How Profound Effectively Treats Cellulite via Collagenesis and Elastogenesis

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Cellulite Description

Cellulite is an aesthetically undesirable cosmetic issue for many post-adolescent women. Its presence is largely observed in the gluteal-femoral regions with an "orange-peel" or "cottage cheese" appearance[1]. The condition is not specific to overweight issues, although increased adiposity will exacerbate the cosmetic appearance.

In the 1980s, Nurnberger and Muller[2] examined the structure of skin and the component subcutaneous tissue. They found that in the female body, the uppermost layer of the subcutaneous tissue consisted of freestanding fat cell chambers, which were separated by vertical walls of connective tissue called septa. The most superficial part of these upright fat chambers was in the form of an arc-like dome, which was weak and easily collapsible when pressure was applied. This pressure could be due to excess weight, fluid retention or lack of strength due to lack of exercise. These larger chambers generated smaller compartments of fat cells (known as papillae adipose) that clustered tightly under the skin. This combination of freestanding fat cell chambers and compartmentalized clusters of fat cells are the elements that create the change in appearance in the skin's surface that we know as cellulite.[3]

More recent publications on cellulite have further confirmed these specific cellulite-related features in dermis as well as subcutaneous layers of the skin.[4-7] In the dermal space, papillae adiposae were shown to be protruding within dermis in the form of intrusion pockets. Figure 1 shows a gross histology of the dermis/subcutis transition where fat pockets are present. The dermal thickness for cellulite patients was also observed to be thinner than in patients with no cellulite.

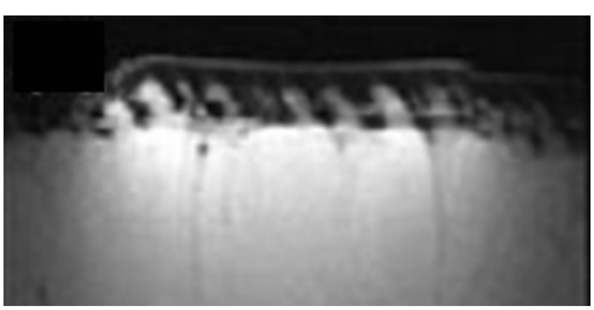

Figure 1 - Fat indentation invading the dermal layer

Figure 2 - Fibrous septae in subcutis perpendicular to the skin surface

Deeper in tissue, samples harvested from female subjects with cellulite have suggested a higher incidence of fibrous septae oriented perpendicular to the skin surface, in sharp contrast to males who tend to have the septae organized in a crisscross fashion and, therefore, do not tend to exhibit cellulite features. The arrangement of fibrous septae perpendicular to the skin surface for a female with cellulite is shown in Figure 2.

This subcutaneous fibrous strand organization tends to create an uneven appearance of the skin surface, which is characteristic of cellulite.

Interestingly, a published study by Marenus[8] concluded that one of the main causes of cellulite was a break down in collagen and elastin fibers that function to keep the skin smooth and firm.

Mechanism of Action

Profound is an innovative micro-needle electrode array used to deliver radiofrequency energy to the reticular dermis and the superficial part of the subcutis (hypodermis). When activated, the electrode array is deployed within tissue. This minimally invasive approach enables temperature sensors within the electrode tips to be strategically positioned in the dermis or subcutis, depending on the selected cartridge (Figure 3).

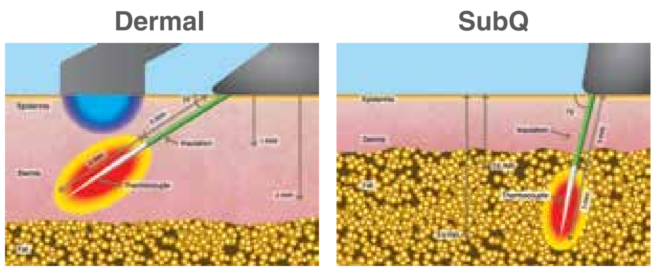

Figure 3 - Dermal and SubQ cartridges

Bipolar RF energy is then delivered between the electrode pairs, creating controlled, fractional treatment zones. During energy delivery, tissue temperature and impedance are actively monitored and used to control the treatment.[9-10] Physicians can, for the first time, select an optimal tissue temperature of 67°C and 4-sec duration as clinical endpoints, which has been shown to maximize clinical results in previously published studies.[11-12]

Treatments targeting the dermis and subcutaneous layers of the skin to restore collagen and elastin, as well as produce tissue remodeling, have a beneficial effect on the appearance of cellulite. The mechanisms of actions are described as follows:

1. **Increases dermal thickness** – An increase in the dermal thickness would create a condition where the hypodermal fibrous strand organization described above would have less tendency to deform the skin's surface and would, then, improve the appearance of cellulite. A thicker and healthier skin would have less tendency to deform due to the underlying conditions in the subcutis and would be less susceptible to exhibit divots and orange-peel features due to papillae adiposae.
2. **Remodels septae** - The organization of subcutaneous fibrous bands called septae play a major role in cellulite. Remodeling these fibrous bands by creating a new spatial organization, and creating younger and more elastic tissue by inducing collagenesis and elastogenesis responses, will make the bundles less prone to deform the skin's surface and create cellulite.
3. **Debulks fat** - A volumetric reduction of the fat lobules contained within the subcutaneous fibrous bands would decrease the local forces responsible for the presence of cellulite, especially in the visible bulging areas.

The proposed mechanisms of action will be further explained and described in the following sections.

Scientific Data

1. **Increases dermal thickness** – It has been shown by Hantash et al.[13] that a dermal treatment with Profound triggers a vigorous anabolic wound healing response capable of creating new dermal volume, containing elastin, collagen, and hyaluronic acid. The wound-healing response of the thermal injuries created by Profound was evaluated to determine the effects on collagen, elastin and hyaluronic acid. The inflammation process was also characterized to better understand the underlying biological sequence involved in the wound-healing process.

   It is well known that heat shock protein HSP47 is of primary importance for collagen production. The histological study from Hantash revealed that HSP47, which is a long-lasting wound-healing regulator of collagen, was first detected two days after the procedure and continued to increase between two and ten weeks. Interestingly, HSP47 was localized within the zones of thermal injuries 2 days post-treatment, and became diffusely spread throughout the dermis from day 28 to week 10.

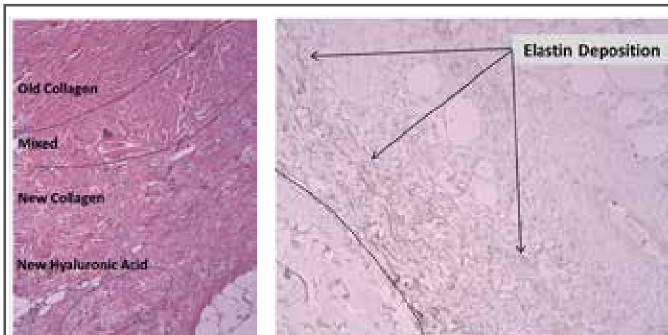

Figure 4: 10-week dermal remodeling after a Profound treatment.
Left panel: neocolagenesis and hyaluronic acid deposition showed after H&E staining.
Right panel: neoelastogenesis showed after elastic - Van Gieson staining method.

This means that the production of new tissue was not restricted to the zones of thermal injuries alone, but was generalized throughout the entire dermis. At ten weeks, new collagen and hyaluronic (HA) deposition were observed by H&E staining (Figure 4, left panel).

More importantly, a profound amount of new elastin was also observed in areas where new collagen was present (Figure 4, right panel). In addition, Polymerase Chain Reaction (PCR) studies revealed a nearly five-fold increase of Tropoelastin 28 days after treatment. Tropoelastin is the basic molecule forming elastin: multiple molecules can bind together to create long elastin polymeric chains. This was the first direct evidence of significant new elastin production after energy-based skin treatment ever reported in the literature.[13]

The authors also reported a low increase of catabolic enzymes (MMPs), responsible for the degradation of collagen denatured by the thermal injuries, and a significant increase of anabolic activities, responsible for adding new tissue. The precisely induced thermal dose in the reticular dermis during a Profound treatment creates a vigorous wound-healing response, which shifts the balance of anabolic/catabolic process toward the anabolic activity – therefore increasing net dermal volume.

In his paper, Hantash[13] suggested that the wound healing response triggered by Profound could provide beneficial effects for the treatment of skin laxity and wrinkles, while providing a natural dermal volumizing effect. The same process can also lead to long-lasting cellulite improvement by increasing the dermal thickness of the treated skin and by improving the flexibility and elasticity of the skin – therefore creating a dermal layer less prone to surface deformation due to the underlying subcutaneous structures, and consequently improving cellulite conditions.

2. **Remodels septae** - It is well accepted by the medical community that perpendicular septae (shown in Figure 2) are especially prominent in women and play a key role in the appearance of cellulite. These fibrous septae are essentially made of stiff collagen bundles and have a tendency to pull on the skin surface and cause the cellulite dimples. Creating thermal injuries using a precise thermal dose of 67°C for 3-4 sec in collagen-rich tissue, such as fibrous septae, has been shown to partially denature collagen and elicit a unique tissue remodeling process.[12] After the creation of optimal thermal injuries, the tissue quickly respond to the treatment by releasing an arsenal of cytokines – the proteins responsible for promoting the wound-healing process. The initial cytokine response recruits macrophages to begin removing damaged tissue. Macrophages then release a second set of cytokines to recruit fibroblasts to the site of injury. Fibroblasts are the key anabolic cells that will replace heated tissue and restore the skin to a more youthful state. As healing progresses, macrophages decline and fibroblasts increase, resulting in the production of new elastin, collagen and hyaluronic acid; therefore remodeling the initial tissular substrate.

   In their seminal paper, Hantash et al.[13] demonstrated that, during the remodeling process described above, the relative expression of tropoelastin (the basic component of elastin) increased by a factor of 5 at three weeks after a Profound treatment. This dramatic increase of elastin level was observed histologically (see Figure 4), and has been shown to improve the mechanical properties of the tissue, which became more pliable with up to 16% improvement in elasticity.[14]

   Therefore, partially denaturing the collagen of the fibrous septae and triggering a remodeling process, where a neocolagenesis and neoellastogenesis response is triggered, will make the septae more pliable and elastic, and alleviate mechanical tension along those septae to lessen the pulling effect on the skin surface to consequently improve the cellulite appearance. As for treatment of laxity, elastin can play a key role in cellulite treatment.

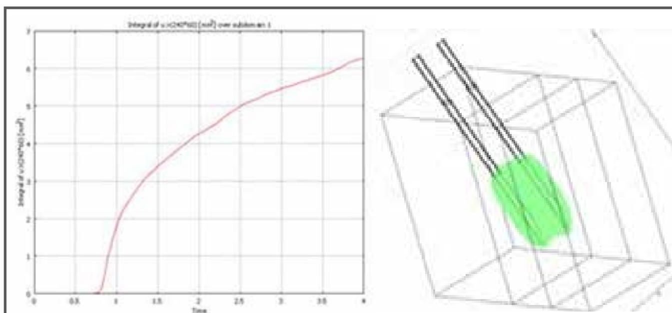

Figure 5 – Left panel: Volume of fat removed by apoptotic response based on the Sapareto-Dewey model. Right panel: Isosurface representing (CEM43=100 min) after one Profound application using settings of 67°C and 4 sec.

3. **Debulks fat** – It has been shown that thermal injuries in collagen-based tissue can trigger collagenesis and elastogenesis. It is also known that the same thermal

injuries can create adipocyte apoptosis and lipid-rich subcutaneous layers. Creating thermal injuries with the Profound SubQ cartridge has, therefore, the capability of reducing fat volume to decompress the fat pockets surrounded by septal network and therefore, improving cellulite appearance.

The adipocyte sensitivity to a time-temperature thermal dose has been previously characterized by Sapareto and Dewey.[15] In the study, the authors demonstrated that the adipocyte's viability was compromised when maintained at 43°C for 100 minutes. They also characterized adipocytes viability time at different temperatures, using an equivalent temperature model, which is expressed in equation [1].

$$CEM43 = \int_0^t R^{T-43}\, dt \qquad [1]$$

where:

CEM 43 is the amount of equivalent minutes at 43°C;

t is the time;

T is the temperature in Celcius;

R = 4 for T ≤ 39°C, and R = 2 for T ≥ 39°C.

The Sapareto-Dewey model, therefore, allows the use of this equation[15] to calculate how long it takes to obtain the equivalent of 100 minutes at 43°C to generate adipocyte apoptosis.

Using the same simulation model already published[10] to mimic the thermal profile created by a pair of bipolar needles implemented in the Profound design, the isosurface representing 100 minutes at 43°C was calculated (CEM43 =100) to characterize how much fat volume would be removed through the apoptotic process. Figure 5 shows the volume per pair of needles.

A volume of 6.2 mm^3 of fat reduction per needle pair was obtained using a setting of 67°C and 4 sec. The total volume of fat reduction obtained through apoptotic process can, therefore, be extrapolated based on the number of needle insertions during treatment.

For example, on a typical 15 x 15 cm^2 thigh area, an average of 200 insertions would be done in one treatment session on one thigh. Therefore, 6.2 mm^3 is the amount of fat affected between one pair of needles.

6.2 mm^3 x 7 pairs of needles x 200 insertions = 8,680 mm^3 (or 8.63 cm^3) per thigh. Assuming one treats both thighs, the total fat reduction for both thighs would be: 8.63 cm^3 x 2 = 17.36 cm^3 for both thighs.

The simulation results presented in this section demonstrate the capability of the SubQ module of the Profound system to create an apoptotic response in adipocytes and, therefore, decrease the total volume of fat contained in fat pockets involved in the appearance of cellulite. Depending on the severity of the patient's cellulite, a denser treatment density will trigger more volume reduction.

Lastly, it is worthwhile noting that the volumetric reduction through lipolysis was not simulated since no mathematical model exists to simulate the process. As a consequence, the total volume of fat reduction obtained by the model above is likely underestimated.

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