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Pilot study of histology aspect of cellulite in seventy patients who differ in BMI and cellulite grading

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Abstract

Background: Cellulite is a topographic alteration of the skin with unknown etiology and is characterized by the presence of a dimpled or puckered aspect, as resembling an orange peel and cottage cheese or as having mattress-like appearance.

Aim: The aim of this research was to find the different histological aspect of cellulite in sixty patients.

Materials and Methods: A total of 60 women, mean age 48.8 (± 11.08) were included in the study. Among these, 11 women were in menopause (18.33%). All patients after physical examination, aesthetic, and dermatological evaluation were subjected to five cellulite biopsies with a 2.0 mm diameter and 1.5 mm in length in the trochanteric region affected by cellulite. The descriptive statistics were performed for each study predictors demographic age, height, bmi, waist, belly, hip thigh, and knee.

Results: The histological analysis of the stained slides showed five different histological features were present in the most of patient.

Conclusion: In conclusion, the outcome of this study shows that the histological evidence does not characterize the different states of cellulite, but several different histological aspects were present in the same patient, which effectively eliminates staging and could consider cellulite as a degenerative disease.

KEYWORDS
adipocytes, cellulite, dermal adipose tissue, pathogenesis, pathophysiology

1 | INTRODUCTION

Cellulite is a topographic alteration of the skin that is characterized by the presence of a dimpled or puckered aspect, as resembling an orange peel and cottage cheese or as having mattress-like appearance.[1] It affects the 80%–90% of post-pubertal women and is mainly localized on the posterolateral thighs, buttocks, and abdomen.[2] It is an aesthetic challenge that requires different cosmetic treatments in order to again a smooth skin.

The clinical classification of cellulite proposed in 1978 by Nürnberger & Muller graded this condition in 3 levels of severity: mild, moderate, and severe.[3] Then, in 2009, Hexsel et al. added also other variables, like the number and depth of hollows and skin flaccidity, so the novel classification comprehended 5 stages.[4] However, for what concerning

the histological analysis of tissues affected by cellulite, the classification proposed by Curri in 1993, is still considered a landmark.[5] The 4 different stages, in order of increasing severity, were as follows: edema, hypertrophy of reticular fibers, micronodules, and macronodules.

The literature agrees for a multifactorial etiology of cellulite that comprehends a genetic predisposition, gender, anatomical and hormonal factors, deficiencies in lymphatic drainage, and microvasculature and lifestyle.[6]

In some particular cases, cellulite can affect also men, like in Klinefelter's syndrome, hypogonadism, estrogen therapy for prostate cancer, androgen deficiency secondary to castration. For this reason, the hormonal function in women and the dysfunction in men have been proposed in the etiology of this condition.[4,7]

Other theories about the etiology of cellulite are based on the different subcutaneous structures between males and females.[3] The studies of Querleux et al. with magnetic resonance imaging (MRI) showed that the percentage of connective tissue septae, perpendicular to the skin, that run from the derma to subcutis are present in a higher percentage in women with cellulite, respect men and females without this condition.[8]

The presence of these septa segregates the adipocytes into channels in the subcutaneous layers but, in the case of fat expansion or edema, the herniation of subcutaneous fat within fibrous connective tissue occurs.[8,9] These theories were confirmed by Mirrashed et al. that correlated the percentage of hypodermic invaginations into the dermis with the severity of cellulite, but were not confirmed by Pierard et al..[10,11]

Curri and Bombardelli proposed that alterations in the vascular and lymphatic microcirculation of the subcutaneous adipose tissues, could promote the neovascularization, the thickening, and the sclerosis of fibrous septae.[12] In cases of altered microcirculation, the increase of glycosaminoglycan (GAG) deposition in capillary walls attracting water would lead to dermal edema, with subsequent vascular congestion, capillary network loss, and tissue hypoxia.[5] This theory was in accordance with Lotti et al. that found extracellular GAG in cellulite samples, but not with Querleux et al. that found no water increase at the dermal-subcutaneous junction.[8,13]

Rossi and Vergnanini in 2000 confirmed that tissue hypoxia, associated with diets rich in carbohydrates, increasing lipogenesis and prolactin, stimulate the growth of adipocytes.[14]

However, the role of chronic inflammation has been considered a risk factor for cellulite etiology and worsening.[15] As shown by Rosenbaum, cellulite can be accompanied by chronic inflammation that alters local tissue, lymphocytes, and macrophages, causing adipolysis and skin atrophy.[16] In particular, a fundamental role in the cellulite development could be played by, mesenchymal stem cells, which are rich in the estrogen receptor. These cells are recruited after stress stimuli, like the oxidative stress, matrix remodeling, and reactive oxygen species production.[17]

The correlation between chronic inflammation and oxidative stress is supported by the increased inflammatory phenotype in the absence of antioxidant defense proteins (eg, superoxide dismutases, heme oxygenase-1, and glutathione peroxidases) or overexpression of reactive oxygen species producing enzymes (eg, NADPH oxidases).[18]

Also some genetic polymorphisms have been associated with an increase of cellulite development.[19]

The pathophysiology of cellulite is and remains controversial; perhaps, this explains the failure of almost all therapeutic procedures.

However, it is very likely that the cellulite is due to a combination of many factors, hormonals, genetics, adipose tissue, microcirculation, and chronic inflammation.[15]

The aim of this study was to find the different histological aspect of cellulite in sixty patients.

2 | MATERIALS AND METHODS

The present observational, cross-sectional study followed the STROBE guidelines for cross-sectional studies[20] and was in full accordance with the Declaration of Helsinki (https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf) and the additional requirements of Italian law.

The participants were selected among a group of Caucasic patients that were subjected to a first visit between September 2016 and February 2020 in the private office site in Modena, Italy.

The inclusion criteria were age 18 years old, female sex, body mass index (BMI) <26, and consent to participate to the study. In all enrolled patients, cellulitis has been detected clinically.

Exclusion criteria were as follows: previous treatments for cellulite, pregnancy, breastfeeding, systemic diseases, cancer, current drugs assumption, radiotherapy or chemotherapy treatment, uncompensated diabetes.

2.1 | Physical examination

The physical examination was conducted as previously described and consisted of[21]:

Anthropometric evaluation (the measurements were recorded as numerical variables): weight, height, BMI, and circumferences (waist, belly, hips, buttocks, right and left thigh and knee).

A total body photograph and multiple close-up standardized photographs of the individual areas.[22]

Postural and baropodometric examination (measurements recorded as dichotomous variables, YES/NO):

-Evaluation of the alignment and symmetry: of the shoulders, evaluation of the lower edge of the shoulder blades, evaluation of the iliac crests, evaluation of the gluteal, and evaluation of popliteal folds
- Presence of valgus or varus deformity of the knees
- Dorsal hyperkyphosis
- Lumbar hyperlordosis
-Cavism or flatness of the feet (evaluated with the aid of a podoscope)

TABLE 1 Descriptive statistics of the main predictors evaluated: age, height, bmi, waist, belly, hip thigh, and knee

	Age	Height	Weight	Bmi	Waist	Belly	Hip	Thigh	Knee
Mean	48.88	162.9	67.69	25.13	74..87	81.82	96.75	55.13	37.85
Std. Deviation	11.05	5.415	6.802	2.062	4.359	5.232	5.671	3.721	2.032
Std. Error of Mean	1.427	0.6991	0.8782	0.2662	0.5627	0.6754	0.7321	0.4804	0.2624
Lower 95% CI	46.03	161.5	65.93	24.60	73.74	80.47	95.29	54.17	37.33
Upper 95% CI	51.74	164.3	69.45	25.67	75.99	83.17	98.21	56.09	38.37

TABLE 2 One-way ANOVA Tukey post hoc test comparison of Histological grades I, II, III, IV, and V

		Numbers			Multiple comparison	
		N = 60	%	Groups	Test	*p* value
Histological Grade I	Yes	52	86.70%	A	A-B	0.8300
	No	8	13.30%		A-C	0.8300
Histological Grade II	Yes	55	91.70%	B	A-D	0.1032
	No	5	8.30%		A-E	0.4015
Histological Grade III	Yes	55	91.70%	C	B-C	>0.9999
	No	5	8.30%		B-D	0.6251
Histological Grade IV	Yes	59	98.30%	D	B-E	0.9558
	No	1	1.70%		C-D	0.6251
Histological Grade IV	Yes	57	95%	E	C-E	0.9558
	No	3	5%		D-E	0.9558

Note: No significant differences were detected by the multiple comparison testing [$p > 0.05$].

2.2 | Aesthetic and dermatological evaluation

The total body skin examination was performed with the patients in standing position with relaxed muscles, and the following parameters were measured:

- Measurements of the following dichotomous variables, (YES/NO): presence of paresthesia or heartburn, telangiectasias, varices, skin stretch marks, scars, positive ulnar fovea sign test, pain at the tissue pinch test, malleolar edema, heaviness in the lower limbs.
  - o All investigations were performed specifically on trochanteric region.
  - o Skin color of the trochanteric region affected by cellulite (no alteration of the color, yellowish-gray tone, skin pallor)
  - o Clinical Appearance through Cellulite Severity Scale (CSS) Adapted from de Godoy[23]
  - o Echographic evaluation (performed with an ultrasound system with a 12 MHz MyLab ™ Gamma linear probe (Esaote touch Genova Italy))
  - o Biopsy sampling of cellulite preceded by local anesthesia with histological analysis with histological analysis: Five cellulite biopsies with a 2.0 mm diameter and 25 mm in length were sampled in all patients in the trochanteric region affected by cellulite, by mean a specific punch (Kai medical, Oyama, Japan).
  - o The samples were visually observed and photographed by 2 independent observers. Each sample was fixed by immersion in 4% paraformaldehyde in phosphate buffer PH 7.2-7.4-0.1 M for 24 hours. Then, the biopsy samples were dehydrated in an ascending series of alcohols and then infiltrated with organic solvents and then with warm liquid paraffin. After cooling, the paraffin solidified, and samples were sectioned at full thickness with a rotary microtome in sections of 5-8 microns. The stains adopted for the sections were as follows: hematoxylin and eosin, Verohef, Weigert, Blu Mallory.
  - o To color the sections obtained, the paraffin was solubilized with organic solvents and the tissue was rehydrated in a descending series of alcohols.
  - o The slides obtained were observed and photographed with a Zeiss Axiophot photomicroscope (Zeiss, Germany) equipped with Nomarsky differential interference contrast. For each patient, 6 biopsy samples were taken, 3 per each side.

2.2.1 | Statistical analysis

The descriptive statistics were performed for each study predictors demographic age, height, bmi, waist, belly, hip thigh, and knee. A logistic regression test was performed to evaluate the association of potential predictors and histological grades I, II, III, IV, and V. The variables individually were associated with each histological grades ($p < 0.05$) according to a multivariable logistic regression model. The histological grades data were evaluated by the one-way ANOVA followed by Tukey post hoc test. The significance level was considered

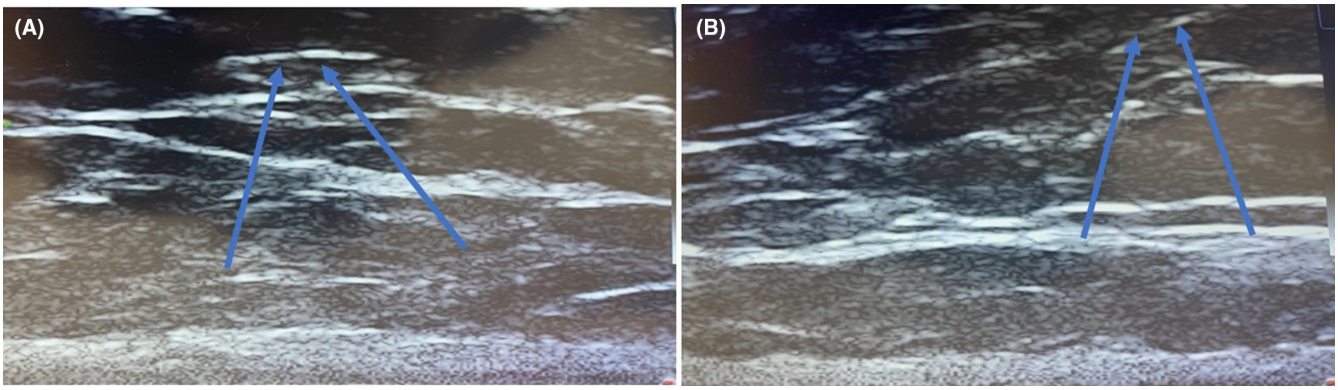

FIGURE 1 A- Fascial bands present with oblique orientation. B- The bands originating from the superficial fascia

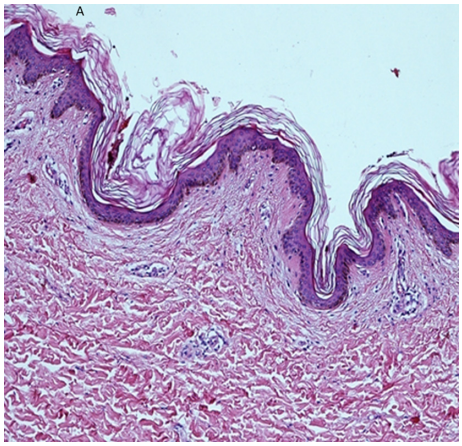

FIGURE 2 No alteration was observed in the epidermis, dermis, and hypodermis. Hematoxylin and eosin staining X10

for $p < 0.05$. Data analysis and statistical testing were performed through a dedicated software package Graphpad 8 (Prism).

3 | RESULTS

A total of 60 women, mean age 48.8 (± 11.08) were included in the study. Among these, 11 women were in menopause (18.33%).

The baseline data obtained from the oral interviews of the patients and from the clinical examination, stratified for the age of the subjects, are shown in Table 1.

3.1 | Physical examination

The physical examination results are reported in Table 2; no patients with postural or baropodometric alterations were found. The average height was 162.88 ± 5.41 cm, the mean weight was 67.69 ± 6.8 Kg, and the average body mass index was 25.13 ± 2.06.

The results of the anthropometric evaluations showed the following average measurements of the circumferences of the waist 74.8 ± 4.3, belly 81.8 ± 5.23, thigh 55.1 ± 3.7, hip 96.7 ± 5.6, and knee 37.8 ± 2 cm.

3.2 | Aesthetic and dermatological evaluation

The skin roughness evaluation found 54 patients (90%) with evident orange peel skin (CSS III) of and 6 patients (10%) with visible alterations after the pinch test (CSS II), 5 in the 20–30 years range, and 1 in the 20–40.

The skin color evaluation of the anatomical sites affected by cellulite found a skin pallor in 3 menopause patients and a yellowish-gray tone in 4 patients with, 1 of these, in the 30–40 years of range, which was affected by an accentuated venous insufficiency. The other 3 patients were in the 50–60 decade. Echographic evaluation showed the obliquely oriented fascial band was the dominant variant seen in all patients. Difference in the band orientation was detected simultaneously in the most patients (Figure 1A,1B). However, the trochanteric region dimples appeared to have a slightly higher percentage of bands originating from the superficial fascia.

3.3 | Histological analysis

The histological analysis of the stained slides at 10X magnification showed that several different histological features were present in the most of patient. In particular, 5 different histological findings were detected simultaneously in the most patients and characterized the appearance of the epidermis, dermis, and hypodermis:

1. Epidermis: no alterations. Dermis: no alterations. Hypodermis: no alterations (Figure 2).
2. Epidermis: no alterations. Dermis: mild edema in the reticular dermis Hypodermis: anisopoikilocytosis; edema in the adipose tract next to the dermis (Figure 3)
3. Epidermis: islands of keratinocyte hypertrophy alternating with flattening of the stratum corneum; reduction of the depth of the dermal spines; alteration of cell replication at baseline. Dermis:

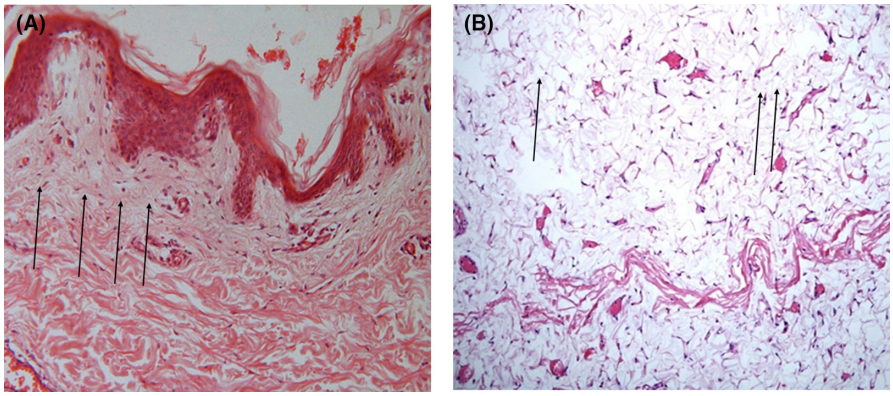

FIGURE 3 A. No alteration was observed in the epidermis, while a mild edema was recorded in the reticular dermis (Arrows). Hematoxylin and eosin staining X10. B. Anisopoikilocytosis; edema in the adipose tract next to the dermis was observed in the hypodermis (Arrows). Hematoxylin and eosin staining X10

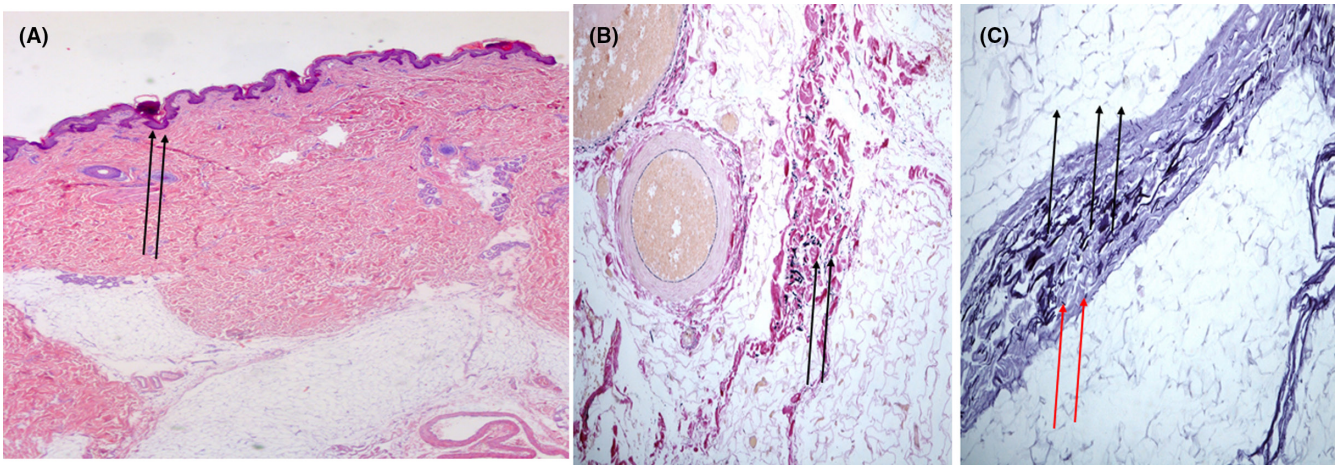

FIGURE 4 A. Islands of keratinocyte hypertrophy alternating with flattening of the stratum corneum was present in the epidermis (Arrows). Hematoxylin and eosin staining X10 B. In the dermis was present: alteration of structural architecture of collagen and elastic fibers, the former have a disordered orientation, the latter are shortened and in some points appear fragmented (Arrows). Hematoxylin and eosin staining X10 C. In the hypodermis: presence of anisopoikilocytosis (Arrows), fibrotic thickening of the collagen that delimited the lobules (Red arrows). Weighert e Mallory staining X10

alteration of the quality of hyaluronic acid; subversion of the regular structural architecture of collagen and elastic fibers, the former have a disordered orientation, the latter are shortened and in some points appear fragmented; alteration of the presence of skin appendages; alteration of the microcirculation with collapse of the arterioles and venules, dilation of the lymphatics; edema in the reticular dermis, thickening of the connective fibers in some points and the presence of adipocytes that seem different in shape and size from the adipocytes of the subcutaneous. Hypodermis: presence of anisopoikilocytosis, fibrotic thickening of the collagen that delimited the lobules; concentric organization of the adipose cells that participate in the formation of micronodules; alteration of the microcirculation both for the arterioles and the venules that appeared collapsed and or de-structured, lymphatic vessels both dilated and absent in the perimeter points of the microns. (Figure 4)

4. Epidermis: as the aspect 3 Dermis: as the aspect 3 with the particular presence of adipocytes. Hypodermis: further thickening of the connective shoots that delimited the micronodules, areas of adipose tissue where the connective shoots appeared lysed; the presence of micronodules that merged with each other; completely altered microcirculation with arterioles and veins devoid of blood content, non-existing lymphatics (Figure 5).
5. Epidermis: as the aspect 3 Dermis: as the aspect 3 but with the presence in the dermal thickness of the skin of adipocytes organized adipose tissue. Hypodermis: a complete subversion of the organization of the adipose tissue, the notable presence of macronodules, in the area of which there were giant adipose cells with calcified concretions inside them; the organization of the microcirculation completely non-existent. Histochemistry revealed that the dermal nodules were mostly composed of adipocytes trapped between type I collagen fibers (Figure 6).

3.3.1 | Statistical analysis

One-way ANOVA Tukey post hoc test comparison of Histological grades I, II, III, IV, and V. No significant differences were detected by the multiple comparison testing [$p > 0.05$]. No correlation with other variable was detected (Table 2).

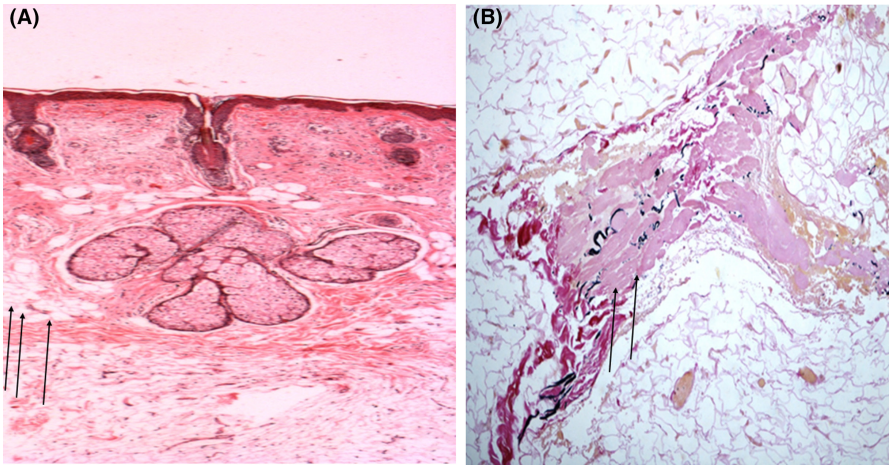

FIGURE 5 A. In the hypodermis was observed the presence of micronodules (Arrows). Hematoxylin and eosin staining X10. B. Alteration of structural architecture of collagen and elastic fibers (Arrows). Hematoxylin and eosin staining X10

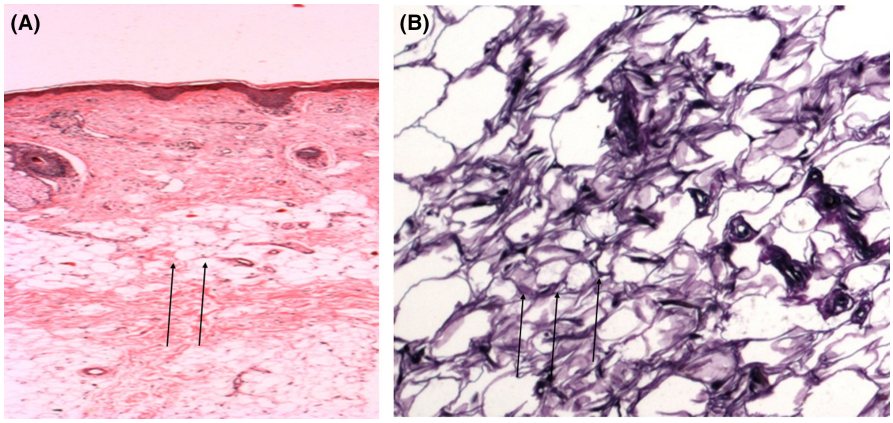

FIGURE 6 A. In the hypodermis was observed the macronodules, in the area of which there were giant adipose cells with calcified concretions inside them (Arrows), the organization of the microcirculation completely non-existent. Hematoxylin and eosin staining X10. B. Histochemistry revealed that the dermal nodules were mostly composed of adipocytes trapped between type I collagen fibers (Arrows). X10

4 | DISCUSSION

One of the main concerns in the evaluation of cellulite is the lack of a precise and reproducible method for quantifying this problem.[2] Indeed, the clinical documentation of cellulite could be very difficult, for the risk of bias concerning the positioning of the patients during the examination, the illumination, background, and camera position.[24] For this reason, it is very important to follow strength guidelines for standardized photography and associate also more objective analysis that comprehend the use of some devices, for the ultrasound evaluation and the measurement of skin parameters of elasticity and hydration.

The primary objective of this study was to correlate the presence of cellulite, evaluated with clinical examination, instrumental analysis, and ultrasounds, we have also performed the histological analysis of cellulite lesions in order to gather more information about the pathophysiology of these lesions.

The ultrasound observations, confirmed that in cellulite lesions the epidermis and dermis were characterized by a rich-echo, while the adipose protrusions of the subcutis were low-echo but interspersed with hyperechoic connective shoots. These observations were in accordance with Bielfeldt et al. that found a correlation between the severity of cellulite and the increase of adipose protrusions in the ultrasound images.[24]

To date, many have written about adipocyte hernias in the dermis, documenting them with MRI ultrasound evaluations, the same evaluations that in 1978 led to define the microscopic anatomy of the subcutis.

New studies and new data have and are highlighting that the situation is not quite, as described by Curri in the early 1970s and completed by Nürnberger and Müller in 1978.[3]

Histology, anatomy, and staging from what emerged in this study appeared totally different.

Therefore, the general architecture of the subcutaneous tissue is not attributable to a fibro-sclerotic connective tissue in which approximately cylindrical adipocytic nodules are incarcerated, with a greater axis perpendicular to the skin plane, separated by fibrous septae of irregular diameter: some were thin and almost torn, others were thickened and retracted, so as to produce the irregularities of the skin surface.

All the histological elements described by previous literature were found in the samples analyzed in this study, confirming that

cellulite is really a multifactorial condition whose pathophysiology is not fully known.

The histological evaluation would seem to confirm what was reported in the classification that Curri made in 1993 when he still did not have the technological means that we now have. Edema was observed, the alteration of the microcirculation was observed, but to date, no one has ever talked about dermal fat.[5]

In the scientific literature, someone has spoken of septations and adipocyte hernias as if the subcutaneous adipose tissue had offshoots in the dermis, only to discover that the adipose cells in the dermis are different from the adipose cells of the subcutis and with 3 different locations: around the hair bulb, around the glands sebaceous and sweat.[8,25] The fat cells organized freely in the dermis were in communication with the subcutaneous but were different and distinct entities.

This calls into question the interpretation that the microscopic anatomy of the subcutis in women is organized in perpendicular lobules.

The evaluations carried out revealed a reduced concentration of oxygen, especially at the dermal level in the areas affected by cellulite, due to the simultaneous alteration of the structure and function of the microcirculation. This ischemia of the adipose tissue and the dermis causes considerable damage to mitochondrial respiration, resulting in a lower ability to regenerate ATP.

As cellulite becomes apparent, there is a progressive increase in the activity of the enzyme nitric oxide synthetase (NOS) in the subcutis, which consequently determines an increased production of nitric oxide (NO •).

A probable hypothesis is that the NO production induced by the diseased subcutis leads to the formation of peroxynitrite, which can contribute to increasing a pro-oxidant condition.

This leads to an increase in the production of free radicals, reducing the bioavailability of nitric oxide in favor of peroxynitrite, which carries out a vasoconstrictive myocontracting proaggregating and pro-inflammatory action (nitrosative stress which is equivalent to the combination between classical oxidative stress and that induced by reactive species of nitrogen), typical of degenerative diseases.[26,27] This theory is in agreement with Conti et al. that performed a proteomic analysis of adipose tissues affected by cellulite and found a high degree of oxidative stress.[17]

In conclusion, the outcome of this study shows that the histological evidence does not characterize the different states of cellulite but several different histological aspects were present in the same patient, which effectively eliminates staging and could consider cellulite as a degenerative disease.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest for the present research.

AUTHOR'S CONTRIBUTION

AS.: Conceptualization, methodology, software, validation, resources, project administration, and funding acquisition. AS., ELI, and DM.: Formal analysis. DM., AS, and RA: Investigation. MP and AS: Data curation, and writing—original draft preparation. AS, MP., DA., LEI., RA., and MM.: Writing—review and editing. AS, ELI., DA., and MP: Visualization. AS and DA.: Supervision.

ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. The study was based in a private specialty Medical practice in Modena (Italy), in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf) and the additional requirements of Italian law. All patients signed informed consent on the adopted procedure.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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