Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2024;33:141-143
doi: 10.15570/actaapa.2024.25

Effectiveness of cellulite treatment with combined enzymatic therapy

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Abstract

Introduction: Cellulite, also known as edematous fibrosclerotic panniculopathy (EFP), affects up to 90% of women and has a significant aesthetic impact. EFP is a multifactorial condition characterized by local circulatory changes, increased adipose tissue thickness, and a fibrotic response involving thick collagen bundles and septa, driven by local hypoxia. Although numerous treatments exist, their effects are typically temporary. This study evaluates the outcomes of four patients with EFP treated using a combined recombinant enzymatic therapy consisting of a lyase, lipase, and collagenase.
Methods: A standardized protocol involving injections of a combined enzyme solution (pbserum Medium™) was administered to the lower limbs in three separate sessions. Pre- and post-treatment photographs were collected for comparative analysis.
Results: All four patients showed improvements in skin appearance and fibrosis, with no systemic or local adverse events reported.
Conclusions: We propose that a treatment strategy targeting the edematous, adipose, and fibrotic components of EFP may offer an economical and pathogenic-based approach for managing this condition in affected women.

Keywords: cellulite, lipase, collagenases, lyase

Received: 27 March 2024 | **Returned for modification:** 29 July 2024 | **Accepted:** 7 September 2024

Introduction

Cellulite, also known as edematous fibrosclerotic panniculopathy (EFP), is a localized metabolic disorder of the subcutaneous tissue that leads to changes in body shape with a significant aesthetic impact (1, 2). It is estimated to affect up to 90% of women (1). Although the exact pathogenesis of cellulite is not fully understood, it is currently regarded as a multicausal condition involving endocrine, metabolic, and circulatory changes (1). The high prevalence of cellulite among women has been linked to sex-specific anatomical differences in skin, subcutaneous fat, and connective tissue, which are influenced by estrogen (3). Imaging and anatomical studies have shown that the adipose cell chambers in women are larger in both height and width compared to men; consequently, adipose cells in women may tend to protrude into the overlying skin (4, 5).

Current evidence indicates a bidirectional pathogenic mechanism in cellulite, involving both local circulatory changes and increased adipose tissue thickness. A fibrotic response characterized by thick bundles and collagen septa, driven by local microcirculatory hypoxia, leads to structural changes in the interstitial matrix and subcutaneous adipose tissue (2). These changes create connections between the skin and subcutaneous fat, resulting in the classic "orange peel" appearance, skin dimples, and surface irregularities associated with cellulite (2). One of the key molecular mechanisms underlying septa formation is the activation of hypoxia-inducible factor (HIF1A) in adipose tissue. During the early stages of adipose tissue expansion, the local microenvironment becomes hypoxic due to an inadequate vascular network. This hypoxia induces HIF1A expression, promoting adipose tissue fibrosis, a state of local inflammation, and impaired endocrine function of the adipose tissue (6).

Evidence suggests that treatments targeting the collagen-rich fibrous septa in cellulite dimples, including mechanical and surgical approaches, are effective (3). However, a combination of recombinant enzymes—namely, a lyase, lipase, and collagenase—targeting the edematous, adipose, and fibrotic components of cellulite, respectively, provides a economical, pathogenic-based, and synergistic strategy for managing this condition. The combined enzyme solution pbserum Medium™ (Proteos Biotech, Spain) is an innovative minimally invasive treatment for cellulite that combines lyase PB72K, lipase PB500, and collagenase G/H PB220. In this case series, we describe the outcomes of patients treated with this minimally invasive combined strategy.

Methods

A prospective pre-post study was conducted to evaluate the effects of a combined enzymatic treatment for EFP. The inclusion criterion was a clinical diagnosis of EFP, with patients that had a history of both invasive and non-invasive treatments for EFP allowed to participate. Exclusion criteria included pregnancy and hypersensitivity to enzyme therapy. Written informed consent was obtained from all participants, and the study design was approved by a local ethics committee.

Data collected included demographic information (age and sex), clinical details (from physical examinations), and a history of previous treatments, including their outcomes and any adverse events. Following a clinical confirmation of EFP and baseline photographic documentation, participants were treated using a standardized protocol. This involved reconstituting pbserum Medium™ (Proteos Biotech, Spain), which includes lyase PB72K, lipase PB500, and collagenase G/H PB220, in 19.5 ml of buffer solution combined with 0.5 ml of 2% lidocaine. The reconstituted product was then injected into each lower limb at specific points (10 injections of 1 ml each) using an aseptic technique. This injection protocol was repeated across three separate sessions, regardless of the cellulite's location or severity (Fig. 1).

Initially, the product was delivered into the deep subcutaneous layer to ensure direct contact between the enzymes and their

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substrates for optimal clinical outcomes. Subsequent injections targeted more superficial planes to ensure thorough distribution into the intradermal layers.

A new set of photographs was taken 2 weeks after the final treatment session for comparative analysis. Due to the descriptive nature of this case-series study, no formal statistical analysis was performed.

Results

Four female patients were included in the study. Baseline data are summarized in Table 1. All participants successfully completed the scheduled treatment sessions, which involved administering the reconstituted combined enzymes at each specified point, in both the deep subcutaneous plane and the superficial intradermal plane.

Improvements were observed in skin appearance and fibrosis, as assessed by the treating physicians, with a notable reduction in cellulite grade. Photographic documentation of the results is shown in Figures 2 and 3. No systemic or local adverse events were reported.

Discussion

In our case series, application of combined recombinant enzymes (lyase PB72K, lipase PB500, and collagenase G/H PB220) was associated with clinical improvement of EFP with a good tolerability profile. EFP is highly prevalent (1); nevertheless, current treatment options are not completely successful, and results are only temporary (1). It is worth noting that combined enzymatic therapy targets all components of EFP, taking into consideration that this cyclical, changing disorder is related to several factors, including genetic predisposition, hormonal levels, microvascular circulation, and connective tissue architecture (1). Bacterial recombinant collagenases from *Clostridium* DNA can induce multiple scissions in the collagen triple helix to induce a complete collagen lysis, resulting in small peptides (7). In addition, recombinant lipases catalyze the hydrolysis of triglycerides to glycerol and free fatty acids and, unlike native lipases, do not require specific cofactors (8). Of note, the recombinant origin of enzymes precludes the potential impact of previous or current hormonal treatment due to the absence of glycosylation in their macromolecular structure.

According to available literature, application of lipase to in-

Table 1 | **Main basal characteristics of the patients.**

Patient	Age	Relevant history	Cellulite localization	Cellulite severity*	Previous treatments
1	32	Unremarkable	Thighs and gluteal area	Grade 1	None
2	45	Unremarkable	Bilateral, trochanteric	Grade 2	Ultrasonic cavitation
3	28	Grade I obesity	Bilateral, trochanteric, and peritrochanteric	Grade 2	None
4	26	Hormonal contraception for 1 year	Bilateral, trochanteric, and peritrochanteric	Grade 3	None

*Cellulite was graded according to the Nürnberger–Müller clinical classification: grade 0 (skin is smooth in both lying-down and standing positions); grade 1: skin is smooth at rest but shows a mattress-like appearance on pinching; grade 2: skin is smooth at rest but has a mattress-like appearance on standing; grade 3: skin has a mattress-like appearance in both lying-down and standing positions.

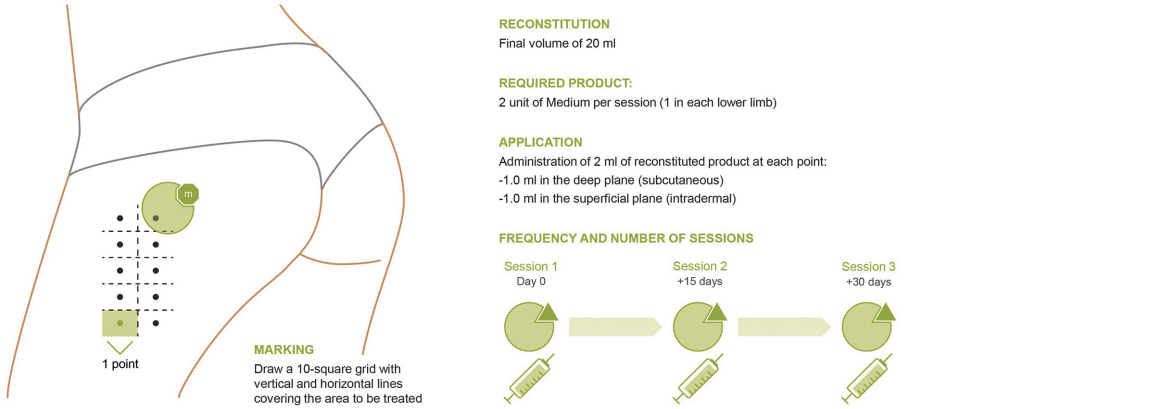

Figure 1 | Overview of the treatment administration protocol.

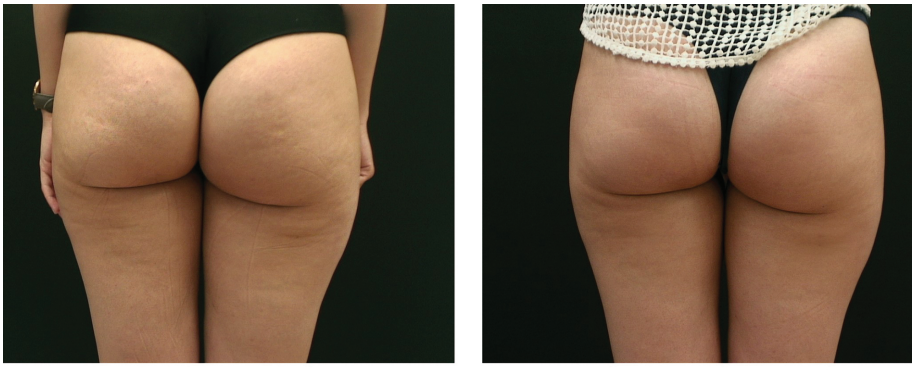

Figure 2 | Patient #1 results at baseline and outcomes 2 weeks after the third session.

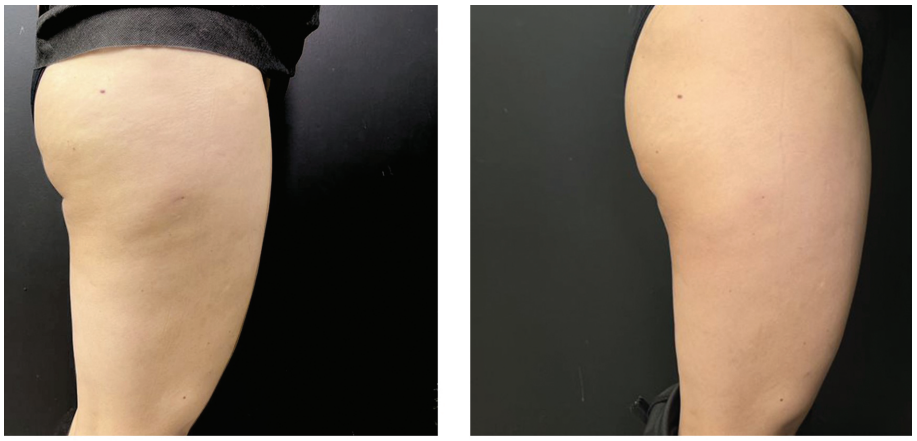

Figure 3 | Patient #2 results at baseline and outcomes 2 weeks after the third session.

duce lipodilution in areas including the thighs has shown clinical effectiveness with a good safety profile (2). The association of a recombinant lyase in the same reconstituted enzymatic combination facilitates the tissue penetration of the other active products and reduces edema at the tissue level (9–11). It is worth noting that the combined enzyme therapy targets several components of cellulite; lipase acts on adipocyte hypertrophy induced by tissue hypoxia, which in turn is increased by the deposition of glycosaminoglycans (GAGs). Presence of GAGs in the capillary walls attracts water, leading to dermal edema (substrate of lyase) and perpetuation of hypoxia (12). Finally, collagenase induces septolysis of adipose tissue, which facilitates the recovery of its normal architecture.

Even though our small sample is a limitation of our study, we emphasize that the combined enzymatic therapy was effective in patients with very different characteristics (weight, receiving hormonal contraception, variable EFP localization and severity, and previously treated). Another limitation is that all participants were female; however, most patients with EFP are women, according to current epidemiological evidence (1).

Conclusions

We conclude that combined enzymatic therapy with pbserum Medium™ (lyase PB72K, lipase PB500, and collagenase G/H PB220) is an effective and safe treatment of EFP in a real-world setting. Future studies with larger samples are warranted to confirm our results.

Conflict of interest

Erick Santaella-Sosa has received honoraria as a speaker for Sinclair. Desirée Castelanich has been a speaker for Proteos Biotech. Jorge López Berroa is the Global Clinical & Medical Head Collaborator of Proteos Biotech SL. Fotini Bageorgou has no conflict of interests to disclose.

Funding

The medical writing was funded by Proteos Biotech.

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