Chapter 25
Treatment of Cellulite

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25.1 Introduction

Cellulite is a common lipodystrophy or skin composition disorder mostly affecting women of different ages from maturation to menopause. Medically named as liposclerosis, edematofibrosclerosis, edematous adiposity, gynoid lipodystrophia, and dermopanniculosis deformans [1–4], cellulite is often referred to as "cottage cheese" or "orange peel" because of its characteristic appearance. The affected skin displays tuberosity, fissures, and depressions mostly on buttocks, thighs, or hips where fat is under the influence of estrogen [5, 6]. Cellulite can also be found in the breasts, in the lower abdomen, arms, and nape—areas where deposition of the adipose tissue is commonly observed [1, 5].

Even though no accurate epidemiologic data exist on its prevalence, it is thought to affect 80–90% of postpubertal women [7] and is rarely seen in men. The common advent around 20–30 years of age has led to the possibility of hormonal etiology.

Goldman described cellulite as a normal physiologic state in postpubescent females that enhances adipose retention to guarantee sufficient caloric availability for pregnancy and lactation [8].

Cellulite is mostly seen in people who are overweight or obese, but also in people having correct body mass [9–11]. However, being overweight exacerbates the presence of cellulite. Some of the contributing factors for cellulite are as follows [12–14]:

1. Genetic predisposition
2. Hormonal imbalance
3. High body mass index
4. Sedentary lifestyle
5. Smoking
6. Inadequate diet

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7. Metabolic disorders like diabetes
8. Cardiovascular diseases
9. Posture defects
10. Emotional disorders

25.2 Histopathology

The epidermis is typical. A discreet perivascular lymphocytic infiltrate is seen in papillary and high reticular dermis, as well as in the normal skin. The collagen fibers in the superior layers of the dermis are to some extent edematous. The eosinophilic coloration of the collagen fibers is lighter than in the normal skin. No sign of fibrosis, sclerosis, or hyalinization is found. The elastic fibers are reduced in the subepidermic plexus; the fragments cling together in the deeper layers of the dermis. In the arrectores musculi pilorum region, there are indistinct signs of edema and, occasionally, of vacuolar degeneration. The blood vessels do not display pathological features. The superior dermis lymphatic vessels are visibly expanded. Fat cells in the subcutaneous tissue appear enlarged. The adipose tissue's septa are normal but may present discreet edema [15].

25.3 Pathophysiology

Cellulite is a complex result of genetic predisposition, and metabolic and biochemical disturbances. Based on magnetic resonance imaging (MRI) and gross ex vivo and in vivo examination, cellulite is postulated to be the result of the herniation of fat through perpendicularly oriented collagen fibrous septa. The collagenous septa course through the subcutaneous tissue, from the deep fascia and attach just under the skin. These septations have variable thickness and distribution in patients with cellulite [16].

When a patient is standing, the fat that encircles the fibrous bands projects outward, giving the "dimpling" appearance of cellulite [17].

Tissue vascularity and inflammation have also been assumed to play a role in cellulite development. It is hypothesized that adipocytes in cellulite prone areas have unique biochemical properties and are more resistant to lipolysis [18]. De Godoy and colleagues [19] hypothesized that an accumulation of fluids in the interstitial space, of both the lymphatic and venous systems, produces the changes that favor the development of cellulite. The accumulation of certain macromolecules results in local inflammation hindering the exchange of particles between both systems which leads to stasis in the lymphatic system that results in cellulite [19]. As a result of stasis, increased microedema results in further stress on the subcutaneous fat layer and surrounding connective tissue and collagen. In response, the number

and thickness of reticular fibers intensifies which leads to accentuation of skin irregularities and ultimately the appearance of cellulite [20].

25.4 Etiopathogenesis

A variety of reasons contribute to the development of cellulite including structural, circulatory, hormonal, and inflammatory factors [21–23].

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

25.4.1 Anatomical and Hormonal Alterations

Anatomical hypothesis is grounded on the fact that there are differences between men and women regarding the structural characteristics of subcutaneous fat lobules and of the conjunctive tissue septa that separate them. According to this philosophy, originally detailed by Nurnberger and Muller [15], the appearance of cellulite is caused by the protrusion of fat in the dermohypodermal junction. This alteration specifically occurs in women, due to the presence of vertical fascial bands. Piérard [24] believes that cellulite is caused by the genetically determined extension of those fascial bands. This, 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.

Men's subcutaneous region is composed of horizontal and diagonal fascial bands, which obstruct the herniation of fat [25]. Cellulite is extremely rare in men with normal levels of androgens, regardless of their weight, due to the genetic and hormonal nature of the architecture of the skin.

Hormonal differences are responsible for the structural variations in the anatomy of women's subcutaneous fat, meaning it is fundamentally regarded as an anatomic alteration [5].

25.4.2 Vascular Alterations

Cellulite is formed with the weakening of cutaneous vascularization, particularly in response to changes of the arteriolar precapillary sphincter in affected areas, in conjunction with deposits of hyperpolymerized glycosaminoglycans in the dermal capillary walls and between the collagen and elastic fibers [16, 22]. The increase 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 septa, leading to variations in the cells and tissular hypoxia.

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—enable the excessive growth of the adipocytes. The enlarged adipocytes, in combination with the growth and hyperplasia of the periadipocyte reticular fibers, form micronodules surrounded by proteins fragments that, later on, cause sclerosis of the fibrous septa, ultimately leading to the appearance of cellulite. Various therapies based on this theory encourage to improve circulation and drainage, with the objective of reducing the dimpled and irregular appearance of the skin [22].

25.4.3 Inflammatory Factors

Inflammatory factors also form the basis of physiopathology of cellulite [26–28]. Though not supported by enough evidence, some studies suggest that septa are responsible for the light inflammation that results in the lysis of the adipocytes and cutaneous atrophy.

Figure 25.1 summarizes the probable factors involved in the etiology of cellulite [29].

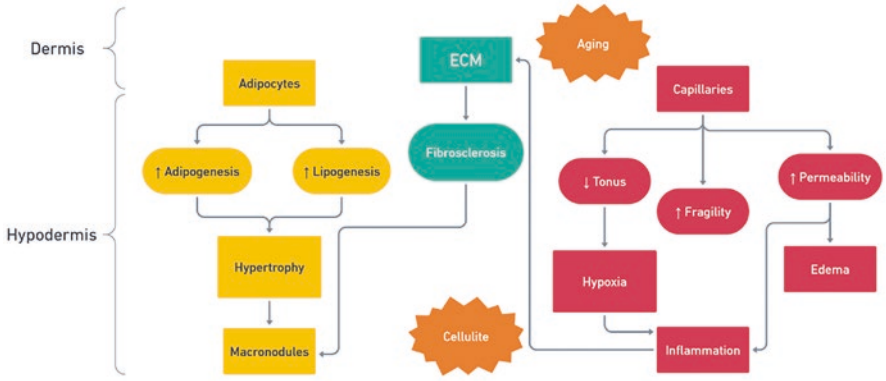

Fig. 25.1 The figure depicts the major factors contributing to cellulite. *eCM* extracellular matrix. (*Reference from Dupont E and colleagues. Clin Cosmet Investig Dermatol. 2014 7:73–88* [28])

25.5 Differential Diagnosis

Cellulite is sometimes referred to as fat or adipose but there exists a vast difference between them. Adipose tissue known as body fat refers to a type of connective tissue made up of adipocytes, collagen, blood vessels, and nerves. Fat tissue resides as two main reservoirs in the body—visceral fat and subcutaneous fat. Body contouring procedures like liposuction and cryolipolysis target subcutaneous fat. Though subcutaneous fat makes up an element of cellulite, not all subcutaneous fat is cellulite. Cellulite results from the underlying subcutaneous fat herniating between subcutaneous fibrous connective tissue which results in nodularity and dimpling of the skin. Hence treatments which aim to reduce subcutaneous fat fail to lessen cellulite. The proposed complex factors that interact in the formation of cellulite are reduced microcirculation, interstitial liquid infiltration (edema), localized hypertrophy of adipocytes, oxidative stress, and persistent low-grade inflammation, combined with extracellular matrix alterations [30–34]. The extensibility, elasticity, and resilience of the skin are also atypical [35].

Cellulite may be confused with **Lipoatrophy** which clinically appears as depressions in the skin and may be the consequence of trauma, a history of steroid injections, post-traumatic fat necrosis, or removal of excess subcutaneous tissue during liposuction.

Infragluteal bulges, folds, or protrusions, frequently referred to as a "banana roll," are the outcome of infragluteal fascial bands present at the base of the gluteal folds that may accentuate adipose tissue inferior to the buttocks [35].

Generalized edema or lymphedema and generalized obesity can also lead to alternating depressions and protrusions of the skin, prominently on the lower extremities, as a result of diminished lymphatic flow or diminished microcirculation.

It is imperative to consider these conditions during the evaluation and treatment since the modalities targeting cellulite may lead to exacerbations in the above-mentioned conditions [35].

25.6 Classification

Two classifications most commonly used in classifying cellulite are Nurnberger and Muller classification and the other proposed by Hexsel.

In 1978 Nürnberger and Müller classified cellulite into grades created on the clinical presentation of the condition [15]:

Table 25.1 Cellulite severity scale variables as proposed by Hexsel

Cellulite severity scale	
Number of evident depressions	0 = No depressions 1 = 1–4 visible depressions 2 = 5–9 visible depressions 3 = 10+ visible depressions
Depth of the visible depressions	0 = No depressions 1 = Superficial depressions 2 = Medium depth depressions 3 = Deep depressions
Morphologic appearance of the alterations of the surface of the skin	0 = No raised areas 1 = Orange peel appearance 2 = Cottage cheese appearance 3 = Mattress appearance
Degree of flaccidity or cutaneous laxity	0 = Absence of laxity 1 = Slight draped appearance 2 = Moderate draped appearance 3 = Severe draped appearance
Nürnberger and Müller classification scale	0 = Zero grade 1 = First grade 2 = Second grade 3 = Third grade

- 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.

Hexsel proposed a new objective classification by using photonumeric gradations [36]. He designed a more complex scale, composed of 5 variables (ranked 0–3) whose total sum classifies the patient into 1 of 3 groups based on severity: light (1–5 points), moderate (6–10 points), or severe (11–15 points).

The 5 analyzed variables are noted in Table 25.1:

The buttock- and thigh-specific Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) (Fig. 25.2) were postulated to resolve the shortcomings of the above classification scales. These new scales evaluated the cellulite severity, employing a photonumeric reference, cellulite severity and corresponding descriptors, from both physician and patient perspectives. The traditional scales of cellulite severity were assessed using the CR-PCSS and PR-PCSS ratings [37].

a Patient Reported Photonemeric Cellulite Severity Scale (PR-CSS) Buttocks

0-None No evidence of cellulite.	**1-Almost none** A few superficial dimples or ridges.	**2-Mild** Several dimples or ridges of which most are superficial.	**3-Moderate** Many dimples or ridges of which most are somewhat deep.	**4-Severe** A lot of dimples or ridges of which many are deep covering most of the skin area.

Clinician Reported Photonemeric Cellulite Severity Scale (CR-PCSS) Buttocks

0-None No dimples or evident cellulite.	**1-Almost None** Few dimples that are superficial in depth.	**2-Mild** Several dimples out of which most are shallow in depth.	**3-Moderate** Many dimples of which most are moderate in depth.	**4-Severe** A lot of dimples with some of more severe depth.

b Patient Reported Photonemeric Cellulite Severity Scale (PR-PCSS) Thigh

0-None No evident cellulite	**1-Almost None** A few superficial dimples or ridges.	**2-Mild** Several dimples or ridges of which most are superficial.	**3-Moderate** Many dimples or ridges of which most are somewhat deep.	**4-Severe** A lot of dimples or ridges of which many are deep covering most of the skin area.

Clinician Reported Photonemeric Cellulite Severity Scale (CR-PCSS) Thigh

0-None No depressions or raised areas.	**1-Almost None** A few depressions or undulations that are mostly superficial in depth.	**2-Mild** Several undulations that are shallow in depth with areas of slight protuberances.	**3-Moderate** Many undulations with alternating areas of protuberances and depressions of which most are moderate in depth.	**4-Severe** A lot of undulations with alternating areas of protuberances and depressions some of more severe depth.

Fig. 25.2 Assessment of cellulite severity using the PR-PCSS and CR-PCSS for the buttocks (**a**) and thighs (**b**). *CR-PCSS* Clinician Reported Photonumeric Cellulite Severity Scale, *PR-PCSS* Patient Reported Photonumeric Cellulite Severity Scale. (@ 2017 Auxilium Pharmaceuticals, LLC. *Reference Neil S and colleagues. Dermatol Surg. 2019;45:1047–1056* [37])

25.7 Treatment

Due to complex, multifactorial and indefinite etiopathogenesis, there is still no effective or absolute treatment. Many therapeutic proposals have been introduced which lack sufficient scientific evidence, durability, and reproducible results. There have been advances in the treatment of cellulite, and the most commonly reviewed treatment options have been discussed ahead.

25.7.1 Past Treatment Modalities for Cellulite

Microvascular Dysfunction and Tissue Edema

1. Methylxanthines (e.g., caffeine)
2. Mechanical stimulation (manually or with the use of a device)
3. Acoustic wave therapy or extracorporeal shock wave therapy

Excessive Subcutaneous Adipose Tissue

1. Weight loss
2. Cryolipolysis
3. High-intensity focused ultrasound
4. Low-level laser therapy (e.g., wavelengths varying from 532 nm, 635 nm, and 808 nm)
5. High-powered laser therapy (e.g., 1064-nm Nd:YAG)
6. Liposuction

Collagen Denaturation and Tissue Laxity

1. Radiofrequency (unipolar, bipolar, or tripolar)
2. Infrared light

Cellulite treatments mentioned in the international medical literature are classically divided into two groups:

- Noninvasive
- Invasive

Both can be further classified as:

– Treatments that do not involve the use of biologically active substances (medications)
– Treatments that involve use of active substances

25.7.2 Noninvasive Treatments Without the Use of Biologically Active Substances

Massage/Endermologie® In this category 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® machine) [28, 38, 39].

Light-Based Devices Intense pulsed light (IPL) and laser belong in this category. IPL is used to stimulate the formation of new collagen and thickening of the dermis, thus making it less susceptible to cellulite. The isolated use of laser is uncommon and scarcely quoted. Many devices combine laser and IPL with massage, vacuum, ultrasound, or multiple techniques in a single device to address several etiopathogenic mechanisms of cellulite such as structural alterations in the collagen, microcirculation, and lymphatic drainage [40].

Dermal Fillers Recently, fillers like poly-l-lactic acid microspheres and calcium hydroxylapatite (CaHA) combined with MFU-V have been used effectively for improving the appearance of cellulite [41]. When combining these procedures on the same day, the energy device is used first, such as MRF or MFU-V, immediately followed by the injectable biostimulatory agent. If the dermal filler is done first, MRF or MFU-V is performed at least 1 week, preferably 1 month, later [42, 43].

Collagenase Clostridium Histolyticum (CCH) It is composed of 2 purified collagenases (AUX-I and AUX-II) that hydrolyze collagen under physiologic conditions, resulting in disruption of collagen structures (e.g., fibrous septa) [44]. CCH is approved by the US Food and Drug Administration for the treatment of collagen-associated disorders and has provided benefits in cellulite too [37, 45, 46].

25.7.3 Noninvasive Treatments with Biologically Active Substances

Topical preparations containing several pharmacological agents have been very commonly used. Topical treatments can be indicated as adjuvant therapies. Agents like methylxanthines, retinoids, lactic acid, and herbal extracts are used alone or in combination. These agents exert their anti-cellulite effects by several biological mechanisms. Methylxanthines such as caffeine, aminophylline, and theophylline have documented action in the treatment of cellulite. Herbal extracts include plants such as forskolin (*Coleus forskohlii*), sacred lotus (*Nelumbo nucifera*), carnitine, and escin, Ginkgo biloba, also rich in flavonoids, *Centella asiatica*, *Ruscus*

aculeatus, and *Carica papaya* [32]. Topical retinoic and related vitamin A derivates have been also used as topical cellulite treatments.

25.7.4 Invasive Treatments with Biologically Active Substances

Mesotherapy consists of the injection of multiple substances including xanthines such as caffeine, aminophylline, and theophylline, into the subcutaneous tissue which lead to lipolysis [23].

Carboxytherapy involves injecting carbon dioxide in the subcutaneous tissue with the target of affecting adipose tissue and circulation [47].

25.7.5 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.

Other options are ultrasonic liposculpture [48–50] and autologous transplant of adipose tissue with the application of Nd-Yag laser in the subcutaneous tissue [51].

A treatment algorithm outlining the different cellulite combination treatment, the timespan of the procedures, and the sequence of treatment is given in Table 25.2.

The algorithm shares the entire spectrum of available cellulite treatments ranging from minimally invasive (Option 1) to the most invasive procedures (Option 3) [52]. The multifactorial etiologies in cellulite can be efficiently dealt by utilizing the combination treatments at times in a single session.

25.8 Conclusion

Cellulite is a condition that negatively impacts quality of life, and there has been enormous growth in available technologies to treat cellulite. Researchers are trying to seek a reliable treatment option for years which can be durable and reproducible. A better understanding of the role fibrous septa play in the pathogenesis of cellulite has led to the emergence of several treatment options that have shown objective, significant, and durable results.

Table 25.2 Algorithm for cellulite treatment

	Option 1	Option 2	Option 3
Volume loss and cellulite	MFU-V or RF	Controlled subcision	Controlled subcision
	PLLA or CaHA	MFU-V or RF	Fat transfer
		PLLA or CaHA	
Excess fat and cellulite	Detergent lipolysis or cryolipolysis	Liposuction or field radiofrequency	Controlled subcision
	1 month later: Controlled subcision	1 month later: Controlled subcision	1 month later: Liposuction or cryolipolysis
Skin laxity and cellulite	MFU-V or RF	Controlled subcision	Controlled subcision
	Controlled subcision	PLLA or CaHA	1 month later 2. MFU-V or MRF 3. PLLA or CaHA
Volume loss/skin laxity and cellulite	MFU-V or RF	Fat transfer	Fat transfer
	PLLA or CaHA	1 month later MFU-V or RF	Controlled subcision
			1 month later MFU-V or RF
Volume loss/excess fat (separate locations) and cellulite	Cryolipolysis or detergent lipolysis	Liposuction	Liposuction
	Controlled subcision	Subdermal RF	Controlled subcision
	PLLA or CaHA	1 month later PLLA or CaHA	1 month later PLLA or CaHA
Skin laxity/excess fat and cellulite	Cryolipolysis or detergent lipolysis	Liposuction	Liposuction
	Controlled subcision	Subdermal RF	Controlled subcision
	MFU-V or RF		1 month later PLLA or CaHA
	PLLA or CaHA		

Reference from Davis DS and others. Cellulite: Patient Selection and Combination Treatments for Optimal Results-A Review and Our Experience. Dermatol Surg. 2019;45 (9):1171–1184 [52]

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