexel scale. This patient underwent 3 sessions of pbserum medical enzymes (Proteos Biotech®).

In the first session, two boxes of High were used, which were prepared with 18 cc of dilution buffer, plus 1.5 cc of high molecular weight HA and 0.5 cc of lidocaine without epinephrine; and the lyophilized enzymes were diluted to 20 ml. High 1.5 HA pbserum was applied to all dimples in the buttock, infragluteal, and trochanteric areas, using a 30-gauge needle from deep to superficial in retroinjection. Additionally, two boxes of Medium 1.5 HA pbserum were applied, constituted with 18



Fig. 1. Clinical images of the visible presence of cellulite in the intergluteal and trochanteric. (A and C) Before High pbserum enzyme treatment and (B and D) 15 days after the combined applied Medium/High HA 1.5 pbserum medical recombinant enzymes treatment (Proteos Biotech®).

cc of dilution buffer, 1.5 cc of high molecular weight HA, 0.5 cc of lidocaine without epinephrine, and the enzymatic lyophilized product. This was applied in the infragluteal and trochanteric areas, the area was gridded, and it was applied from deep to superficial, symmetrically, with 1 cc points every 2 cm, covering an area of 20x20 with each box. A total of 3 sessions were performed spaced 15 days apart. Improvement in dimples, as well as in the elasticity and tonicity of the treated areas, was observed in each session.

Case 2

A 36-year-old woman, with no relevant medical history, underwent liposuction 5 years ago in the abdominal area with fat transfer to the buttock area and multiple cellulite treatments (radiofrequency, carboxytherapy, manual massages) for years without improvement. The patient took no medication, did not smoke, did not have a healthy diet, and exercised regularly. She sought our consultation to improve the appearance of her cellulite. On exploratory examination, grade III cellulite was observed according to the Doris Hexel scale. This patient underwent 3 sessions with pbserum medical enzymes (Proteos Biotech®).

In the first session, one box of High was used, prepared and applied in the same manner as in case 1. Two boxes of Medium were also applied in the same manner as in the previous case. A total of 3 sessions were conducted spaced 15 days apart. Improvement in dimples, as well as in the elasticity and tonicity of the treated areas, was observed in each session.

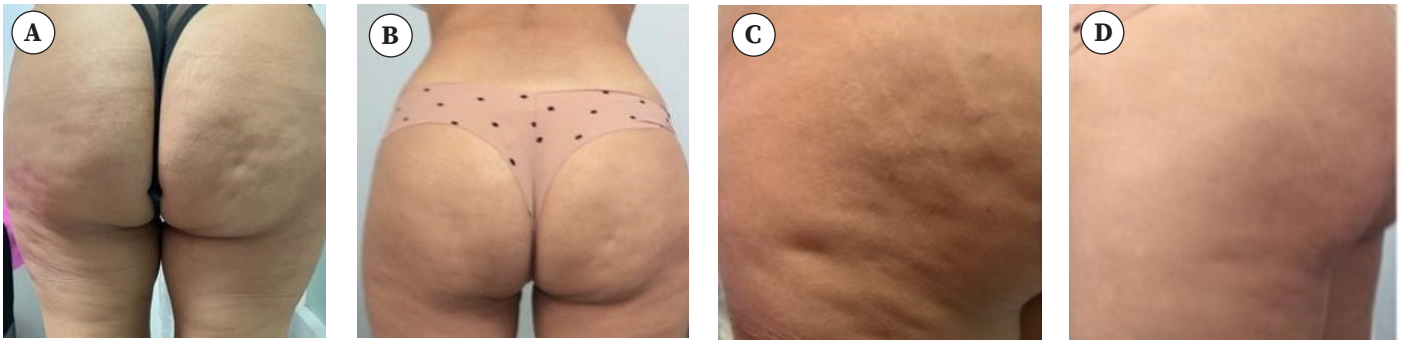

Fig. 2. (A and C) After 30 days of the combined applied PB Serum Medical HA 1.5 Medium/High recombinant enzymes (Proteos Biotech®) treatment and (B and D) 45 days after the session of control and medical monitoring.

DISCUSSION/CONCLUSION

In histological studies of cellulite, areas of adipose tissue protrusion from the hypodermis to the dermis are observed, along with an alteration in the arrangement of fibrotic septa in the hypodermis. These septa are perpendicular to the skin and thicker in dimpled areas, and thinner and radially arranged in areas where adipose tissue protrudes into the dermis, resulting in the dimpled appearance of cellulite. Consequently, alterations in subcutaneous cellular tissue and the dermis manifest as the external appearance of cellulite (18).

Based on the pathophysiology of cellulite observed in histological sections and imaging studies, we could infer that enzymes act at all levels to achieve an improvement in cellulite. One of the most important qualities of pbserum medical enzymes is their action on fibrous tracts where other treatments are less effective. Collagenase is the only protease that has the property of cleaving the bonds between the X-glycine-proline protein prevalent in collagen, allowing us to remodel the abnormally thicker collagen fibers generated in cellulite dimples, and restoring the network of these fibers. Lipase allows us to hydrolyze triglycerides into glycerol and fatty acids, resulting in a reduction in the size of adipocytes. This helps decrease the protrusion of fat cells into the dermis and thus improve the elevations in the quilted appearance of cellulite. High molecular weight HA (>107 kDa) is a glycosaminoglycan that improves hydration in the extracellular matrix; it regulates inflammation

and has a vital function in the early stages of inflammation; it promotes cell migration and proliferation, and regulates adhesion and angiogenesis during tissue repair, facilitating optimal wound healing (22-24). Lyase is the enzyme responsible for the degradation of glycosaminoglycans, and also increases the permeability of connective tissue, allowing for a broader action of enzymes (9, 20, 21).

Based on this knowledge, we decided to use enzymes in the High combination, due to its higher concentration of Collagenase in the deeper depression areas to release these fibrous tracts. We performed enzymatic subcision to remodel these areas with thick collagen fibers, especially in the gluteal area where we did not want to lose fat volumes, and in the deep dimples of the infragluteal and lateral thigh area. The Medium enzyme combination was used in the infragluteal and lateral thigh area where we aimed to improve cellulite, as well as in unwanted fat volumes.

In each session, a spectacular visual improvement was evident, as well as enhanced skin elasticity and firmness. These results also improved the emotional state of the patients and thus their overall quality of life.

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The journey of patient Cecilia



Dr Erick Santaella-Sosa

From our clinics, we always seek the best way to care for our patients. We strive to get to know them better, understand them deeply, learn about their concerns, needs, and worries, what causes them pain or frustration. It's important that our patients feel listened to, cared for, understood, so that we can earn their trust. After this step, we can explain their issues from our clinical perspective, always in connection with how they are experiencing it. This way, we'll achieve a better understanding, education, and peace of mind for the individual. Once this point is reached, we'll be able to offer them the best therapeutic alternatives and, of course, our advice, to reach a solution that satisfies not only our patients' desires but also our clinical goals.

Some will come with a treatment choice already made that they want to try, others will arrive apprehensive because it's their first experience of improvement they'll undergo; and some more, will simply arrive and ask for the best solution to their situation, which, of course, we'll try to make available to them, as is the case of our dear patient Cecilia, whom we are going to learn a little more about her experience with cellulite and her journey to us.

One day in the office, Cecilia came to see me, a charming girl. "Good morning, -Cecilia, how can I help you?" Cecilia directly told me: -"I have fat legs and I want to slim them down. I've heard about some injections and I want to try them." At that moment, before examining her, I asked her - "How do you feel?" Her first words were: - "bad, I feel depressed." Digging deeper into her daily life, her social life, and her emotional state, Cecilia confessed to me that she felt self-conscious, had received unpleasant comments, and that's why she always wore pants and didn't go to places like beaches or pools. She had restricted her social life and also had no intimate relationships, for fear of what people might say about her appearance. Among the things she had done to fix it were exercise and diet, as well as treatments with equipment, but she said frustrated, that no matter what she did, she didn't see results. She also went to a plastic surgery clinic before, where they advised her on liposuction, although they didn't guarantee that she would have good results, so she ruled it out. She didn't know what else to do, until a friend of hers told her that pbserum might be able to help her. Looking for information on the internet, she came across our social media, where we explained the treatments with pbserum, and she made an appointment with us.

I then began the physical examination; the appearance of orange peel skin was evident. Cecilia stood up, we pinched different areas of her affected skin with our thumb and index finger; at times she said it hurt. We were dealing with a patient with edematofibrosa panniculopathy in the thighs. I felt relieved at that moment knowing in advance everything we could do for her with pbserum. I explained to her at this point what the treatment consisted of and the results she could achieve. Cecilia also felt happy and excited as it was the first time she had been told about the process through which the treatment would help her in her situation. That's how we scheduled the first session. At first, she was a little scared, as it was the first time she had undergone injectable treatment. With so much misinformation on the internet about injected treatments with disastrous results, she was a little worried. Indeed, it is worrying to inject solutions that often, instead of benefiting, can harm a patient. However, I explained more in-depth about the process in which pbserum enzymes are produced and how sophisticated and safe they were. This gave Cecilia the courage and confidence to dare to try them.

Upon returning for the second session of pbserum, Cecilia told me that

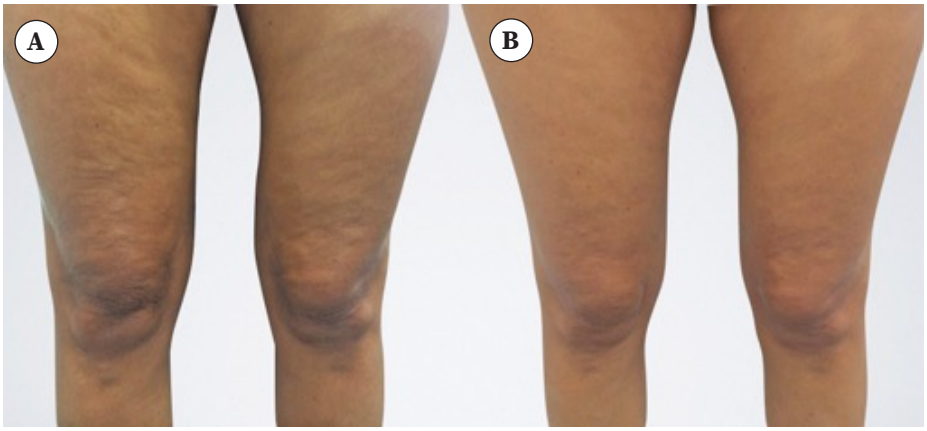

Figure 1. Cecilia´s legs: A) Before the treatment with pbserum and B) after the treatment with pbserum.

she had already noticed an improvement, her skin felt less swollen and even less irregularities; her excitement had tripled, she was very happy (Figure 1).

In addition to the pbserum sessions, Cecilia followed some guidelines to incorporate into her lifestyle that would favor achieving the expected results. For this, we gave her guidelines to follow a diet low in carbohydrates, saturated fats, and sodium. Also, regular exercise was essential, one in which she felt comfortable, where she worked on strength, endurance, or a combination of both. One funny thing I remember is telling her that cardiovascular exercise is not for everyone, as we have mistakenly been led to believe that cardiovascular exercise is the only type of physical activity that helps us control weight.

After the fourth session with pbserum, Cecilia was a different person, she felt like a beautiful woman with confidence. Her legs had decreased in volume, in adipose tissue, the irregularities in the skin were practically nil, and her texture was very smooth. Cecilia could wear any type of clothing and regained her social life with friends, partners, and also her self-esteem and confidence in situations where she would show her body, such as the pool or the beach. Cecilia was now comfortable with her body, and her quality of life was very good. And all thanks to pbserum.

Psychological impact of orange peel skin



Camino Olmedo



CELLULITE: AN UBIQUITOUS CONCERN

Cellulite, a common skin condition characterized by the dimpled or "orange peel" appearance of the skin, affects a significant proportion of the population, primarily women. While cellulite is not a medical condition treated by general physicians, its psychosocial impact should not be underestimated. This article delves into the multifaceted psychosocial effects of cellulite, shedding light on its implications for mental well-being, self-esteem, body image, and overaII quality of life.

Cellulite affects individuals of aII shapes, sizes, and ages, making it a nearly universal concern. It can manifest on various body areas, including the thighs, buttocks, abdomen, and arms. Despite its prevalence, society often stigmatizes cellulite, perpetuating unrealistic beauty standards and leading to detrimental psychological consequences.

PSYCHOLOGICAL IMPLICATIONS

Cellulite is viewed as an aesthetic issue rather than a disease1, but the significance of it is substantial, due to it is associated with profound negative psychosocial effects. Body dissatisfaction, psychosocial distress, anxiety, feeling as sadness or guilt, onset of eating disorders and decreased quality of life are highly prevalent among females with cellulite[2,3].

These women feel also embarrassed, more than 40% of women report receiving embarrassing comments about their cellulite[3]. The embarrassment and self-consciousness stemming from cellulite can lead to social withdrawal and avoidance behaviors. Individuals may avoid wearing certain clothing, participating in social activities, or even intimate relationships due to cellulite-related concerns. This problem suggests a great social impact in their lives[4,5] and pushes women to search a solution. Ninety-three percent of women want to know how to improve their cellulite6 and 78% report feeling the need to seek treatment[3].

Women suffering from cellulite feel impotence and frustration. A survey conducted in 2020 to 2000 women with cellulite concluded that women most commonly think about their cellulite at certain times, including when looking in the mirror (65%), at the beach or pool (54%) and during warmer weather (46%). Many of these women tried to improve their cellulite using various methods, including exercise (71%), diet (58%), topical treatments (36%), massages (25%) and in-office procedures (12%). However, 74% of women surveyed said that "no matter what I do, I will always have cellulite"[6].

TREATMENT IMPLICATIONS

Recognizing the psychosocial implications of cellulite is critical in the field of aesthetic medicine. Healthcare providers should not only address the physical aspects of celluli-

te but also consider its psychological toll. Treatments that improve cellulite appearance can have a positive impact on self-esteem, sociability, quality of life and overall mental well-being[2,4].

CONCLUSION

Cellulite, despite being a benign condition, can have profound psychosocial consequences. Its influence on body image, self-esteem, psychological distress, social behaviors, and quality of life cannot be underestimated. It is essential for healthcare professionals to adopt a holistic approach when addressing cellulite, considering both its physical and psychosocial aspects to promote overall well-being and confidence in those affected.

By recognizing and addressing the psychosocial impact of cellulite, we can strive for a society that embraces diversity in body shapes and sizes while providing support and solutions for those seeking relief from the psychological burden of this common condition.

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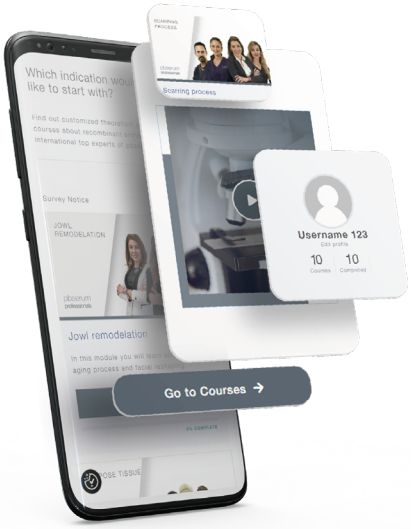
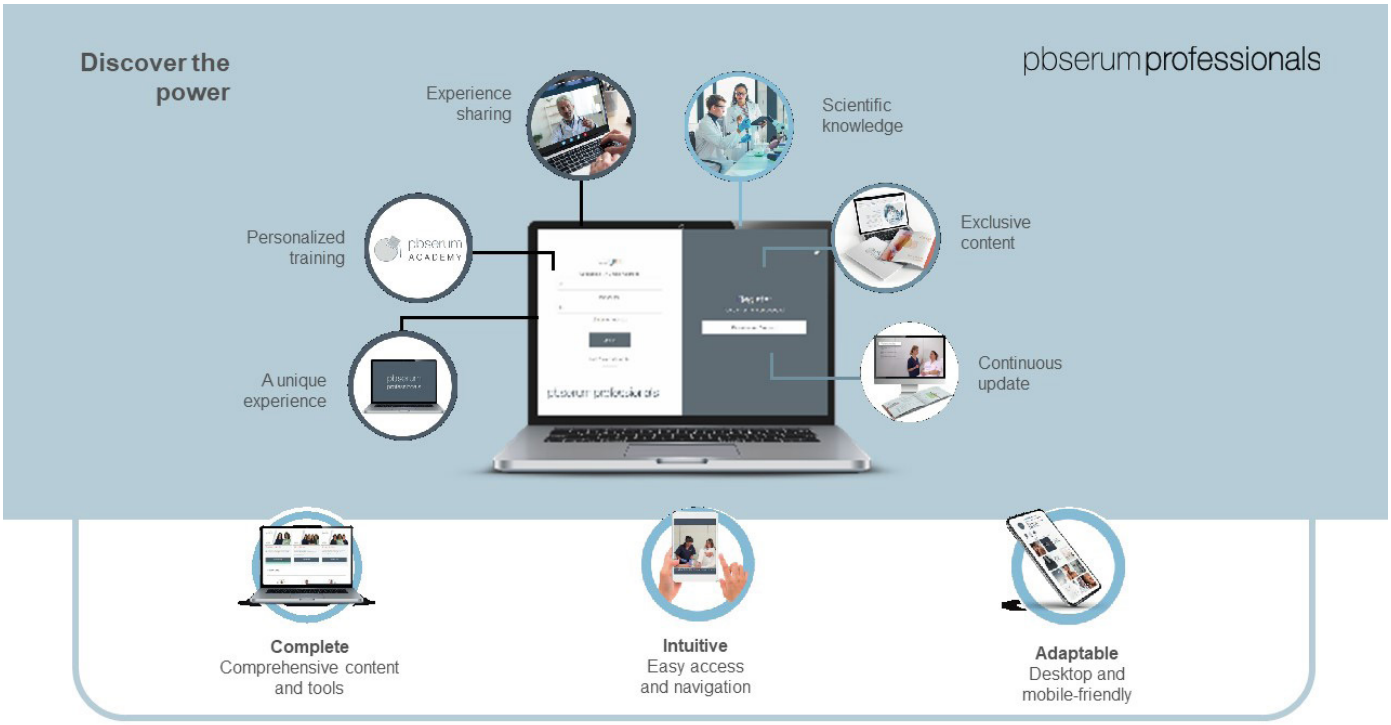
With great satisfaction and enthusiasm, we are pleased to present the conclusion of our first volume of our issue “Enzymes and Skin Science,” dedicated to the fascinating topic of cellulite. Throughout this volume, we have delved deeply into the underlying biological mechanisms, the latest research, and innovations in the treatment of this common skin condition, providing a comprehensive and up-to-date insight for the medical community.



First and foremost, we would like to express our sincere gratitude to all the distinguished doctors and healthcare professionals who have dedicated their time and attention to collaborate with such impressive content and to all of you reading the articles in this volume. Your interest and commitment to continuous education are fundamental to advancing the field of dermatology and aesthetic medicine.



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