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# Cellulite: a review

## Cellulite: artigo de revisão

**ABSTRACT**

Although the term cellulite is inadequate, since it does not refer to cellular subcutaneous tissue inflammations or infections, it is conventionally used to describe a female condition that is characterized by a wavy appearance of the skin's surface in some areas of the body. It constitutes a frequent complaint and an important concern for the majority of women and, due to its complex, multifactorial, and not completely known etiopathogenesis, there is still no effective and definitive treatment. Consequently, many therapeutic proposals, either based on poor quality publications or lacking sufficient scientific evidence, have been introduced. Topical treatments are not effective, though some can be indicated as adjuvant therapies. There is currently no technology able to correct the structural alterations of the female adipose tissue and deep dermis. That status clearly depends on the development of technologies based on the selective photothermolysis principle aimed at treating superficial hypodermal fat and the deep dermis. This article presents a review of the epidemiology, etiopathogeny, histology, clinical classification, and methods for the diagnosis, evaluation, and treatment of cellulite.

**Keywords:** cellulitis, cellulite/histopathology; cellulitis/treatment.

**RESUMO**

*Apesar de o termo celulite ser inadequado, já que não se trata de inflamação ou infecção do tecido celular subcutâneo, está consagrado pelo uso para definir condição feminina caracterizada pelo aspecto ondulado da pele de algumas áreas corporais. Constitui queixa frequente e problema importante para a maioria das mulheres e, por ter etiopatogenia complexa, multifatorial e incompletamente conhecida, não há tratamento eficaz e definitivo. Sendo assim, proporciona uma gama de propostas terapêuticas sem evidências científicas suficientes e outras baseadas em publicações de qualidade questionável. Sabe-se que tratamentos tópicos são ineficazes, embora alguns possam ser coadjuvantes. Até o momento, não há tecnologia disponível que possa corrigir as alterações estruturais do tecido adiposo feminino e da derme profunda. A perspectiva, sem dúvida, dependerá de tecnologia baseada no princípio da fototermólise seletiva para a gordura superficial da hipoderme e para a derme profunda. Este artigo apresenta uma revisão da epidemiologia, etiopatogenia, histologia, classificação clínica, métodos para diagnóstico e avaliação e tratamento da celulite.*

**Palavras-chave:** celulite; celulite/histopatologia; celulite/tratamento

**INTRODUÇÃO**

The term *cellulite* has been used to describe the dimpled and irregular appearance of the skin, with a texture similar to an orange peel or cottage cheese. It is typically found in women, mainly in the thighs and buttocks<sup>1-6</sup>. The term has its origins in French medical literature from more than 150 years ago<sup>3,7</sup>. Cellulite is also known as: edematous adiposity, gynoid lipodystrophy and dermopanniculosis deformans<sup>3,8-10</sup>. Although there is no morbidity or mortality associated with cellulite – it is not a disease – it remains a frequently important aesthetic concern to a great number of women<sup>9</sup>. Cellulite is very prevalent in women and tends to occur in areas where the fat is under the influence of estrogen, such as the hips, thighs and buttocks<sup>1,2</sup>.

Cellulite can also be found in the breasts, in the lower abdomen, arms and nape – curiously in the areas where the female standard of deposition of the adipose tissue is observed <sup>1,3</sup>.

A high rate of occurrence (between 85% and 98%) is verified in post-pubescent women of all racial backgrounds; however it occurs more frequently in Caucasian women <sup>11</sup>. It seems that there is an influence of hormonal factors. Almost omnipresent in post-pubescent women <sup>4,7</sup>, it is rarely seen in men; however it can affect those with androgenic deficiency, such as patients with Klinefelter's syndrome, hypogonadism, post-castration patients and patients who received estrogen therapy for prostate cancer. In those cases, the cellulite becomes more severe with the worsening of the androgen deficiency <sup>3</sup>.

Although cellulite can be found in any area with excess deposits of adipose tissue, obesity is not a necessary condition for its occurrence <sup>12</sup>. It is considered a physiological response, nevertheless its structural and metabolic characteristics are not clearly identified. Although there have been attempts to link modifications in metabolism and in the biochemistry of the adipose tissue to the occurrence of cellulite, there is no evidence of primary differences in physiology, blood flow, biochemistry or metabolism in the adipose tissue of affected and non-affected areas <sup>2</sup>.

Although highly prevalent, only a limited number of studies has been published in the international literature – and many reach contradictory conclusions, which impedes the implementation of treatments <sup>3,8</sup>. There are many reasons for the lack of quality investigations on the subject. On one hand, the availability of an enormous amount of pseudo-scientific information makes serious investigations less attractive to researchers. On the other hand, in Anglo-Saxon countries, where a large part of the scientific research is conducted, the theory that has been prevailing does not consider cellulite to be a nosologic condition for studies, regarding it as a physiological expression of female adiposity <sup>8</sup>.

## ETIOPATHOGENESIS

Although cellulite's etiology is unknown, a variety of causes seem to contribute to its development, including structural, circulatory, hormonal and inflammatory factors <sup>1,3,13,14</sup>.

The three main etiologic hypotheses are based on: anatomical and hormonal alterations, microcirculation, and chronic inflammatory processes.

### Anatomical and hormonal alterations

Cellulite's anatomical hypothesis is based on the differences between men and women regarding the structural characteristics of subcutaneous fat lobules and of the conjunctive tissue septae that separate them. According to this theory, originally detailed by Nurnberger and Muller <sup>12</sup>, the emergence of cellulite is caused by the protrusion of fat in the dermo-hypodermal junction. This alteration specifically occurs in women, due to the presence of vertical fascial bands <sup>3,12,14</sup>. Piérard <sup>6</sup> believes that cellulite is caused by the genetically determined extension of those fascial bands. This elongation, in turn, weakens and makes the

base of the dermal conjunctive tissue thinner, and allows the protrusion of fat into the dermo-hypodermic junction, causing the dimpled skin. Those herniations of fat in the dermis are typical of the female anatomy; their presence has been confirmed by ultrasonography in low density regions intermixed in the dermis <sup>5,15,16</sup>. Men's subcutaneous region is characterized by horizontal and diagonal fascial bands, which comprise a structure that obstructs the herniation of fat <sup>17</sup>.

Since cellulite is present in a large number of post-pubescent women and is rarely found in men who do not present androgenic deficiency, it is highly probable that the female hormones play a fundamental role in its etiopathogenesis <sup>1</sup>. Cellulite is extremely rare in men with normal levels of androgens, regardless of their weight, <sup>14</sup> due to the genetic and hormonal nature of the architecture of the skin. In a study employing ultrasonography techniques to examine the total thickness of the skin of affected and non-affected areas of the thigh, later biopsied (wedge biopsy), Rosenbaum attempted to determine whether undulations on the skin resulted from herniations of fat in the dermis or not <sup>12</sup>. With that objective, seven healthy adult women with cellulite and three healthy non-affected control individuals (a woman and two men) were examined. Both the affected and the non-affected women presented an irregular and discontinuous dermo-hypodermic junction, characterized by the protrusion of fat into the dermis. By contrast, the dermo-hypodermic transition in the studied men was smooth and continuous <sup>3</sup>.

Although there are several hypotheses to explain the occurrence of cellulite, the strongest one maintains that hormonal differences are responsible for the structural variations in the architecture of women's subcutaneous fat, meaning it is fundamentally regarded as an anatomic alteration <sup>1</sup>.

### Vascular alterations

In a revision article, Rossi and Vergnanini described a multifactorial basis for the etiology of cellulite <sup>10</sup>. Based on Curri's descriptions, <sup>18,19</sup> metabolic and structural events were detailed. According to that theory, cellulite forms with the deterioration of cutaneous vascularization, particularly in response to alterations of the arteriolar pre-capillary sphincter in affected areas, in conjunction with deposits of hyperpolymerized glycosaminoglycans in the dermal capillary walls and between the collagen and elastic fibers <sup>3,14,20</sup>. The rise in capillary pressure increases the permeability of the venular capillaries and causes the retention of excess liquid in the dermis, among the adipocytes and the interlobular septae, leading to changes in the cells and tissular hypoxia <sup>3,14</sup>.

The increase in lipolytic resistance resulting from hypoxia and the increase in lipogenesis – caused by the action of estrogen, prolactin, and a diet rich in carbohydrates – facilitates the excessive growth of the adipocytes. The widened adipocytes, in conjunction with the growth and hyperplasia of the periadipocyte reticular fibers, form micronodules surrounded by proteins fragments that, later on, cause sclerosis of the fibrous septae, ultimately leading to the emergence of cellulite. The

general effect of this physiopathologic process would be a reduction of blood flow and of the lymphatic drainage of the affected areas. This theory encouraged the development of many therapies that tried to improve the tissular circulation and inefficient drainage, with the objective of reducing the dimpled and irregular appearance of the skin<sup>14</sup>.

### Inflammatory factors

Some authors, based on subjective reports of the understanding of cellulite, suggest an inflammatory basis for the condition's physiopathology<sup>4,7,21</sup>. Kligman<sup>13</sup> has reported on the diffuse aspect of the chronic cellular inflammatory process, with macrophages and lymphocytes (in the fibrous septae) based on skin biopsies<sup>21</sup>. Kligman concluded that the septae are responsible for the light inflammation that results in the lysis of the adipocytes and cutaneous atrophy. Other authors, however, have not found evidence of inflammatory processes or lysis of the adipocytes in cellulite<sup>6,7,12</sup>.

### HISTOPATHOLOGY

The epidermis is always normal. In the papillary and high reticular dermis, as well as in the normal skin, a discreet perivascular lymphocytic infiltrate is observed. The collagen fibers in the superior layers of the dermis appear slightly edematous. The eosinophilic coloration of the collagen fibers is slightly less intense than in the normal skin. No indication of fibrosis, sclerosis or hyalinization is found. The elastic fibers are reduced in the subepidermic plexus; the fragments tend to group together in the deeper layers of the dermis. Intercellular glycosaminoglycans have been identified as mucoid edemas between the deep dermis collagen fibers. These substances do not show a higher degree of polymerization in immunohistochemistry. In the *arrectores musculi pilorum* region there are clear signs of edema and, occasionally, of vacuolar degeneration. The blood vessels do not show pathological characteristics. The superior dermis lymphatic vessels are, however, almost always visibly distended. Fat cells in the subcutaneous tissue, when observed individually, appear enlarged. The adipose tissue's septae are normal, possibly displaying discreet edema. No alteration is detected in the immunohistochemistry<sup>12</sup>.

### CLASSIFICATION

In 1978 Nürenberger and Müller classified cellulite into grades based on the clinical presentation of the condition:<sup>12</sup>

Grade 0: absence of alterations of the cutaneous surface;

Grade I: the surface of the affected area is flat when the patient is lying on his or her back or standing up, however the alterations can be observed when the area is pinched with the fingers or is under contraction of the local musculature;

Grade II: an "orange peel" or "padded" appearance is evident without any pinching or muscular contraction when the patient is standing up;

Grade III: the alterations described in Grade II are present and combined with elevations and nodulations;

The fact that only qualitative (and not quantitative) param-

eters were taken into account in this classification method has raised concerns regarding its application as a tool to evaluate therapeutic efficacy before and after treatment, given its great subjectivity and dependency on the evaluator.

In light of these considerations, a new methodology was proposed and published by Hexsel<sup>22</sup>, aimed at more objectively classifying cellulite by using photonumeric gradations. The author designed a more complex scale, composed of 5 variables (ranked 0 to 3) whose total sum classifies the patient into 1 of 3 categories of severity: light (1-5 points), moderate (6-10 points) or severe (11-15 points). The 5 analyzed variables are: A - number of evident depressions; B - depth of the visible depressions; C - morphologic appearance of the alterations of the surface of the skin; D - degree of flaccidity or cutaneous laxity; E - grade of the Nürenberger and Müller classification scale;

This classification method still needs to be tested for applicability and validated in order to be accepted in the international literature; it may either include or replace the Nürenberger and Müller classification method.

### Diagnostic and evaluation methods

There are various diagnostic methods for cellulite, from simple and cost effective approaches such as anthropometrical measurements, to complex and expensive processes such as nuclear magnetic resonance. Notwithstanding, there is no unanimously accepted method, for such concepts depend on variables such as cost, degree of invasiveness, risks, and accessibility. As a result, several techniques have been proposed, including:

1) Macrophotography: a simple method that involves the costs of the photographic materials (including lighting and a standardized background) and a professional trained to evaluate the pictures. This method is ideally used in conjunction with other methods, since it can only evaluate the visible clinical appearance of cellulite, and is dependent on a qualified professional able to standardize the pictures<sup>23</sup>.

2) Anthropometrical measurements: an objective method in which the weight, height, circumferences and cutaneous pleat measurements indicate the degree of obesity and the distribution of body fat, which represents an indirect measure of cellulite. This method is flawed, since not all individuals with alterations in these parameters present cellulite, and improvement in these parameters does not necessarily translate into improvement in the condition<sup>10,24</sup>.

3) Bioimpedanciometry: this method attempts to be more precise than the anthropometrical measurements by accessing tissues through an alternating electric current that travels the body through electrodes placed on the upper and lower limbs. This technique quantifies lean body mass, body fat mass and total body water mass in percentage terms. Nevertheless, it presents the same vulnerabilities as the anthropometrical method regarding the analysis of the cellulite itself, and the inability to evaluate the microcirculation of the adipose tissue<sup>10</sup>.

4) Xerography: method that evaluates tissues based on their diverse radiotransparency or radiopacity (i.e., different tissular densities) using X-ray in an electromagnetic field altered by

electrostatically charged selenium. It can measure the depth and the limits of the layers of the tegument, however it is not yet capable of evaluating microcirculation. Additionally, there is a risk of exposure to the ionizing radiation<sup>10</sup>.

5) Bidimensional echography: method that is capable of analyzing the morphology of the subcutaneous tissue and, therefore, of the tissue altered by cellulite. It evaluates nodulations, irregularities, thickness, depth, edema and even the limits of the dermis. It is a non-invasive method (using frequencies from 7.5 to 40MHz) that can evaluate the tissue's microcirculation, however it depends on the availability of the appropriate equipment and a team trained in the technique<sup>10,23,24</sup>.

6) Anode Thermography: non-invasive method that thermally maps the tissue altered by cellulite and grades the alteration. Several factors can influence the results, including the humidity and temperature of the examination room and patient exposure to sun, fever, menstrual cycle, and smoking<sup>10,24</sup>.

7) Computerized tomography: a low accuracy method to evaluate adipose tissue that is rarely employed<sup>10,24</sup>.

8) Nuclear magnetic resonance: a method that provides structural analyses of the adipose tissue and its architecture, however it does not evaluate microcirculation. It has improved, using new techniques and more advanced equipment that allows an ever increasing detailing of the images of tissues<sup>10,24,25</sup>.

9) Laser doppler flowmetry: method that quantitatively evaluates tissular microcirculation through the application of a 632nm laser beam; the laser's radiation reflection by the tissues and erythrocytes is calculated<sup>24,26</sup>.

10) Skin biopsy followed by histopathologic examination: this method invasively and directly accesses the normal or altered subcutaneous tissue and analyzes its microstructure. It employs appropriate staining techniques such as Hematoxylin-*es*osin for histological analysis; Alcian-blue for mucopolysaccharides; Periodic Acid-Schiff (PAS) for basal membranes; Weigert-Van Gieson for elastic and collagen fibers, and smooth muscles; and Masson's Trichrome for collagen fibers and dermic muscles<sup>10</sup>.

## Treatment

The cellulite treatments described in the international medical literature are classically divided into two groups: non-invasive and invasive. In turn, the non-invasive treatments are divided into two subgroups: treatments that do not involve the use of biologically active substances (medications) and those involving the use of active substances.

Non-invasive treatments without the use of biologically active substances 1) Massage/*Endermologie*<sup>®</sup>: diverse massage methods are described in the literature; lymphatic drainage is the most widespread, due to the hypothesis that alterations in the physiological lymphatic drainage are linked to cellulite's etiopathogenesis. Massage can be performed manually or using devices designed to obtain higher speed and consistency (e.g., *Endermologie*<sup>®</sup> machine). The literature is divided regarding the effectiveness of such treatments; some comparative studies demonstrate improvement, while others do not.<sup>27-29</sup>

2) Light-based devices: intense pulsed light (IPL) and laser

belong in this category. IPL is used to stimulate the formation of new collagen, thickening the dermis and, therefore, making it more similar to the male dermis – which is less susceptible to cellulite. However, the only study on IPL available so far lacks the adequate design and methodology to prove efficacy and clinical improvement: it is not blind, there is no control group or histological analysis, and a biologically active substance was applied on one of the arms studied<sup>30</sup>.

The isolated use of laser is uncommon and scarcely quoted. One study reports that 1,210 and 1,720nm waves were capable of selectively reaching adipose tissue cells, however it was carried out in animals and there are no commercial devices for such application in human patients<sup>31</sup>. Many devices combine laser and IPL with massage, vacuum, ultrasound or multiple techniques in a single apparatus. Such group comprises the largest commercially available class of devices and features in the greatest number of studies published recently – and has the greatest marketing appeal. The justification for such facts is that these devices address several etiopathogenic mechanisms of cellulite such as structural alterations in the collagen, microcirculation, and lymphatic drainage. In a monocentric, randomized, comparative and prospective study, a device that combines massage with an 810nm laser diode (*TriActive*<sup>®</sup>) demonstrated clinical improvement comparable to that of other equipment that combines infrared light and radiofrequency with massage (*VelaSmooth*<sup>®</sup>). However, the *TriActive*<sup>®</sup> study had no control group, a small patient sample, and the before and after treatment evaluation methods were insufficiently objective<sup>32</sup>. Further studies employing the *VelaSmooth*<sup>®</sup> device are referenced in reviews on the theme, all with questions regarding their methodology and significance<sup>1</sup>. One controlled study reported the effectiveness of combining two low energy laser wavelengths with massage; however this study presented conflicts of interest<sup>33</sup>. Another device that combines infrared light, radiofrequency, and massage (*ELOS* technology) was analyzed separately and found to be effective, yet it presented several problems in its methodology – such as the absence of a control group, small sample size, and ethical issues and conflicts of interest – which call the results into question<sup>34</sup>. The use of monopolar or bipolar radiofrequency (*Thermacool*<sup>®</sup> and *Accent*<sup>®</sup>, respectively) has been cited, although such devices are FDA (US Food and Drug Administration regulatory agency) approved for use in wrinkles only<sup>1</sup>. The combination of monopolar and bipolar radiofrequency in a single device was analyzed in a study that suggested positive effects in the reduction of body circumference measurements and, consequently, in the manifestation of cellulite. Despite the fact that this was a pilot study, the methodology was flawed (not blind, uncontrolled)<sup>35</sup>. A new non-invasive treatment technique – based on low energy, non-focused shock waves – was described and assessed through changes in the ultrasonographic pattern of the dermis and the subcutaneous tissue, before and after treatment. This new technology, however, requires studies that are better designed and more representative if the efficacy and safety of these technologies are to be proven<sup>36,37</sup>. Transdermal focused ultrasound (*UltraShape*<sup>®</sup> and

IPLosonix®), although not yet approved for use in the treatment of cellulite, presented positive results in the improvement of the corporal contour, however it still requires further studies to be accepted as a therapy for treating cellulite<sup>38-40</sup>.

#### Non-invasive treatments with biologically active substances

The availability of topical products for treating cellulite – which are supported by well designed and controlled studies, with their efficacy and safety properly proven – is very limited. Those that present better, however discreet, results are retinoids and methylxanthines. The *Asian Centella* and the *Sillicium* are advertised as effective, notwithstanding the limited number of studies<sup>1</sup>. Hundreds of other substances are advertised as being effective – without, however, presenting any evidence, therefore being of questionable results<sup>1,3,10,41</sup>.

#### Invasive treatments with biologically active substances

There are citations on the use of injectable products that use the mesotherapy technique.

The methods and injectable product range vary greatly and none has proven its efficacy in the treatment of cellulite, although, in theory they could improve the physiopathology of cellulite<sup>42</sup>. A relevant issue is the utilization of dispensed products with contamination risks and systemic side effects based on the use of, for instance, thyroidian hormones. Among the techniques that involve injections of theoretically active substances, there are few reports on the use of carbon dioxide (carboxytherapy), which was described by Brandi<sup>43</sup>. To date, however, there is no evidence to reinforce its efficacy and safety<sup>44</sup>.

#### Invasive treatments without biologically active substances

Subcision is the invasive surgical technique in which a needle is introduced in the subcutaneous tissue, and subsequently moved parallel to the cutaneous surface with the objective of rupturing the fibrous tissue bands that have a relevant role in cellulite's etiopathogenesis. While this technique finds good acceptance even in the absence of controlled clinical studies, there is a risk of recurrence and adverse effects such as persistent erythema and hyperpigmentation<sup>45,46</sup>. While liposuction is the gold standard surgical technique for reducing adipose tissue, it has not demonstrated very satisfactory results in treating cellulite, for it can be ineffective, present recurrence or even worsen the clinical picture. Other options such as ultrasonic liposculpture can be more successful in treating cellulite, but there are few studies on this technique<sup>47-49</sup>. More recently, a new and seemingly promising technique that combines the autologous transplant of adipose tissue with the application of Nd-Yag laser in the subcutaneous tissue was described, however it requires more studies<sup>50</sup>.

#### CONCLUSION

Cellulite is a female condition that does not cause morbidity, but has a significant aesthetic impact. It is important to understand what is already proven about its etiopathogenesis and consider treatments that can (though minimally) improve the condition without causing physical damage and frustrated expectations. Increasingly it becomes evident that the only means of correcting alterations observed on the skin's surface will be through technologies that are capable of reaching the deep dermis and the superficial adipose tissue safely. ●

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