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LETTER TO THE EDITOR

Adipocyte Membrane Lysis Observed After Cellulite Treatment Is Performed with Radiofrequency

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Cellulite is considered a disease of the subcutaneous fat layer that appears mostly in women and consists of changes in fat cell accumulation together with disturbed lymphatic drainage, affecting the external appearance of the skin [1]. Changes observed in the fibrotic septae between fat cells, reduction of the metabolic rate, and thus congesting tissue affect the external aspect of skin, with alteration of the skin surface that appears bumpy and uneven. Cellulite starts at puberty in almost all women, and when the deposition becomes excessive, it is a condition that is difficult to control and treat. Various treatment modalities with varying degrees of success have been proposed [2]. Reports suggest that radiofrequency (RF) electrical energy is effective when used on and absorbed by the affected tissue [3, 4]. RF current produces a heating effect that depends on current mode and intensity as well as on the natural resistance or impedance of the skin to the passage of electricity. Electrical impedance of the skin rises with increasing depth and coarser collagen elastin fibers. Impedance will decrease with an increase in blood content in the treated area due to continuous application of treatment. On the other hand, progressive heating of tissue leads to reduced impedance. The RF thermal effect is “blind” to the natural skin pigmentation and is transmitted deeper than light, thus exerting action on the subcutaneous layer.

RF can be monopolar or bipolar. In most monopolar RF devices, a single electrode is applied to the skin while the other electrode is fixed to a remote part of the patient’s body. In bipolar RF, electricity passes along a well-defined arc through the target tissue from one electrode to the other. For bipolar RF, the depth reached by the electricity, according to physics, is one half the distance between the electrodes. The idea of combining RF with infrared (IR) light treatment for a more superficial heating, together with mechanical massage and suction, has gained support in the past few years [5]. Synergistic action on treating cellulite has been achieved with promising clinical results [6].

The product Vela Smooth™ (Syneron®, Yokneam, Israel) incorporates mechanical massage and suction, IR light, and RF electrical current. The latter delivers up to 20 W at 1 MHz, and IR light is emitted over a waveband of 700–2000 nm. Both energies, electrical and optical, are applied simultaneously to the cellulite area. At the same time, mechanical massage is given together with suction action up to around 400 mbar of negative pressure. All these combined treatments are delivered through the handpiece which is manually applied to the skin by the person giving the treatment. The specific geometry of the electrodes and the vacuum impact upon inserting the skin between electrodes provide deep RF penetration when the handpiece is moved over the skin. The handpiece permits treatment at different intensities.

Treatment in the trials of this report was given at the highest intensity. The purpose of our study was to check the histologic condition of cellulite in the buttock before and 2 h after a single treatment. The study was approved by the Ethics Committees of the Antoni de Gimbernat Foundation. All ten patients selected for the study had a similar cellulite condition in both buttocks, i.e., degree 3 according to the classification by Rossi [7]. Patients were informed of the purpose of the study and signed a consent form for biopsies. Sets of parameters for treatment were constant during the

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entire single session and were administered for 30 min with around six to eight passes on only one buttock, randomly selected. Treatment was always given to all patients by the same trained user who was an expert with this technique. Constant application of treatment makes heat develop by absorbed electrical RF energy and optical IR energy and impacts heating propagation in the dermis and hypodermis. Superficial skin temperature measured with an IR surface thermometer at the time of RF treatment sessions was never over 44°C. Presumably, the inside tissue temperature was higher because electricity passing between electrodes occurred deep in the dermis and the external temperature detection is a consequence of heat propagation from the inside first "targeting" that layer in the skin.

The pretreatment and posthistologic conditions of the buttock in the area of the treated cellulite was examined in all ten patients. The nontreated buttock served as the control. The areas selected for biopsies had similar characteristics and location in both buttocks.

Patients underwent 2-mm-deep skin biopsies that were taken before and 2 h after only one treatment as previously described. Samples were processed in a routine manner and stained with hematoxylin & eosin (HE/EO). Samples were taken from both buttocks at the same time. After-treatment biopsies were taken from the adjacent area to the first biopsy, approximately 2 cm away. The same procedure was performed on the nontreated control buttock. This elapsed posttreatment time was ascertained from a pilot study in which specimens taken immediately after treatment showed little or no change, and the presence of an inflammatory reaction in samples taken much more than 2 h after treatment or on the following day masked the treatment effects being analyzed.

In the treated buttock, the epidermis had normal configuration and the keratin layer was respected with no particular changes. Various samples had some loss of the papilla crests in the dermis. There was moderate edema in the dermis which was particularly visible in the papillary and superficial layers. The tissue did not show any thermal damage to the dermis or epidermis, i.e., no necrotic denaturation process.

In the subcutaneous tissue, adipocytes showed signs of membrane rupture and changes related to incipient necrosis. Fat cells showed alteration in physical integrity with various forms of cell membrane rupture (Fig. 1). Besides membrane lysis, adipocytes without rupture showed thickening of their membrane as a sort of stiffness, with pronounced deletion and reduction of fat tissue mass (Fig. 2). Comparatively, no particular changes were noticeable in adiposites in the nontreated contralateral buttock in samples taken 2 h after treatment of the other buttock, which were identical to those before-treatment samples (Figs. 3 and 4).

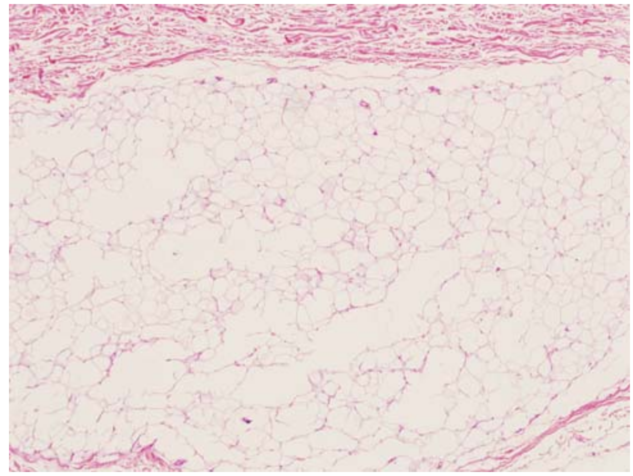

Fig. 1 Skin 250 × HE/EO, 2 h after treating the buttock. Transition from deep dermis to subcutaneous tissue. Adipocytes show membrane lysis in different shapes. Reinforcement of cell membrane in remaining adipocytes of different shapes. Space free because of ruptured cells

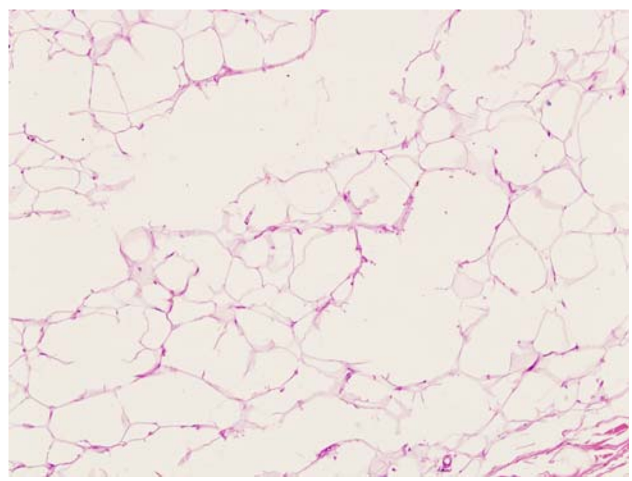

Fig. 2 Skin 400 × HE/EO. Membrane breakage of adipocyte cells that appear in different shapes and sizes with thicker membrane. Membrane is darker in color, with some stiffness and reinforcement

Because heat is required to initiate collagen and/or fat cells denaturation, it is apparent that the temperature developed by RF inside the tissue, e.g., at the subcutaneous fat layer level, was producing alterations in the subcutaneous skin layer. Adipocyte matrix properties manifested marked changes in their characteristics as membrane lysis decreases volume and thickening of their membrane.

RF heating of various skin layers results in various effects, each of which is broadly determined by the volume of tissue and time dependence of temperature. RF interaction with fat produces thermally induced changes that exploit properties of the adipocyte, mainly composed of water and fat enriched by all cell structures and directly charged by lipids. Theoretically, lipids under heat tend to

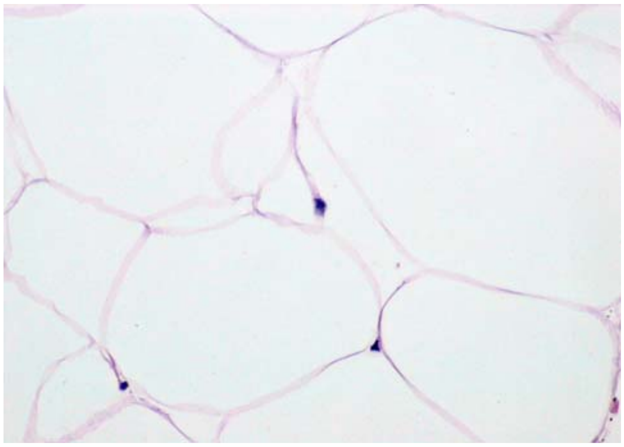

Fig. 3 Skin 400 × HE/EO, 2 h after not treating the contralateral buttock. Adipocytes are of normal conformation with their nucleus pushed to the periphery. Membrane is fine and of normal aspect. The whole sample is similar in its characteristics to the before-treatment samples

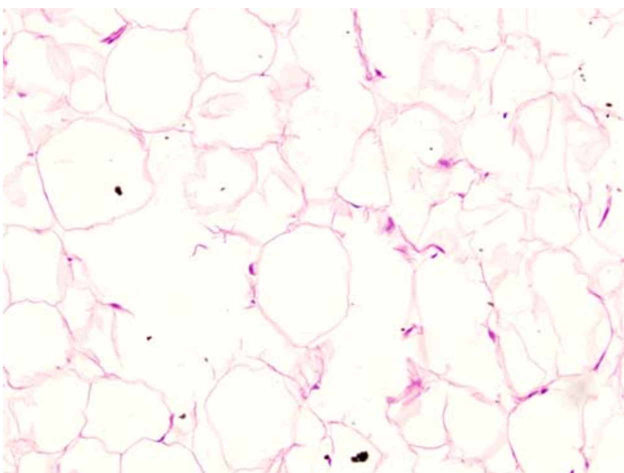

Fig. 4 Skin 400 × HE/EO. Adipocytes show lysis and membrane thickening. There is also reduction of fat tissue mass when compared with the normal nontreated sample

dissociate and melt and to conduct effects to the membrane producing their lysis and loss of their internal lipid contents. A slow increase in tissue axial temperature may preserve the viability of deeper fat cells so that the whole process would lead to tissue repair after the therapeutic lesions that occur under RF treatment. Tissue restoration activity will lead to clinical benefits with improvement of the cellulite condition.

In the tissue repair process, the increased cell function and the local changes of lymphatic drainage and modification of vascular flow play significant roles [4]. The neighboring dermis layer and fibrous septae, between adipocytes, mainly rich in collagen fibers and fibroblasts, provide fiber overgrowth after the "trauma" of RF treatment.

The length of the treatment session would also play a significant role: the nonspatial selectivity of heating skin by RF permits impact in the subcutaneous fat layer and its adipocytes. Thus, cells suffering from membrane lysis will be a consequence of the extra axial temperature increase gradient, e.g., due to prolonged exposure, and, in particular, those cell packages experiencing higher stress because of a temperature increase will rupture their membranes first. A change in temperature slope would coincide with cell membrane breakage. This is supported by the fact that in post-treatment samples there were packages of adipocytes with membrane lysis while surrounding cells appeared normal.

Experimental studies in the skin have demonstrated that heat shock proteins (HSP 70 family), which are overexpressed following an increase in temperature gradient in tissue, could be involved in the process of adipocyte manifestation [8]. A temperature increase, bringing tissue to 45°C or greater, could induce a coordinated expression of growth factors such as TGFβ1, which is known to be a key element in the inflammatory response and the fibrogenic process [9]. It has already been demonstrated that 12 min of heating at 45°C produced HSP70 expression. This duration can be reduced to 1 min if the maximum temperature reached is 50°C [10].

The combination of treatments offered by the device used in these trials has been clinically used by us on more than 100 patients. Treatment is noninvasive and produced very good results in the clinic. However, despite our histologic observations discussion is still open on how the overall mechanism of RF therapeutically affects cellulite. Future histology studies must assess "optimal" parameters with respect to penetration of RF thermal effects, and the necessary increase in temperature that leads to beneficial cellulite changes. Investigations of adipocyte circumstances and viability after RF treatment are currently in process. Determination of RF thermal effects and the shape of its intensity gradient during the session would help to obtain higher efficacy and, moreover, maintenance of clinical effects over time.

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