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Review Article

Cellulite: a review of its physiology and treatment

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Cellulite affects 85–98% of post-pubertal females of all races. While not a pathologic condition, it remains an issue of cosmetic concern to a great number of individuals. Despite its high prevalence, there have been few scientific investigations into the physiology of cellulite. There have only been a few dozen peer-reviewed articles devoted to cellulite in the medical literature in the past 30 years. There is no definitive explanation for its presentation. This greatly complicates the ability to treat or improve it. The four leading hypotheses that purport to explain the physiology of cellulite include: sexually dimorphic skin architecture, altered connective tissue septae, vascular changes and inflammatory factors. Treatment modalities can be divided into four main categories: attenuation of aggravating factors, physical and mechanical methods, pharmacological agents and laser. There are no truly effective treatments for cellulite. *J Cosmet Laser Ther* 2004; **6**: 181–185

Introduction

Cellulite describes the orange peel or cottage cheese-type dimpling of skin seen most commonly on the thighs and buttocks.[1–3] The term 'cellulite' has its origins in the French medical literature of more than 150 years ago.[4] Synonyms include: adiposis edematosa, dermopanniculosis deformans, status protrusus cutis, and gynoid lipodystrophy.[5,6] The term 'cellulite' has penetrated both the medical literature and lay media. There is no morbidity or mortality associated with cellulite and, therefore, it cannot truly be described as a pathologic condition.[5] Cellulite remains, however, an issue of cosmetic concern to a great number of individuals.

Between 85% and 98% of post-pubertal females display some degree of cellulite. It is prevalent in women of all races[7] but is more common in Caucasian females than in Asian females.[8] There appears to be a hormonal component to its presentation. It is rarely seen in males and almost ubiquitous in post-pubertal females.[1,4] It is seen more commonly in males with androgen-deficient states such as Klinefelter's syndrome, hypogonadism, post-castration states and in those patients receiving estrogen therapy for prostate cancer. Interestingly, the cellulite becomes more severe as the androgen deficiency worsens in these males.

Cellulite can be located in any area of the body that contains subcutaneous adipose tissue.[4] Certain areas are, however, more susceptible, such as the upper outer thighs, the posterior thighs, and buttocks. Cellulite can also be found on the breasts, the lower part of the abdomen, the upper arms, and the nape of the neck – interestingly, all areas in which the female pattern of adipose deposition is observed. Although cellulite may be found in any area where excess adipose tissue is deposited, obesity is not necessary for its presence.[7]

Despite its high prevalence, there have been few scientific investigations into the physiology of cellulite. There have only been a few dozen peer-reviewed articles devoted to cellulite in the medical literature in the past 30 years. There is no definitive explanation for its presentation. This greatly complicates the ability to treat or improve it.

Physiology

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Sexually dimorphic skin architecture

The 'anatomic' hypothesis of cellulite is based on gender-related differences in the structural characteristics of subcutaneous fat lobules and the connective tissue septa that divide them. According to this theory, originally detailed by Nürnberger and Müller, the appearance of cellulite, i.e. 'pits' and 'dells', or dimpled skin, is caused by herniations of fat, termed 'papillae adiposae', that protrude from the subcutis through the inferior surface of a weakened dermis at the dermo-hypodermal interface.[7] These herniations of fat into the dermis are a characteristic of female anatomy and their presence has been confirmed by ultrasound imaging as low-density regions among denser dermal tissue.[2,9,13]

In a study using sonography to examine full-thickness wedge biopsies from affected and unaffected portions of the thigh, Rosenbaum and co-workers attempted to determine whether the dimpling of the skin seen in individuals with cellulite results from fat herniations into the dermis.[2] They examined seven healthy adult females with cellulite as well as three healthy unaffected controls, consisting of one woman and two men. Affected female subjects and the unaffected female control both demonstrated an irregular and discontinuous dermo-hypodermal interface characterized by protrusions of fat into the dermis, whereas the dermal-adipose tissue connective tissue border in male subjects was smooth and continuous.

Altered connective tissue septae

Although the Nürnberger and Müller hypothesis maintains that the presence of cellulite is determined by fatty protrusions through the dermal-hypodermal interface,[7] Piérard and co-workers found no correlation in their study between the extent of these protrusions and clinical evidence of cellulite, thereby questioning their relevance in the physiology of the condition.[3] In a study using autopsy specimens from the thighs of 24 previously healthy 28–39-year-old women with cellulite and a control group consisting of 11 men and four women without cellulite, the authors reveal important distinguishing characteristics within the micro-architecture of the subcutaneous connective tissue strands, well below the level of the dermal-hypodermal interface.[3] Thirteen of the women in the study group demonstrated overt dimpling without pinching, or 'full-blown cellulite', whereas the remaining 11 women exhibited cellulite only with the application of pressure, a phenomenon termed 'incipient cellulite' or 'cellulite-prone'. The authors conclude that persistent skin dimpling results from continuous and progressive vertically oriented stretch within these hypodermal collagen fibrous strands, a process that weakens the connective tissue buttress and allows for fat herniation.

Vascular changes

In a review of cellulite, Rossi and Vergnanini describe a multifactorial basis for the etiology of cellulite.[6] Based on descriptions by Curri[10,11] and others, the authors detail the metabolic and structural events that lead to cellulite formation (referred to as gynoid lipodystrophy). According to their theory, the process originates with deterioration of the dermal vasculature, particularly in response to alterations of the pre-capillary arteriolar sphincter in affected areas coupled with deposition of hyperpolymerized glycosaminoglycans (GAGs) in the dermal capillary walls and within the ground substance between collagen and elastin networks. Increased capillary pressure leads to increased capillo-venular permeability and the retention of excess fluid within the dermis, inter-adipocyte and inter-lobular septae. GAGs, which have hydrophilic properties, raise the interstitial pressure and additionally attract water. Edema causes cellular changes that ultimately result in vascular compression, vessel ectasia, decreased venous return and tissue hypoxia. Hypoxia, coupled with the increased proteoglycan deposition in dermal collagen and elastic fibers, triggers fibroplasia, collagenesis and capillary neoformation. Focal capillary rupture and micro-hemorrhage are noted histologically at this stage.

Increased lipogenesis, presumably triggered by estrogen, prolactin and diets rich in carbohydrates, in concert with increased lipolytic resistance caused by hypoxia, leads to adipocyte hypertrophy.[6] Enlarged adipocytes, together with hypertrophy and hyperplasia of the peri-adipocyte reticular fibers, leads to the formation of micronodules, or enlarged, grouped adipocytes surrounded by clumps of protein fibers. In time, continued edema, vascular congestion and hypoxia lead to thickening and sclerosis of the fibrous septae in the superficial adipose tissue and deep dermis, causing a padded appearance.

Although Lotti and others support the finding of increased edema and abundant GAG deposition at the lower dermal/subcutaneous junction in affected patients with cellulite,[4,5] this observation has not been replicated by additional studies.[3,7,9]

Inflammatory factors

Based on the subjective reporting of tenderness upon compression in some patients with cellulite,[4,12] several authors have suggested an inflammatory basis for its pathophysiology.[1,12] In a perspective on cellulite, Kligman has reported the diffuse appearance of chronic inflammatory cells, including macrophages and lymphocytes, in the fibrous septae from biopsies of cellulite.[12] According to Kligman, the septae are the source for a low-grade inflammation that results in adipolysis and dermal atrophy. Others, however, find no evidence for inflammation or adipolysis in patients with cellulite.[3,4,7]

Treatments

There are numerous therapies that have been advertised and employed to 'treat' cellulite.[1,6] Despite multiple therapeutic modalities, there is, at best, little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective or based upon patient self-assessment. Other data rely on subjective

assessment or patient satisfaction. In fairness, evaluation of therapeutic interventions for cellulite is difficult secondary to confounding factors, such as diet and exercise, as well as the absence of standard criteria used to assess treatment response.[6] Some of the studies utilize thigh measurement and photography to assess improvement, which are far from precise. The best objective and standardized tools to accurately assess response to cellulite treatment are ultrasound and MRI imaging, which should be employed in future studies.[2,9,13]

Treatment modalities can be divided into four main categories: attenuation of aggravating factors, physical and mechanical methods, pharmacological agents and laser.[6]

Attenuation of aggravating factors

Cellulite-aggravating factors include stress, weight gain, sedentary lifestyle and hormonal contraceptives.[6] Although weight loss, diet and exercise have been cited as means of improving cellulite,[6,7] there are no studies to date that confirm this speculation.

Many patients confuse weight gain with the appearance of cellulite. It is important to note that obesity does not cause cellulite. Adipocyte volume alone does create cellulite. Cellulite is present in nearly all lean females and very few obese males. Still, cellulite becomes more clinically apparent with weight gain. Moreover, weight loss does diminish the appearance of cellulite even if it does not alter the physiological reasons that produce it. Therefore, diet and exercise should be encouraged as an initial step in the treatment of cellulite.

Physical and mechanical treatments

Endermologie. The basis for various massage-suction techniques used for cellulite treatment rests on the premise that the condition is caused by impaired circulation. Endermologie ES1 (LPG Systems, Valence, France), or skin kneading, is a non-pharmacological treatment developed in France in the 1970s, which employs mechanical means to mobilize the subcutaneous fat in affected areas of the body.[14] This technique utilizes a patented, electrically powered hand-held machine used specifically for the purpose of cellulite reduction. As the machine is moved over affected areas of the body, folds of skin protected by nylon stockings are sucked into the machine and kneaded between two revolving rollers, a process that is claimed to improve the disorganization of the subcutaneous tissue structure and improve lymphatic drainage.[1,14] This procedure can be performed during twice-weekly visits consisting of sessions that last 10–45 minutes.[1,14,15] Despite the high cost of Endermologie, there is little evidence to support its efficacy.[16]

Collis and co-workers conducted a 12-week, randomized, controlled trial of 52 women to examine the effectiveness of either Endermologie or aminophylline versus a combination of both.[14] There was no statistical difference in the thigh measurements between the patients. While 11 of 35 patients using Endermologie showed improvement by self-evaluation, these benefits were attributed to weight loss secondary to diet and exercise rather than to skin kneading. Although the authors conclude that Endermologie is not effective in the treatment of cellulite, one commentator has criticized the 10-minute length of the Endermologie treatments in the study as 'not adequate' and suggests 15–20-minute treatments as more appropriate.[15] Furthermore, self-assessment is not a standardized, objective criterion for evaluating cellulite.

Liposuction. Liposuction is another method for treating cellulite.[17] Although standard suction lipoplasty has been purported by some as an excellent means to improve body contouring,[18] others have reported an increased dimpled skin appearance after liposuction.[19] Whereas ultrasonic liposculpturing may perhaps emerge as a superior, potentially safer, less destructive technique for cellulite reduction than traditional liposuction,[20] liposuction is still not a recommended treatment for cellulite given the potential for a poor cosmetic outcome.

Subcision. Subcision is another invasive method employed to improve cellulite.[21] It purports to correct the anatomical structure of subcutaneous fat that produces cellulite by severing fat septae. In subcision, after injection of local anesthesia, a 16 or 18-gauge needle is inserted into the subcutaneous fat and then directed in a parallel direction to the epidermis. It is then used to shear fat septae.

Hexsel and Mazzuco investigated subcision as a treatment in 232 patients aged 18–52 years with clinically apparent cellulite.[21] Over 78% of patients were satisfied after one treatment, 20% were partially satisfied and 1% were unhappy. There were no objective criteria by which to assess improvement limiting the value of this study. Side effects were not insignificant and included pain, bruising (3–6 months), hyperpigmentation (2–10 months) and skin puckering.

Phosphatidylcholine. Phosphatidylcholine injections have been used to treat localized fat accumulation in such disorders as HIV lipodystrophy and lipomas.[22] Rotunda and colleagues have identified sodium deoxycholate, a detergent that produces non-specific destruction of cell membranes, as the major active ingredient in this therapy.[22] There is no current scientific evidence to show its efficacy in treating cellulite.

Pharmacological agents

Pharmacological agents used for the improvement of cellulite include xanthines, retinoids, lactic acid, and herbals.[1,6] Although there are numerous topical treatments that are available over-the-counter at pharmacies, spas and boutiques[1] and via the Internet at cellulite websites,[23] there are no large-scale studies demonstrating the effectiveness of any of these therapies. Only two agents, aminophylline and retinoids, have been critically evaluated. Aminophylline, a xanthine, is a phosphodiesterase inhibitor, which stimulates beta-2 agonist receptor activity. The agent has been

employed as a therapy for asthma as well as a diuretic.[14] Recently, it has been recommended for use in its topical form as a treatment for cellulite.[16,24] Applied directly to the affected areas of dimpling, aminophylline cream is purported to migrate into the subcutaneous fat and cause a local lipolysis of adipocytes, thereby reducing the size of hypertrophic fat cells and disrupting adipocyte clumping. Collis and co-workers, who evaluated the effectiveness of 2% aminophylline with 10% glycolic acid cream, concluded that this therapy was not effective in improving the appearance of cellulite.[14] Patients using aminophylline treatment showed improvement in only three of 35 cases by self-evaluation.

Based on the hypothesis that cellulite appears as a consequence of a weakened dermis in concert with an expanding fat tissue mass that protrudes through, Kligman and others have suggested a role for retinol in the treatment of cellulite. Tretinoin has been shown to increase the deposition of collagen in the photodamaged dermis of mice and humans.[25,26] A thicker, stronger dermis may restrict movement of the more mobile fatty tissues below, thereby preventing herniation. Kligman and co-workers performed a small, double-blind study, which examined the effects of a pro-drug, topical retinol, on the treatment of cellulite in 20 healthy women.[27] Topical retinol was placed twice daily on one thigh for a period of 6 months. Placebo cream was placed on the other thigh. Thirteen of 19 patients reported subjective improvement of the feel and appearance of their cellulite on the thigh treated with study drug. The investigator's ratings were in concordance with 12 of the 13 who reported a beneficial effect. Another 6-month randomized, placebo-controlled study of topical retinol treatment for cellulite in 15 patients aged 26–44 years showed no clinical efficacy in treating overt cellulite, but did show some improvement in the patients with 'incipient cellulite', or the mattress phenomenon-type cellulite. A shift in the phenotype of connective tissue cells in retinol-treated patients was evidenced by a two- to fivefold increase in factor XIIIA+ dendrocytes in the dermis and fibrous strands of the hypodermis.[28] However, without objective means of measuring clinical improvement, including the use of MRI and ultrasound, it is difficult to recommend retinoids as an effective treatment for cellulite.

The herbal product Cellasene, a product containing Gingko biloba, sweet clover, sea-weed, grape seed oil, lecithins and evening primrose oil, has been marketed internationally as a 'miracle cure' for cellulite. A parallel placebo-controlled clinical study comparing the effects of Cellasene with those of a control cream on the appearance of cellulite in 24 women aged 25–45 years failed to reveal significant changes after a 2-month course.[29] Of note, seven of the 11 women using the study cream gained weight. It is important to note that many of the ingredients in purported topical treatments for cellulite are not known and thus the risk for adverse effects may be increased. In one study, there were 232 ingredients in the 32 different 'cellulite creams' examined, with botanicals, emollients and caffeine predominating.[30] One-fourth of these materials have been noted to cause allergies.

Lasers: the future

The next frontier in the treatment of cellulite may be lasers. Currently, there are numerous investigations into the possibility of non-invasive correction of cellulite. One of these systems is the VelaSmooth system (Syneron Inc, Richmond Hill, Ontario, Canada). It combines near-infrared light at a wavelength of 700 nm, continuous-wave radiofrequency and mechanical suction. Twice-weekly treatments for a total of eight to ten sessions have been recommended. There are no large-scale studies demonstrating its efficacy. The TriActive Laserdermology (Cynosure Inc, Chelmsford, MA, USA) is another system that is FDA-approved for the treatment of cellulite. It combines six near-infrared diode lasers at a wavelength of 810 nm, localized cooling and mechanical massage. Treatments three times a week for 2 weeks and then biweekly treatments for 5 weeks are suggested. Again, there are no data to support its efficacy in patients. Still, laser therapy may hold promise in the possibility of effectively treating cellulite.

Conclusion

In summary, there is currently no scientifically proven treatment for cellulite. There are currently hundreds of devices and medications that purport to treat cellulite. Most of the evidence supporting their efficacy is anecdotal, subjective or non-existent. There are many opportunities for further investigation, including non-invasive forms of treatment such as laser.

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