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CASE REPORT

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Recombinant enzymes' effect on scarring and fibrosis

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ABSTRACT

Introduction: worldwide, a large number of surgical procedures are performed daily for aesthetic purposes, often providing excellent outcomes in terms of appearance enhancement. However, these interventions are not exempt from adverse effects, including visible skin alterations such as hypertrophic scars and fibrosis, which may negatively impact patients' physical and emotional well-being.

Case description: Three cases of patients with hypertrophic scars and/or fibrosis following surgical interventions were treated using an injectable cocktail of recombinant enzymes. From the first treatment session, all patients reported positive changes. Post-treatment evaluation showed improvements in tissue mobility, sensitivity, pain, and visible appearance of the affected areas. These physical improvements were accompanied by a noticeable enhancement in patients' emotional state.

Conclusions: Treatment with an injectable cocktail of recombinant enzymes may represent a beneficial therapeutic option for managing hypertrophic scars and fibrosis after surgical interventions, contributing to both physical recovery and improved quality of life.

Keyword: recombinant enzymes, hyaluronic acid, collagenase, hypertrophic scars, fibrosis, keloid

Introduction

It is estimated that 234.2 million surgical procedures are performed worldwide each year (1), involving excisions and wound healing with consequent scarring. Among these surgical interventions, we find abdominal or pelvic operations and cosmetic surgeries, with liposuction and abdominoplasty being the most common (2). These operations often yield spectacular results for the patient's appearance and emotional well-being; however, they can have significant side effects if not performed properly, for example, when the intervention is not carried out accurately, or an incorrect technique is used, or also when the patient's selection is not adequate, his expectations are unrealistic, or the postoperative treatment is incomplete. One of the most common sequelae observed is scarring and fibrosis.

Scars can be normotrophic if the wound healing has been conducted properly, that means, without infection, with a normal behavior of the fibroblasts, and with the generation of an adequate granulation tissue (3). Alternatively, atrophic, hypertrophic, and even keloid scars may appear when wound healing is abnormal (4).

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In a hypertrophic scar, there is an overproduction of connective tissue and collagen fibers above the skin, respecting the margins of the original wound. They may produce burning or itching and be particularly sensitive to touch (4-6). In fibrosis, there is an excessive accumulation of fibrous connective tissue, such as collagen and fibronectin, in and around inflamed or damaged tissue (7,8).

The scars and fibrosis can affect mobility, color, and quality of the skin, sensitivity of the zone, and be uncomfortable for the patient. Scars are visible impairments that could change the patient's perception of their image, so some affected people adapt by concealing these marks; they become less sociable, lower self-confidence, and have a detrimental impact on their personal and professional relationships (9-11).

In these case series, we show our protocol with recombinant enzymes (HA 2.0 High PBserum, Proteos Biotech S.L.) to treat postsurgery fibrosis and scarring processes to obtain physiological outcomes, but also from the psychological point of view.

Methods

Each patient received between 2 and 3 units of recombinant enzymes (HA 2.0 High PBserum, Proteos Biotech S.L.) per session. Each unit consisted of a vial of enzyme reconstituted with 2ml of hyaluronic acid (HA) and 20 mL of buffer solution. In Case 3, five treatment sessions were performed, as marked clinical improvement was observed after each session. In Cases 1 and 2, treatment was concluded after the fourth session because the maximum clinical benefit was considered to

have been achieved, and an additional session was deemed unlikely to provide any further appreciable improvement. Injections of 0.5 cc at each point were administered with a 30G x 13 mm needle, since it was impossible to use a cannula due to the hardness of the tissue: 0.4 cc in retrotracing longitudinal injection technique from deep to superficial inside the scar (in the marginal area) and 0.1 cc superficial; in some points, the fan technique was used with 0.5 cc.

Clinical response was assessed based on patient-reported outcomes and observable changes following treatment sessions.

Before entering the study, all patients underwent a complete history and physical examination. They received detailed information regarding the study's objectives, potential risks and benefits, and their rights as subjects. They provided written informed consent, which included authorization for product application, photographic documentation, data processing, and the publication of collected data and images.

Cases presentation

Case 1: This is a 35-year-old woman with a hypertrophic scar of approximately 6 inches long and 3 inches high, and post-traumatic fibrosis in the lower abdomen, resulting from a liposuction and an abdominoplasty 2 years ago. She received carboxytherapy for several months. The patient could not sit properly, due to scar stiffness and fusion of the scar to deep tissue; the whole area was hard to the touch, with a vertical growth of 0.5 cm in some points; and she had lost sensitivity in some zones and in others she had hypersensitivity, causing her pain even to the touch; the scar had a reddish-purple color, different from her skin; and it had also formed an indentation that deformed her figure. All these aspects affected her psychologically, triggering depression for years. The patient received 2 units of HA 2.0 High-PBserum per session. A total of 4 sessions every 15-20 days were performed. The patient noticed improvement already after the first session. At the end of the treatment, the patient saw how she had recovered the sensitivity in the area; she could sit properly and dress herself, no longer using girdles and other molds, since now her abdomen had regained uniformity; the patient described it as "the tissues peeled off from the depth". The area recovered its mobility, and the coloring was uniform with her skin tone, thus attenuating the appearance of the scar (Fig. 1). The patient improved psychologically, both in her mood and in the perception of her image, which produced an important change in her life.

Case 2: A 33-year-old man presented with several post-surgical hypertrophic scars in the scapula area, produced in his childhood when he received 3 operations for aneurysmal bone cysts. In one area of the scar, he had lost sensitivity and experienced discomfort. In addition, it was a mark that evoked an unpleasant memory for the patient. He received 2 units of HA 2.0 High-PBserum per session, for a total of 4 sessions every 15 days. The patient noticed improvement from the first application, and after the entire treatment, he saw that he had recovered sensitivity and had less discomfort. In addition, the scar went from being somewhat rigid to more mobile and elastic, and the appearance of the scar was different, attenuating the mark and thus improving the emotional aspect of the patient (Fig. 2).

Case 3: This is a woman, 35 years old, with post-surgical fibrosis after liposuction, 1 year ago. The woman presented with pain in the entire abdominal area, with a sensation of stretching and crumpling of the skin, and she felt strings in the interior that tightened the entire zone. In addition, the coloration was purple, in a branching pattern. In this patient, 3 units of High-PBserum were administered per session, as the treatment area was considerably larger than in the other cases. A total of five treatment sessions were performed at 15-day intervals. The therapeutic approach was designed to address fibrotic bands, nodules, and overall skin quality, as the entire abdominal region was involved, in contrast to the other patients, in whom treatment was primarily confined to the scar itself. At the fourth treatment session, collagenase combined with vitamin C (Lift+, PBserum, Proteos Biotech S.L.) was incorporated into the treatment protocol to provide a multi-layered therapeutic approach. Lift+ was injected into the superficial dermis using both the nappage technique and a very superficial fanning technique with a cannula, with the aim of improving skin texture and overall skin quality, which were significantly compromised. For adhesions, superficial injections of 0.2 cc every 2 cm^2 were administered. For fibrotic nodules, 1.5 cc per nodule was administered, using a retrograde injection technique from deep to superficial inside the fibrotic nodule three times at different angles (0.5 cc per angle). The patient noticed improvement in the second session, and at the end of the three sessions, the patient had no

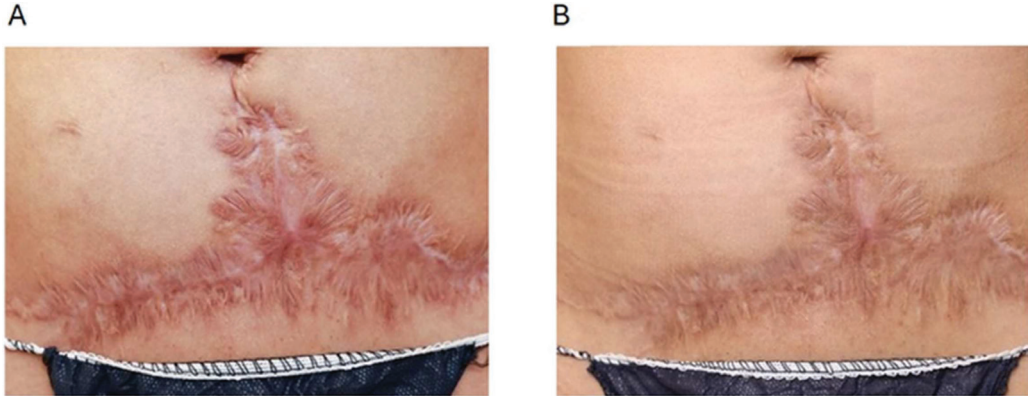

FIGURE 1 - Hypertrophic scar and fibrosis of patient 1. A) Before treatment with recombinant enzymes. B) After the end of the treatment with recombinant enzymes.

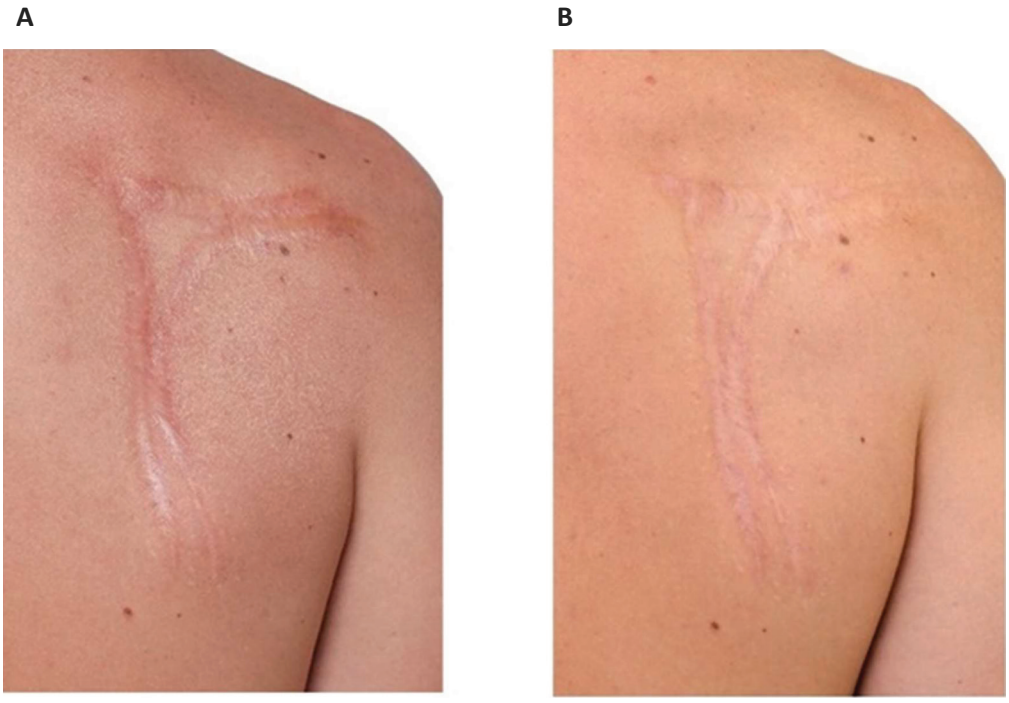

FIGURE 2 - Hypertrophic scars of patient 2. A) Before treatment with recombinant enzymes. B) After the end of the treatment with recombinant enzymes.

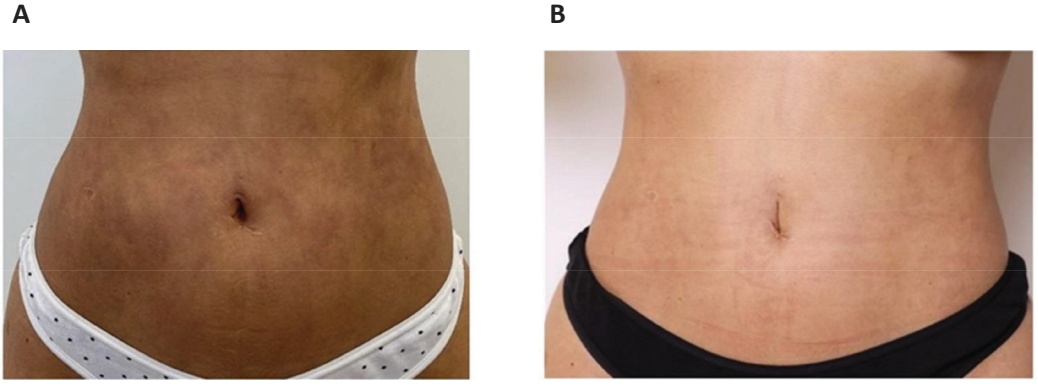

FIGURE 3 - Fibrosis of patient 3. A) Before treatment with recombinant enzymes. B) After the end of the treatment with recombinant enzymes.

more pain, the sensation of the tight area was eliminated, and the purple marks disappeared, unifying the coloration with that of the skin (Fig. 3). The patient also experienced an emotional change, improving her quality of life.

Discussion

Scars, keloids, and fibrosis occur because of an altered process of wound healing. There is a proliferation of fibrotic connective tissue with many cellular signaling processes involved. There is a dysregulation of cellular mechanisms, leading to an increase in growth factor production. Consequently, an exacerbated fibroblast proliferation, neovascularization, fibronectin, and collagen synthesis are carried out. At the same time, the metalloproteinase activity is also altered, triggering a decrease in collagen degradation and an increase in collagen I versus III (12).

In our case series, we show how the cocktail of recombinant enzymes together with high molecular weight HA improves the appearance of the skin, increases sensitivity, and decreases the stiffness of the patients' area. Although our findings are derived from case reports and therefore carry the inherent limitations associated with the absence of a standardized study protocol, they are consistent with and further support the evidence reported in a multicenter clinical study conducted in 2021 (13), where 42 patients and 44 scars were treated with recombinant enzymes and decreased pruritus, pain, thickness, irregularities, and stiffness of hypertrophic, atrophic and keloid scars from the first application.

Previous studies have noted that the amount of accumulated HA in hypertrophic scars and keloid tissue was lower than in healthy skin (14,15). In an *in vitro* study, Hoffmann (16) showed that high molecular weight HA decreased fibrosis

and reduced the manifestation of keloids. In a mouse model of endometrial fibrosis, Zhu showed how treatment with high molecular weight HA significantly decreased the area of fibrotic tissue (17). In our cases, we provide high molecular weight HA into the skin layers, enhancing hydration, modulating inflammation, and creating an optimal environment for the tissue repair process, which is supposed to reduce the amount of fibrotic tissue in our patients.

The collagenase enzyme has also been successfully used for the treatment of different pathologies where there is an accumulation of fibrotic tissue, such as Dupuytren's disease, Peronie's disease, and arthrofibrosis (18-20). Bae-Harboe (21) used collagenase in six patients with keloid scars, achieving a 50 % reduction in size ($p = 0.02$). Kang (22) used collagenase and triamcinolone in keloid and hypertrophic scars, showing a 33% reduction in scar volume, although this result was only temporary. In our patients, collagenase is thought to be responsible for degrading the collagen fibers, triggering new tissue remodeling, and preventing inflammation and apoptosis (23).

Current treatments for hypertrophic scars include both noninvasive and surgical approaches; however, their effectiveness remains variable and is frequently limited by recurrence, side effects, and insufficient high-quality clinical evidence. Novel therapies such as botulinum toxin A, mesenchymal stem cells, and fat grafting have demonstrated encouraging preliminary outcomes, although most evidence comes from small patient cohorts and preclinical studies (24,25). In this context, our findings indicate that collagenase, together with HA, could represent a promising adjunctive therapeutic approach, as both were associated with improvements in scar appearance and stiffness according to patient reports. In addition, enzyme therapy may provide advantages over intralesional corticosteroids, which are linked to adverse effects such as hypopigmentation and skin atrophy (26). Overall, these findings emphasize the need for more rigorous research.

In our case series, we also collected their testimonies to know how their emotional state has changed, compiling for the three cases a remarkable improvement in their mood and quality of life. However, this represents a limitation of the study, as no validated questionnaire was used. Further studies incorporating validated psychological assessment tools are needed to obtain more accurate data.

Conclusion

In conclusion, the treatment of hypertrophic scars and fibrosis with recombinant enzymes improves the appearance of the skin, increases sensitivity, decreases stiffness, and has a positive impact on the emotional state of patients. It is necessary to continue conducting studies in this field; however, the use of recombinant enzymes could be an alternative to other treatments with fewer side effects.

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Disclosures

Conflicts of Interest: The author, Mireia Carratalá Górriz, declares that there is no conflict of interest regarding the publication of this article. The authors Camino Olmedo, Valeria Kopytina, and Jorge López Berroa are employees of the company Proteos Biotech, and they received a salary for this purpose.

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