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Review Article

Cellulite: A review of the current treatment modalities

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Abstract Cellulite is a dermatological condition that affects 80- 90% of postpubertal women across all races and makes the skin surface to resemble an orange peel or a mattress. There are several theories postulated to explain the aetiopathogenesis of cellulite, and a number of different therapeutic regimens have been developed in recent years, from topical treatments to mechanical or energy-based devices. In this article, the currently available treatment modalities are reviewed in the light of the recent literature.

Key words
Cellulite, collagen septae, cosmeceuticals, radiofrequency, subscision, laser, extracorporeal shockwave therapy, dermal filler, carboxytherapy.

Introduction

Cellulite is a multifactorial dermatological condition that is present in 80-90% of postpubertal women of all races and is a very frequent cause of cosmetic concern.[1-2] Cellulite has been referred to by several synonyms including edematofibrosclerotic panniculopathy, gynoid lipodystrophy, nodular liposclerosis, panniculopathy, panniculosis, adiposis edematosa, dermopanniculosis deformans, and status protrusus cutis[3] and was first described by Alquin and Pavot in 1920 and originally thought to be "interstitial edema associated with an increase in fat content".[1]

There are various theories propounded in the literature to explain the etiology and pathophysiology of cellulite and it appears to be multifactorial, with sexual dimorphism of subcutaneous connective tissue, the effects of localized disturbance in tissue tension, and local circulatory and inflammatory abnormalities, all projected as potential factors that play some important role.[4]

This condition is different from generalized obesity because obesity is characterized by adipocytes undergoing hypertrophy and hyperplasia whereas in cellulite has large, metabolically stable adipocytes that are limited to lower body areas including pelvis, thighs, and abdomen.[1]

Therapeutic options to relieve the condition range from topical treatments to mechanical or energy-based devices and it is still difficult to point out an exclusive and effective single treatment for this condition.[3,5]

This review aims to update about the available treatments in cellulite reduction along with their safety and efficacy profile.

Methods

The original articles, reviews, case series and case reports dealing with the Cellulite were searched in PubMed, HINARI, Scopus, Google

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Scholar, Web of Science, Semantic Scholar and ResearchGate after search on following terms: "cellulite" AND ("physiopathology" OR "etiopathogenesis" OR "etiology" OR "management"). Only the articles published in English were included and time limits were set between years 2000-2020. Reference lists in all the selected articles were examined and used to identify additional articles for inclusion.

Phenotype and anatomy

Cellulite has a distinct phenotype, with the skin topography changing to a surface that resembles an orange peel or a mattress, visible either spontaneously or after provoking manoeuvres. Pierard *et al*.[6] on the basis of biopsy study of cellulite found that there was uneven thickness, fibrosclerosis, shortening and retraction of the collagen septae across samples, secondarily leading to the herniation of subcutaneous fat lobules through the dermohypodermal junction, finally resulting in the creation of the dimples and depressions that characterize cellulite.

Magnetic resonance imaging studies have also confirmed that cellulite depressions are associated with irregular conformation and a significant increase in thickness of the subcutaneous fibrous septa though, the relationship between septae thickness and cellulite severity has not been established.[7]

Epidemiology

There is little epidemiologic data available on the exact prevalence, incidence, and associating factors of cellulite and a figure of 80–90% prevalence in postpubertal female patients is mentioned in literature.[1,2]

The high estrogen states, including pregnancy, nursing, and chronic use of oral contraceptives may lead to worsening of cellulite. Rapid weight gain and obesity can worsen the appearance of existing cellulite making depressions more prominent, although diet, exercise, and lifestyle, however, do not appear to be associated with its development.[4]

Cellulite in male patients is rarely reported and is predominantly an outcome of androgen deficiency secondary to castration, hypogonadism, Klinefelter's syndrome, or estrogen therapy for prostate cancer.[8]

Treatment modalities

Many treatments raging from topical treatments and injectables to mechanical or energy-based devices have been studied and published with claims of being able to improve the appearance of cellulite[5,9] as shown in **Figure 1**. These modalities are used solo or in combinations.

Cosmeceuticals

Cosmeceuticals are the topical products that are placed between cosmetics and pharmaceuticals and are intended for the enhancement of both the health and aesthetics of the skin. Topical agents combined with vigorous massage, constitute the earliest attempts to improve cellulite. Normally, they are recommended to treat mild-to-moderate cellulite or else used as an adjuvant treatment for severe cellulite[9] as they cannot reverse or very significantly alter the fundamental cutaneous architectural disturbance existing in cellulite.[7]

The main challenge that these therapies face is transport the active ingredients to their target in

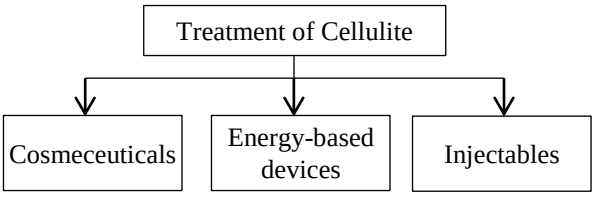

Figure 1 Current treatment modalities of Cellulite.

Table 1 Cosmeceuticals for cellulite and their mechanism of action.

Mechanism of Action	*Agents*
1. Increase in the microcirculation flow.	Ginkgo biloba, Pentoxifylline Centella asiatica, Ruscus aculeatus, Silicium Papaya (Carica papaya), Pineapple (Ananas sativus), Red grapes (Vitis vinifera), Cynara Scolymus, Ivy, Melillotus officinalis.
2. Reduction of lipogenesis and promotion of lipolysis.	Methylxanthines, beta-adrenergic agonists, alpha -adrenergic antagonists.
3. Restoration of the normal structure of dermis and subcutaneous tissue.	Retinoids (vitamin A)
4. Prevention of formation or else scavenging off free-radicals.	Alpha-tocopherol (vitamin E) Ascorbic acid (vitamin C) Ginkgo biloba Red grapes (Vitis vinifera).

sufficient concentration to have a therapeutic effect.[1]

There is a wide range of ingredients used in cosmeceuticals for cellulite and they may be divided in 4 major groups according to their mechanism of action[10] as shown in **Table 1**. However, the most extensively evaluated ingredients include methylxanthines (aminophylline, theophylline, and caffeine) and retinoids. It is hypothesized that methylxanthines improve cellulite by stimulating lipolysis and inducing inhibition of the enzyme phosphodiesterase, which leads to increase in the concentration of cyclic adenosine monophosphate (cAMP).[1] The most useful and safest methylxanthine is caffeine, which is normally used in concentrations of 1-2%. Velasco *et al*.[11] found in a study showing that an emulsion with caffeine caused a reduction of 17% on the diameter of the fatty cells compared with the control but gel was found to be inadequate vehicle for incorporation with caffeine.

Retinoids are believed to improve cellulite by increasing dermal thickness, increasing angiogenesis, increasing the number of active fibroblasts and synthesizing new connective tissue components.[1] Machinal-Quelin *et al.*[12] investigated the mechanism of action of retinol and concluded that retinol inhibits the adipo-conversion of human preadipocytes, suggesting that the mechanisms of this antiadipogenic action imply at least in part inhibition of CCAAT-enhancer-binding protein trans-criptional activity.

Hexsel and Soirefmann[9] have noted that the patients using topical treatment for cellulite, even after knowing the limited effects of topical products, achieved significant positive impact in self-esteem and compliance when they are using topical treatment. Sainio *et al*. studies the safety profile of cosmeceuticals and found that one fourth of the substances used in their manufacture have the potential to cause allergy and hence cautioned that the risk of adverse effects should be taken into account when using cellulite creams.[13]

Energy-based devices

Energy-based devices that harness power from various sources such as lasers, light, radiofrequency (RF), and acoustic waves are being extensively reported in literature as means of improvement of cellulite.

Massage LPG endermologie (Endo-Systems, LLC, Fort Lauderdale, FL) is a well-tolerated and effective mechanical massage system approved by The United States Food and Drug Administration (US-FDA) for cellulite treatment. It is believed to painlessly stimulate the skin to reactivate dormant cellular activity. The treatment usually consists of about 15-20 sessions wherein the hand-held massage roller is

used by rolling the head over the desired areas. Improvement has been seen after about six treatments though it is unclear from published data how durable these effects are on long term.

Kutlubay *et al*.[14] conducted study in 2013 to evaluate safety and efficacy of LPG endermologie by enrolling 118 women (mean age, 34.59±8.02 years). The LPG treatment sessions were performed twice weekly and continued for at least 15 sessions. The outcome was clinically evaluated using digital photography for cellulite grade assessment and 69% of the patients were satisfied with the results. Gulec[15] also conducted a similar study and however found this device is mildly effective in reducing the cellulite grade or improving its orange-peel appearance.

Radiofrequency (RF) generates electrothermal effects painlessly in the dermal/ subcutaneous plane by the impedance of electricity flow through the tissue delivered via electrodes.[16]

The elevation of the tissue temperature at the target area results in stimulation of collagen denaturation, remodelling and neocollagenesis and triggering of lipolysis.[1] Trelles *et al*.[17] studied the histological findings observed in biopsies taken after a single RF treatment and found changes in shape, size, and lipid content, as well as in cytoplasmic and nuclear morphology. After RF treatment adipocytes were more polyhydric, with irregular, degenerated membranes, with less or no lipid content and apoptotic changes. They postulated that RF treatment on cellulite produces a decrease in lipid content of cells as well as changes in the adipocyte membrane which will lead to cell rupture and the death and extrusion of lipid content out of the cell.

Depending on the electrode or generator configuration, RF devices come in various types which include older first-generation versions (e.g., unipolar, monopolar, and bipolar) to the latest generation (e.g., X -Polar, multipolar, multigenerator, and temperature-controlled) devices.[18-19]

Alexiades M *et al*.[20] demonstrated that unipolar RF device is safe for the treatment of cellulite in a randomized, blinded, split-design, controlled study employing a quantitative four-point grading scale. They observed a trend towards improvement in all patients following a mean of four treatments at 2-week intervals though the clinically visible and quantified improvement did not achieve statistical significance.

In another study, Alexiades *et al*. in 2018[21] reported an achievement of a procedural success rate of 93% at 6-month follow-up after having received 1 subcutaneous microneedle RF treatment (67°C/ 4-second duration) with a bipolar fractional radiofrequency (RF) device. Procedural pain level was 3.74±1.96 on a 10-point scale and there were no adverse events. 75% of subjects were satisfied with the results.

Mlosek *et al*.[22] studied the effectiveness of tripolar radiofrequency in cellulite and monitored the progress by classic and high-frequency ultrasound and found that cellulite was reduced in 89% of the women who underwent RF treatment and it was documented that there occurred a decrease in the thickness of the dermis and subcutaneous tissue, an increase in echogenicity reflecting on the increase in the number of collagen fibres, decreased subcutaneous tissue growing into bands in the dermis, and the reduction of oedema.

Some latest RF devices also integrate electricity with other forms of energies in their technological design, such as infrared light, vacuum suction, and pulsed-electromagnetic fields.[1,18] Specifically, significant improvement

in cellulite has been reported with application of Velasmooth and Velashape systems (Syneron Medical) that combine infrared light, bipolar RF, and mechanical manipulation of the skin with suction and massage.[1] The suggested mechanism of action includes enhancement of circulation, stimulation of the adipocyte metabolism, and mechanical stretching of the fibrous cords.

In a study by Sadick and Mulholland,[18] 35 female subjects with cellulite were given 8 to 16 treatments twice weekly with the VelaSmooth device and 100% of patients showed some level of improvement in skin texture and cellulite. Alster and Tanzi[23] used a novel combination bipolar radiofrequency, infrared light, and mechanical tissue manipulation device and achieved sustained improvement though maintenance treatments were suggested to further enhance the clinical results achieved.[23]

Some other U.S. Food and Drug Administration (FDA) approved RF devices for treatment of cellulite include a monopolar RF device named Exilis Elite (BTL Aesthetics, UK), a multipolar RF device with pulsed magnetic fields named Venus Legacy (Venus Concept, Ontario),[24] a multigenerator RF device marketed as Endymed Body Shaper (Endymed) and ThermiRF (Thermi Aesthetics, CA) which is a novel temperature-controlled RF device with internal probes.[1]

Laser Laser and light devices deliver energy to the dermis/ subcutaneous plane and heat up the local tissue, which can improve the appearance of cellulite by stimulating collagen remodelling and increase in the microcirculation. They do not have any substantial impact on adipolysis or even disruption of the fibrous septa that characterize cellulite, but they have the potential to improve the aesthetics of the skin by smoothening the surface.[1,25]

Minimally invasive side-firing fibre 1440-nm Nd:YAG laser has been the variant that has been shown satisfactory in cellulite management. Usually a single treatment is required, and clinical improvement of cellulite with high subject satisfaction is achieved with minimal adverse events.[1] DiBernardo *et al.* in two studies published in 2013[26] and 2016[27] found this tool to be safe and effectiveness was maintained at least 1-year post treatment.

Sasaki demonstrated the maintenance of improvement at 2 years post treatment.[28] Peterson and Goldman[29] propose that the patients who want smoother skin with less visible cellulite can undergo a series of laser treatments and then return for additional treatments as necessary.[29] Nootheti *et al.*[30] conducted a single center, randomized, comparative, prospective clinical study to determine the efficacy of the VelaSmooth system versus the Triactive laser system (Cynosure) for the treatment of cellulite and concluded that both the TriActive and VelaSmooth provide improvement of cellulite though there was a statistically significant increase in the incidence of post-treatment bruising with the VelaSmooth.

Acoustic wave therapy (AWT) In acoustic wave therapy (AWT) pressure waves are transmitted to the subcutaneous tissue which in turn are postulated to promote lipolysis, improve local blood flow, enable lymphatic drainage, and stimulate the production of new collagen.[1] The acoustic waves are low-energy and delivered either as defocused extracorporeal shock wave therapy (ESWT)[31] or as radial shock waves over multiple treatment sessions with any requirement of topical anaesthesia as the resultant is only minor pain.

A study by Nassar *et al.*[32] evaluated the efficacy of ESWT administered over eight sessions

during 4 weeks to 15 patients and concluded that ESWT was efficient in the improvement of body contour (i.e., reduction of circumference and fat layer) as well as in the appearance of cellulite 3months after treatment. Adatto *et al*.[33] studied the efficacy and safety of acoustic wave therapy (AWT) using extracorporeal pulse activation technology (EPAT) to manage cellulite and found the AWT/EPAT treatment using the D-ACTOR 200 (STORZ MEDICAL AG, Switzerland) to be a safe and effective.

Christ *et al*.[34] reported a study enrolling 59 women, aimed at stimulation of metabolic activity in subcutaneous fat tissue by means of EPAT and confirmed the effects of acoustic wave therapy on biologic tissue, including stimulation of microcirculation and improvement of cell permeability. Skin elasticity values gradually improved over the course of EPAT therapy and revealed a 73% increase at the end of therapy. At 3- and 6-month follow-ups, skin elasticity had even improved by 95% and 105%, respectively. Side effects included minor pain for 3 patients during therapy and slight skin reddening.

Subcision Subcision is an established surgical procedure that releases the reticular dermis from tethering by underlying fibrous septal bands within subcutaneous adipose tissue leading to redistribution of subcutaneous tension forces, mitigating fat protrusion, and reallocation of fat lobules into spaces created by the procedure, thereby improving the clinical appearance of cellulite.[35]

Subcision is carried out only for the cellulite depressions that are manifested at rest and not for depressions visible only with muscle contraction. Depressions are marked immediately before the procedure with the patient standing in a relaxed position.[4] The procedure is carried out on outpatient basis after direct percutaneous infiltration of dilute lidocaine (0.1%) and sodium bicarbonate (8.4%) with epinephrine (1:1,000,000) in physiologic saline which produces complete local anaesthesia and haemostasis of cutaneous and subcutaneous tissues.[4] Post-procedure, patients are recommended to avoid strenuous physical activity for 1-2 weeks and use compressive garment for 2-4 weeks.

Subcision can be undertaken with manual, vacuum- assisted, or laser-assisted methods.

i. *Manual subcision* An 18-G non-coring needle/ forked cannula is inserted 1-2cm into the subcutaneous adipose tissue layer, parallel to the skin surface and by repetitive cutting motions until a dissection plane is created and fibrous bands cut. Proper technique and skill is a must because subcision performed too superficially can result in excessive elevation or necrosis of the skin whereas subcision performed too deep may produce negligible improvement in the targeted depressions.[35] Other post-treatment adverse events include hematoma formation, painful bruising for up to 4 months in 90% of subjects and hemosiderin pigmentation lasting up to 10 months.

   Hexsel D *et al*.[36] satisfactorily treated two patients with severe buttock cellulite with a single session of manual subcision using an 18-G non-coring needle. MRI studies of each buttock of each patient, performed before and after treatment, demonstrated severing of the underlying perpendicular thick fibrous septal band though overall subcutaneous adipose tissue architecture and fat lobule morphology had remained the same.

ii. *Vacuum-assisted subcision* A novel vacuum-assisted system (Cellfina system; Ulthera, Inc., Mesa, AZ, USA) was developed, providing

precise control of anaesthesia infiltration (integrated 22-G needle) and user-selected treatment depth (6 or 10 mm) and area (5 cm or 3×6 cm) with a 0.45 mm microblade thereby avoiding the dependence upon the operator skills and potential inconsistency as are the problems with manual subcision.[37] Multiple studies have reported significant single-session improvement without recurrence as far as 3-4 years post-treatment.[38-39]

The adverse effects include ecchymosis, edema, palpable firmness, and transient tingling and mild aching pain that may last up to 6 months posttreatment.

iii. *Laser-assisted subcision* Percutaneous sub-dermal delivery of laser energy to create targeted disruption of subcutaneous fibrous septae has also be reported. A 1440 nm device with a 1000m side-firing laser fibre tip (Cellulaze system; Cynosure, Inc., Westford, MA, USA) has been shown to be safe and effective for the treatment of cellulite.[4,40] Adverse events (e.g., edema and ecchymosis) are mild and transient.[40]

Ultrasound Ultrasound seems to be an efficacious, effective, and safe modality for correction of cellulite and used both high frequency and low-frequency sound waves to heat and melt away fat cells. Its efficacy as a monotherapy lacks substantial evidence and hence can be a useful adjunct to other treatments. Adverse effects are minimal including procedural pain, post-procedure erythema, and swelling.[41]

Moravvej *et al*.[42] evaluated the efficacy of focused ultrasonic lipolysis on abdominal cellulite treatment by enrolling twenty-eight consecutive subjects (age: 37.8±8 years) for weekly transdermal focused ultrasonic lipolysis (Med Contour, General Project Ltd., Florence, Italy) and vacuum drainage for a maximum of eight sessions and found the treatment to be effective.

Injectable treatments for cellulite

Injectables including active biologic agents and dermal fillers have been used to treat cellulite, with promising results in recent years.

Collagenase Clostridium histolyticum Collagenase clostridium histolyticum (CCH) are the enzymes isolated and purified from the fermentation of Clostridium histolyticum and they have been recently tried for the treatment of cellulite after their intralesional use was found useful in Peyronie's Disease. Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase) are not immunologically cross-reactive and have different specificities; mixed in a 1:1 ratio, they become synergistic and provide a very broad hydrolysing reactivity toward collagen.[43-44] Thus, they can hydrolyse the triple-helical region of collagen and potentially cause lysis of subdermal collagen rich dermal septa thereby disrupting the tethering found in cellulite.

Sadick NS *et al*.[45] in 2019 published the results if a randomized, double-blind study enrolling 375 women with moderate or severe EFP of the buttocks or posterolateral thighs. They found that CCH significantly improved EFP appearance versus placebo and recommended further evaluation of CCH for cellulite. The most common adverse events were self-resolving injection site related like bruising and mild tolerable pain.[45]

Dermal fillers Another up-to-date option to treat cellulite is the new generation dermal fillers injections, such as calcium hydroxyapatite

(CaHa) and poly-l-lactic acid microspheres. These fillers have been used extensively to treat scars and can also be applied to smoothen the cellulite- induced skin irregularities. Casabona and Pereira[46] evaluated the effects of microfocused ultrasound with visualization (MFU-V; Ultherapy) in combination with diluted calcium hydroxylapatite (CaHA; Radiesse) on cellulite appearance and on neocollagenesis by enrolling 20 women and found the combination treatment with MFU-V and diluted CaHA administered once, to be significantly effective in improving skin laxity and the appearance of cellulite on the buttocks and upper thighs.

Carboxytherapy Carboxytherapy refers to percutaneous infusion of medical carbon dioxide for therapeutic purposes. Carboxytherapy originated at the Royal Spas of France in 1932 with the treatment of patients afflicted by peripheral arterial occlusive disease and in recent years, it has been applied for cellulite management. Studies have demonstrated that carboxytherapy improves skin elasticity, improves circulation, encourages collagen repair and destroys localized fatty deposits.

Pianez *et al*.[47] conducted a pilot study wherein ten women, 29±6.1 years, were selected and administered eight treatment sessions, with an interval of 7 days between sessions. Standardized digital photographs were used to assess the severity of cellulite, and panoramic images were collected by ultrasound diagnosis. The evaluations were performed before the first treatment (baseline) and 7 days after the last treatment session of carboxytherapy. After the treatment, there was a significant reduction (P=0.0025) of the cellulite, and this improvement had correlation with the improvement in the organization of the fibrous lines and the disposal of adipose tissue lines of the treated regions observed through the panoramic ultrasound images diagnosis. The study concluded that carboxytherapy is an effective technique of treatment of cellulite in the gluteal region and posterior thighs of healthy women.

Carboxytherapy may however generate local pain that is considered the main limiting factor in clinical practice. Sadala *et al*.[48] assessed the effect of transcutaneous electric nerve stimulation (TENS) on pain intensity during carboxytherapy in patients with cellulite in the gluteal region and found it to be very effective and promising. Eldsouky and Ebrahim[49] recently compared the efficacy of carboxytherapy with mesolipolysis using phosphatidylcholine (PPC) and found the two to be equally effective.

Conclusion

There is a wide range of therapeutic options that attempt to treat cellulite, but single procedure can be considered an absolute success on long term basis. Topical agents, injectable treatments, and energy-based devices can ameliorate the appearance of cellulite to a satisfactory degree, but can never eradicate cellulite completely. Newer tools and innovations are evolving and currently, a combination approach where using multiple available options strategically and in a staged manner may yield the best clinical outcomes

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