ELSEVIER

Seminars in Cutaneous Medicine and Surgery

Cosmeceuticals for Cellulite

Doris Hexsel, MD,*,† and Mariana Soirefmann, MD, MSc*,†

Cellulite is characterized by alterations to the skin surface, presenting as dimpled or puckered skin of the buttocks and posterior and lateral thighs. It mainly affects women. Cellulite occurrence is believed to be due to structural, inflammatory, morphological and biochemical alterations of the subcutaneous tissue. However, its pathogenesis is not completely understood. Topical treatments for cellulite include many agents, such those that increase the microcirculation flow, agents that reduce lipogenesis and promote lipolysis, agents that restore the normal structure of dermis and subcutaneous tissue, and agents that scavenge free radicals or prevent their formation. There are many cosmetic and medical treatments for cellulite. However, there is little clinical evidence of an improvement in cellulite, and none have been shown to lead to its resolution. The successful treatment of cellulite will ultimately depend upon our understanding of the physiopathology of cellulite adipose tissue.

Semin Cutan Med Surg 30:167-170 © 2011 Elsevier Inc. All rights reserved.

KEYWORDS Cellulite, cosmeceuticals, physiopathology, topical treatments, microcirculation flow, lipogenesis, lipolysis, free-radicals

Cellulite is characterized by dimpled or puckered skin of the buttocks and posterior and lateral thighs (Fig. 1). This condition has also been described as resembling an orange peel, cottage cheese, or as having mattress-like appearance.[1] Published studies suggest that approximately 85% of postadolescent women have some degree of cellulite.[2,3] In men, this condition is very rare as the result of differences in the connective tissue.[1] Cellulite appears to be the result of localized adipose deposits and edema within the subcutaneous tissue. In women, bands of connective tissue are oriented longitudinally, from deep fascia to the dermis. These bands are the fibrous septae that segregate fat into channels. As the fat layer expands, it is projected superficially, creating a puckered appearance of the skin.[4,5] The criss-crossing pattern of the connective tissue in the thighs and buttocks of men, which holds the fat layer, prevents the projection of the adipose tissue on the skin surface.[4,5]

Recently, Hexsel et al[6] published a study on the depressed lesions of cellulite. Results of the magnetic resonance imaging analysis showed that cellulite depressions on the buttocks were significantly associated with the presence of underlying thick fibrous septa. It was found that all fibrous septa in the examined areas were perpendicular to the skin surface and most of them were ramified.

Physiopathology of Cellulite

Cellulite occurrence seems to be attributable to structural, inflammatory, morphologic, and biochemical alterations in the subcutaneous tissue.[7] There is evidence that hormones influence the formation of cellulite. Estrogen stimulates lipogenesis and inhibits lipolysis, resulting in adipocyte hypertrophy. This mechanism may partially explain the greater prevalence of this condition in women. Other evidence of the hormonal influence on cellulite is its presence in most women, its usual onset at puberty, and its exacerbation during pregnancy, nursing, menstruation and its connection with oral contraceptive use.[8]

There is evidence that deficiencies in lymphatic drainage and microvascular circulation are associated with cellulite development. In areas in which circulation and lymphatic drainage are decreased, such as the buttocks and thighs, they are more predisposed to the increase of microedema within the subcutaneous fat layers, leading to accentuation of skin irregularities.[3,9] Postinflammatory alterations, genetics, weight gain, and lifestyle may also be contributing factors to the development of cellulite.[7]

*Brazilian Center for Studies in Dermatology, Porto Alegre, RS, Brazil.
†Cosmetic Dermatology at the Department of Dermatology, Pontificia Universidade Catolica do Rio Grande do Sul, Porto Alegre, RS, Brazil.
Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and Dr Soirefmann reported no conflicts. Dr Hexsel has been a consultant for Vichey.
Address reprint requests to Doris Hexsel, MD, 782 Drive Timoteo, 90570-040, Porto Alegre, RS, Brazil. E-mail: doris@hexsel.com.br

1085-5629/11/$-see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.sder.2011.06.005

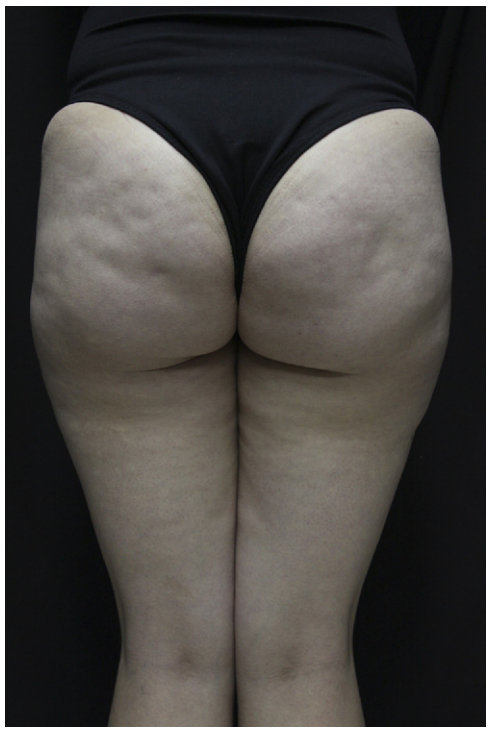

Figure 1 Clinical aspect of cellulite.

Topical Treatments

Cosmeceuticals represent a new category of products placed between cosmetics and pharmaceuticals that are intended for the enhancement of both the health and beauty of the skin.[10] These products are found in many forms, including vitamins, peptides, growth factors, and botanic extracts (Fig. 2). In particular, cosmeceuticals containing topical vitamin formulations are increasing in popularity in skin care.[11]

However, available cosmeticeuticals show little effect in improving cellulite, and none has been shown to lead to its complete disappearance. It is unlikely that topically applied pharmacologic agents can alter the fundamental cutaneous architecture existing in cellulite-prone areas.[12] Therefore, various treatments currently available are only partially or temporarily effective,[7] and topical treatments are being considered as an adjunctive cellulite treatment.[1]

Figure 2 A flower bed of different medicinal plants in the Botanical Garden in Rio de Janeiro, Brazil.

Table 1 Topical Therapies for Cellulite, Based on Mechanism of Action

Mechanism of Action	Agents
Increase 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*
Reduce lipogenesis and promote lipolysis	Methylxanthines β-adrenergic agonists α-adrenergic antagonists
Restore the normal structure of dermis and subcutaneous tissue	Retinol (vitamin A)
Prevent free-radical formation or scavenge free-radicals	Alpha-tocopherol (vitamin E) Ascorbic acid (vitamin C) *Ginkgo biloba* Red grapes (*Vitis vinifera*)

Data adapted from Hexsel et al.[1]

Topical anticellulite preparations may be divided in 4 major groups according to their mechanism of action. These treatments include agents that increase the microcirculation flow, reduce lipogenesis and promote lipolysis, restore the normal structure of dermis and subcutaneous tissue, and prevent free radical formation or scavenge free radicals (Table 1). Several pharmacologic agents available for the treatment of cellulite lack scientific evidence of long-term efficacy. Only two agents, aminophylline and retinoids, have been critically evaluated.[12]

Agents That Increase the Microcirculation Flow

This group includes most of the drugs that are available as anticellulite topical treatments. *Ginkgo biloba* is a member of the Ginkgoaceae family. The leaf extracts contain substances, such as flavonoids (e.g., quercetin, campherol epicathecol derivatives), biflavones (ginkgetin), and terpenes (ginkgolide B), among others.[13] These substances reduce blood viscosity, inhibit the platelet-activating factor, increase red blood cell deformability, diminish vascular permeability and improve vascular wall tone, leading to an improvement in microcirculation.[14]

Ginkgo biloba also has flavonoids, which act as antioxidant and anti-inflammatory agents.[13] In topical formulations, the glycolic extract is used in a concentration of 5%-10% and the dried extract in 0.2%-2% concentrations. However, there are some reports in the literature of cases of hypersensitivity to ginkgo contained in anticellulite products. The recommended concentration is 1%-3%.[14]

Pentoxifylline may be used transdermally for cellulite treatment. It improves microcirculatory perfusion because of its effect on hematological factors, such as erythrocyte shape, platelet aggregation, and plasma fibrinogen concentration.[1] *Centella asiatica* extract has been used for cellulite treatment as it purportedly enhances microcirculation and acts as an anti-inflammatory agent. This product may be used as a topical or systemic agent for cellulite treatment. In its topical formulation, *Centella asiatica* may be used in concentrations from 2% to 5%.[1]

Ruscus aculeatus is a potent venous vasoconstrictor. It has flavonoids that enhance capillary resistance and decrease vascular permeability and edema, which leads to an improvement in lymphatic drainage.[15] The extract of this plant is frequently used in concentrations from 1% to 3%.[16] Silicium is a structural element of the connective tissue that has the ability to regulate cellular metabolism and cellular division. It may be useful for cellulite because it modifies venous capillary and lymphatic permeability.[1]

Papaya (*Carica papaya*) and pineapple (*Ananas sativus, Ananas comosus*) fruits and leaves have anti-inflammatory and antiedema effects.[17,18] Topical formulations are available in concentrations from 2% to 5%. Dermatitis and eczema are rare side effects.

Red grapes (*Vitis vinifera)* are very rich in tannins, which are antioxidants that diminish lipid peroxidation. They have procyanidins, which increase the permeability of lymphatic and microarterial vessels. In topical products, the essential oil is used in concentrations from 2% to 7%.[14]

Chophytol or artichoke (*Cynara scolymus*) has numerous enzymes, cynarine, ascorbic acid, caffeoylquinic acid derivatives, and flavonoids. It has an antiedema and diuretic effect, as well as a stimulating effect on the circulation.[13]

Common ivy (*Hedera helix*) leaves have flavonoids, such as rutosid and rutinosid, and saponins, such as hederin, hederacosid, and hederagenin.[13,19] Their fruits have saponins, especially hederin, and the trunk has gomoresins and saponins. All saponins improve venous and lymphatic drainage and reduce edema. The compound hederin also has an analgesic and anti-inflammatory effect, vasoconstrictor and antiexudative proprieties, and can also reduce capillary permeability. It activates the circulation which aids drainage of the infiltrated tissue and reduces inflammation. Allergic reactions have occurred in more than 65 cases of patients who used topical products containing ivy.[20]

Ground ivy (*Glechoma hederacea)* has flavonoids, triterpenoids, and phenolic acids. It is used for cellulite treatment in concentrations of 2%.[14] *Melilotus officinalis* has an active ingredient contained in the flowers and leaves. One of the components of this botanic extract is coumarin, which reduces lymphatic edema and diminishes capillary permeability. The recommended concentration is 2%-5%.[14]

Figure 3 The *Coffea arabica* plant.

Agents That Reduce Lipogenesis and Promote Lipolysis

Methylxanthines, such as caffeine, aminophylline, theophylline, and theobromine, are classified as β-agonists and are the main category with documented action in the treatment of cellulite.[21-24] The most useful and safest methylxanthine is caffeine, which is normally used in concentrations of 1%-2%. Caffeine can be extracted from the coffee beans of the *Coffea arabica* (L) plant (Fig. 3). It penetrates the skin very easily, which facilitates its absorption and action.[25] Caffeine acts directly on adipose cells, promoting lipolysis, inhibiting phosphodiesterase, and thus augmenting cyclic AMP. It activates the triglyceride lipase enzyme and breaks down triglycerides into free acids and glycerol. Caffeine also has a stimulating effect on the cutaneous microcirculation. Recently, Velasco et al[26] published a study showing that emulsion with caffeine caused a reduction of 17% on the diameter of the fatty cells compared with the control.

Aminophylline stimulates β2-adrenoreceptor activity and causes a localized lipolytic effect. Collis et al evaluated the effectiveness of topical aminophylline gel in combination with 10% glycolic acid and concluded that this therapy fails to improve cellulite. A total of 52 women completed a 12-week, randomized controlled trial that investigated the effectiveness of a twice-daily application of aminophylline cream and twice-weekly treatment with Endermologie. No statistical difference existed in measurements between legs for any of the treatment groups (paired t test, $P > 0.4$).[27] Although it has been hypothesized that topically applied aminophylline can penetrate through the dermis to cause significant lipolysis, this has not been scientifically proven.[12] Beta-adrenergic agonists, such as isoproterenol and adrenaline, and alpha-adrenergic antagonists, such as yohimbine, piperoxan, phentolamine, and dihydroergotamine, have also shown the ability to cause lipolysis.[1]

Agents That Restore the Normal Structure of Dermis and Subcutaneous Tissue

Topical retinoic acid and related vitamin A derivatives have been used as topical cellulite treatments.[1] Published studies have shown that topically applied retinol, 0.3% during a period of six months or more improves cellulite.[28,29] Kligman et al[28] studied a group of 20 women with moderate cellulite on the thighs. They were treated twice daily with 0.3% retinol cream on one side, and the other side was treated with the vehicle for six months. Thickness measurements by ultrasound scanning significantly increased on the retinol sides, but were unchanged on the vehicle side. Machinal-Quélin et al[29] investigated the mechanism underlying the antiadipogenic effect of retinol. The authors 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 transcriptional activity.

These effects may be related to the known effects of retinoids (increasing dermal collagen thickness and improving the contour of elastic fibers). Retinol itself can act as an antiadipogenic agent by inhibiting the differentiation of human adipocyte precursor cells.

Agents That Scavenge Free-Radicals or Prevent Free Radical Formation

Vitamins, such as ascorbic acid and vitamin E may work as antioxidants, protecting dermal and subcutaneous cell membranes from free radical toxicity. Also, certain vitamins may improve microcirculation. Red grapes (*Vitis vinifera*) are rich in tannins, which are antioxidants that diminish lipid peroxidation.[1]

Conclusions

Topical agents are often used by women to treat cellulite. Normally, they are recommended to treat mild-to-moderate cellulite and as an adjuvant treatment for severe cellulite. Our previous experience, including the results of a study with a small number of patients using topical treatment for cellulite, shows that even knowing the limited effects of topical products, there is a significant positive impact in self-esteem and also in the patients' compliance when they are using topical treatment. Newer therapeutic modalities continue to evolve without much understanding of the complex nature of cellulite. The successful treatment of cellulite will ultimately depend on an improvement in the understanding of the physiopathology of cellulite adipose tissue.

References

1. Hexsel D, Zechemeister do Prado D, Goldman MP: Topical management of cellulite, in Goldman M, Hexsel D (eds): Cellulite: Pathophysiology and Treatment. London, England, Informa Health Care, 2010, pp 62-68
2. Draelos ZD, Marenus KD: Cellulite. Etiology and purported treatment. Dermatol Surg 23:1177-1181, 1997
3. Harvard Women's Health Watch Cellulite meltdown. Harv Health Pub Group 5:7, 1998
4. Querleux B, Cornillon C, Jolivet O, et al: Anatomy and physiology of subcutaneous adipose tissue by in vivo magnetic resonance imaging and spectroscopy: Relationships with sex and presence of cellulite. Skin Res Technol 8:118-124, 2002
5. Piérard GE, Nizet JL, Piérard-Franchimont C: Cellulite: From standing fat herniation to hypodermal stretch marks. Am J Dermatopathol 22: 34-47, 2000
6. Hexsel DM, Abreu M, Rodrigues TC, et al: Side-by-side comparison of areas with and without cellulite depressions using magnetic resonance imaging. Dermatol Surg 35:1471-1477, 2009
7. Khan MH, Victor F, Rao B, et al: Treatment of cellulite: Part I. Pathophisiology. Am Acad Dermatol 62:361-370, 2010
8. Rossi ABR, Vergnanini AL: Cellulite: a review. J Eur Acad Dermatol Venerol 14:251-262, 2000
9. Cellulite GMP: A review of current treatments. Cosmet Dermatol 15: 17-20, 2002
10. Martin KL, Ailor SK: An ounce of prevention. Mo Med 108:64-68, 2011
11. Manela-Azulay M, Bagatin E: Cosmeceuticals vitamins. Clin Dermatol 27:469-474, 2009
12. Khan MH, Victor F, Rao B, et al: Treatment of cellulite: part II. Advances and controversies. J Am Acad Dermatol 62:373-384; quiz 385-6, 2010
13. Botanicals AFS: A Phytocosmetic Desk Reference. Boca Raton, FL, CRC Press, 1999
14. Hexsel D, Orlandi C, Zechmeister do Prado D, et al: Botanical extracts used in the treatment of cellulite. Dermatol Surg 31:866-873, 2005
15. Rubanyi G, Marcelon G, Vanhoutte PM: Effect of temperature on the responsiveness of cutaneous veins to the extract of Ruscus aculeatus. Gen Pharmacol 15:431-434, 1984
16. Berg D: Venous constriction by local administration of ruscus extract [in German]. Fortschr Med 108:473-476, 1990
17. Carle R: Anti-inflammatory and spasmolytic botanical drugs. Breast J Phytother 1:32-39, 1990
18. Pineapple, in The Lawrence Review of Natural Products—Monograph System. Facts and Comparisons. St. Louis, MO, Wolters Kluwer, 2001
19. Facino RM, Carini M, Stefani R, et al: Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from *Hedera helix*, *Aesculus hippocastanum*, and *Ruscus aculeatus*: Factors contributing to their efficacy in the treatment of venous insufficiency. Arch Pharm (Weinheim) 328:720-724, 1995
20. Sainio EL, Rantanen T, Kanerva L, et al: Ingredients and safety of cellulite creams. Eur J Dermatol 10:596-603, 2000
21. Lesser T, Ritvo E, Moy LS, et al: Modification of subcutaneous adipose tissue by a methylxanthine formulation: A double-blind controlled study. Dermatol Surg 25:445-462, 1999
22. Draelos ZD, Marenus KD: Cellulite. Etiology and purported treatment. Dermatol Surg 23:1177-1181, 1997
23. Bertin C, Zunino H, Pittet JC, et al: A double-blind evaluation of the activity of an anti-cellulite product containing retinol, caffeine, and ruscogenine by a combination of several non-invasive methods. J Cosmet Sci 52:199-210, 2001
24. Dias M, Farinha A, Faustino E, et al: Topical delivery of caffeine from some commercial formulations. Int J Pharm 182:41-47, 1999
25. Potard G, Laugel C, Baillet A, et al: Quantitative HPLC analysis of sunscreens and caffeine during in vitro percutaneous penetration studies. Int J Pharm 189:249-260, 1999
26. Velasco MV, Tano CT, Machado-Santelli GM, et al: Effects of caffeine and siloxanetriol alginate caffeine, as anticellulite agents, on fatty tissue: Histological evaluation. J Cosmet Dermatol 7:23-29, 2008
27. Collis N, Elliot LA, Sharpe C, et al: Cellulite treatment: A myth or reality: A prospective randomized, controlled trial of two therapies, endermologie and aminophylline cream. Plast Reconstr Surg 104:1110-1114, 1999
28. Kligman AM, Pagnoni A, Stoudmayer T: Topical retinol improves cellulite. J Dermatol Treat 10:119-125, 1999
29. Machinal-Quélin F, Dieudonné MN, Leneveu MC, et al: Expression studies of key adipogenic transcriptional factors reveal that the antiadipogenic properties of retinol in primary cultured human preadipocytes are due to retinol per se. Int J Cosmet Sci 23:299-308, 2001