REVIEW ARTICLE

Cellulite's aetiology: a review

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Abstract

Cellulite, highly prevalent among women, represents a serious problem for many of them, and one of their main aesthetic concerns. It is difficult to pinpoint its aetiology and physiology/pathophysiology, as there are many factors that are involved in it, affect it, and many processes that are taking place simultaneously and sequentially. Our objective is therefore, to review the scientific scholarship on cellulite to explore the causes of its origin. We carried out a preliminary search of the Medline, Cochrane, and Web of Knowledge databases covering the period from 1978 to April 2011. As there is no specific key word for the phenomenon at hand, we used the following descriptors: *adipose tissue, subcutaneous fat, subcutaneous tissue, connective tissue, skin, skin disease* and *dermis*. This resulted in a retrieval of 26 articles contributing to relevant information on the aetiology of cellulite. As a result of our first research, we concluded that cellulite is a physiological phenomenon or at least, that it has a physiological origin, which is characteristic of women, and multi-causal, with the coexistence of a number of factors that trigger, perpetuate, or exacerbate it. The outstanding factors include, among others, connective tissue architecture, oestrogen action, microvascular alterations and certain genetic and hormonal characteristics. All of them provide us with future and novel clues to cellulite treatment, and is necessary to take some or all of these factors into account in developing an effective therapy. However, we are aware of the necessity of further investigation in this field.

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Introduction

Cellulite, highly prevalent among women,[1–18] represents one of women's main aesthetic concerns and reasons for requesting cosmetic treatment.[4,14,19–22] Despite this, cellulite has received little scholarly attention, with only a few publications in this field.[3,8,23–26] This makes it difficult to pinpoint cellulite aetiology because of the many factors and processes involved that take place simultaneously and sequentially. The first description of cellulite was given by Alquiler & Pavot[27] (Table 1), where cellulite appears as an aesthetic disturbance secondary to traumatic, topical, infectious, or glandular stimuli. However, in recent decades, authors have suggested a physiological cause.[3,13,16,21,28–34] Some definitions are listed in Table 1. Given this context, we reviewed cellulite scholarship to clarify, in so far as possible, its aetiology.

Materials and methods

We searched Medline, Cochrane and Web of Knowledge (WOK) databases from 1978 (the year in which Nürnberger & Müller[2] published their first article) to April 2011. Given the absence of a specific descriptor for cellulite, we used the ones listed in Table 2, using in Medline and in WOK subheadings and subject areas displayed in this chart. In Cochrane Library, we used only the listed descriptors.

When different descriptors were crossed using Boolean AND, a large number of items were retrieved, but not many relevant articles were found. This led us to perform a hand-operated review of the articles retrieved that addressed the phenomenon at hand (cellulite), and discarded those described with the keyword 'cellulitis' defined in Mesh.[35]

This search procedure resulted in a total of 219 items, from which we selected those that provided relevant information about the aetiology and/or physiology/pathophysiology of cellulite. A total of 26 articles were analysed.

Results

Traditionally, there are three main theories for cellulite aetiology. The first, is based on the architectural subcutaneous

Table 1 Definitions of cellulite

Authors	Cellulite definition	References
Alquier & Pavot	Non-inflammatory complex cellular dystrophy of the mesenchymal tissue caused by a disorder of water metabolism, which produced saturation of adjacent tissues by interstitial liquids	27
Merlen & Curri	Segmental and localized lipodystrophy of the subcutaneous connective tissue that was in part influenced by venous and lymphatic disease, as well as by vasomotor insufficiency secondary to dysfunction of the sympathetic nervous system	50
Goldman	A normal physiologic state in postadolescent women. A state that maximizes adipose retention to ensure adequate caloric availability for pregnancy and lactation	13
Blanchemaison	A lipodystrophy, which has an associated increasing of hypodermic adipose tissue, swelling and periadipocitaire fibrosis. Those three actors are variably present	22
Piérard	A physiological condition … results of a combination of the gender-related dimorphism of the hypodermal connective tissue and the mechanobiological effects of tissue tensions inside this tissue	54

Table 2 Descriptors used in databases searches (left). Subheadings used in Medline database search (centre). Subject areas used in Web of Knowledge database search (right)

Descriptors	Subheadings (Medline)	Subject areas (Web of Knowledge)
Adipose tissue	Abnormalities	Endocrinology and metabolism
Subcutaneous fat	Anatomy and histology	Physiology
Subcutaneous tissue	Growth and development	Biology
Connective tissue	Blood supply	Cell and tissue engineering
Skin	Metabolism	Dermatology
Skin disease	Physiology	Pathology
Dermis	Pathology	Anatomy and morphology
	Physiopathology	

tissue (ST) differences between genders, and on alterations in the connective tissue (CT). The second, regards vascular changes and the presence of oedema in the intercellular matrix of affected areas as the possible causes. The third, which has currently been reformulated, considers the existence of a chronic inflammatory process secondary to the hormonal activity of the menstrual cycle as the main cause. A fourth line of research has recently been proposed by Emanuele[36–38] who has studied genetic influences. The four theories will be considered separately in the following subsections.

Subcutaneous connective tissue architecture

Nürnberger & Müller[2,39] were the first to put forward this theory. They observed major differences between male and female subcutaneous CT. This differentiation occurs by the ninth month of pregnancy and is due to the action of androgens and their effect on fibroblast activity.[39]

These authors described the female hypodermal CT as being arranged radially or perpendicular to the skin surface, forming rectangular compartments, literally as '*standing fat-cell chambers*', in the surface layer of ST separated by CT septa (Fig. 1). The '*papillae adiposae*' that protrude into the dermis breaking into the

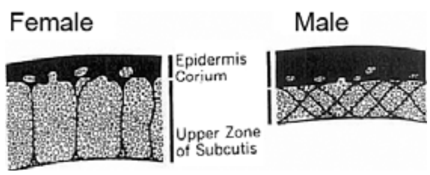

Figure 1 Schematic representation of the sex-typical differences of the inner structure of the skin and subcutaneous tissue of the thigh and hip (Reproduced from Nürnberger & Müller[2] with permission).

reticular layer. By contrast, in men, these septa adopt an oblique zigzag pattern, creating smaller and polygonal compartments (Fig. 1). This difference means that, when subjected to pressure changes, female adipocytes, papillae adiposae and fat-cell chambers must adapt their shape without changing their volume. This causes the papillae to extrude into dermis–hypodermis interface, thus modifying the appearance of the skin surface in the so-called '*mattress phenomenon*', a major sign of cellulite present in almost 100% of women according to those authors. Nürnberger & Müller[2,39] therefore argue that cellulite is a typical female characteristic, not a pathological process, triggered by an increase in hypodermic pressure, a state which they are called '*status protusus cutis*' (Fig. 2).[2,39] In men, only androgen-deficient men have a pattern like women, thus showing that it is hormonally dependent and not genetically determined.[2]

Rosenbaum[40] observed a discontinuous and irregular dermis–hypodermis interface, and highlighted that, in women with cellulite, the CT structure did not differ substantially between affected and unaffected areas, concluding that this architecture is independent of the cellulite process, and the existence of a CT '*sexual dimorphism*' is responsible for cellulite appearance. This situation is exacerbated in the case of an increase in adipose or aqueous volume of the ST being a relationship between fat content, body mass index (BMI) and degree of cellulite. However, according to the author, weight loss can reduce the appearance of cellulite, but does not improve the structural characteristics.

Piérard[24] reconfirmed these structural differences, finding a lumpy dermis–hypodermis interface in women due to the protrusion of adipose lobules, regardless of the appearance of any outward signs of cellulite, and the existence of a complex three-dimensional mesh of hypodermal CT consisting of strands of collagen fibres rather than true septa limiting the adipose lobules.

This author observed no correlation between the protrusion extent and severity of cellulite, as protrusion of the papillae adiposae into dermis–hypodermis interface is common in zones with and without cellulite in female samples.

Piérard noticed how in incipient cellulite,[2] a padded appearance right after pinch test is due to the state of hypodermic connective mesh that tightly binds the dermis to deeper layers in areas in which the fibres are fibrosclerotic and thicker. In contrast, in dermo-panniculosis deformans,[2] the spontaneous appearance of dimples is associated with the presence of large adipose lobules bound only by thin, or even absent, CT.

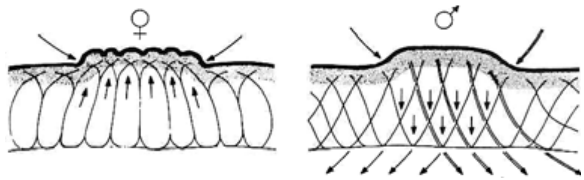

Figure 2 The pinch test on the skin of the thigh of a woman (left) and a man (right). In women, the fat-cell conglomerations of the upper part of the subcutis (standing fat-cell chambers, and papillae adiposae) protrude upon the overlying cutis. That produces deformation and pits, i.e. the mattress phenomenon or status protrusus cutis. In men, merely folds and furrows are produced (Reproduced from Nürnberger & Müller[2] with permission).

This finding was later confirmed by Mirrashed[41] who observed how connective tissue density is tightly related to the degree of cellulite. Women with high BMI and major presence of cellulite have weaker and less dense CT. This had already been noted by Nürnberger & Müller[2,39] who argued in favor of the importance in cellulite evolution of the degeneration of CT as part of the normal ageing process.

This aspect has been studied by other authors:

- Quaglino[42] found that the diameter of collagen fibres is greatest between 10 and 29 years, and begins to decline after 30 years, reaching minimum values after the age of 60. This author also reports that collagen fibres represent approximately 70% of the CT during the second decade of life, and decrease to 40% after 60 years of age.
- Ortone[10] observed that, regardless of age, (i) skin thickness is approximately 30% greater in women with Grade 2 cellulite;[2] (ii) the presence of cellulite corresponds to a thinning of the dermal layer, a greater length of the dermis–hypodermis interface, a decrease of dermal density; and (iii) biomechanical parameters of skin elasticity and extensibility that are negatively affected by the degree of involvement of cellulite. As women with cellulite present skin characteristics typical of older ages, the author argues that its presence is a cause of premature skin ageing.

Querleux[43] described in great detail the three-dimensional architecture of this subcutaneous CT, identifying three types of fibre: parallel, perpendicular and oriented at 45° to the skin surface and to Camper's fascia. The author noted that women with cellulite have a higher percentage of perpendicular and oblique fibres than women without cellulite or men, and concluded that the model originally proposed by Nürnberger & Müller constitutes an oversimplification.

Dobke[44] observed that, women without cellulite, had a better quality skin – firmer, with less compliance, laxity and capacity for deformation – in the upper posterior part of the thigh. By contrast, women with cellulite, presented greater laxity and weakness of the dermis and CT, which extended into the superficial fascia. Adding to increased interstitial pressure and the negative effects of ageing, this favours CT support disruption, making it more likely that fatty tissue may herniate into the dermis. The author noted that there were no differences between the two groups in tissue quality in the upper back area. This led him to conclude that the alterations are not due exclusively to genetics, but also to environmental, behavioural, metabolic, endocrine, gravitational factors or changes in volume. He also stressed that theories appealing to a multifactorial aetiology needed to be taken into account.

Mirrashed[41] observed how fibrous septa were thicker in men whereas adipose lobules present in women were larger in those with cellulite, with their invaginations being correlated with the degree of cellulite in the affected areas. Men also have thinner adipose tissue than women, whose topmost layers of subcutaneous tissue are thicker.

The author noted that, in individuals with high BMI, cellulite susceptibility is determined by the lower density and relative weakness of CT, as had been suggested by Piérard.[24] Notably, there is a significantly smaller amount of fibres between adipose lobules, where indentations in dermis are larger, and the dermis itself is significantly thinner than in unaffected areas. The percentage of adipose tissue relative to CT at dermis–hypodermis union and hypodermis is similar in men and women with little cellulite, whereas women with a higher degree of cellulite show a clear decrease in CT.

In individuals with low BMI, the appearance of cellulite appears to be related to differences in adipose tissue itself. There is an increase in its thickness with large lobules in women with a higher degree of cellulite, with this being the only difference found in this group between affected and unaffected areas.

Therefore, the appearance of cellulite would be determined in women with a low BMI by adipose tissue thickness, which may explain why these women are generally less affected, and in women with a high BMI by the quality of the CT, according to the findings of Piérard[24] and Dobke.[44]

Smalls[5] observed that cellulite severity is correlated with weight, BMI, thigh diameter, the fat percentage of the body segment and the architecture of the dermis–hypodermis interface. It is also positively correlated with tissue compliance and negatively with its rigidity.

This author subsequently analysed the direct effect of fatty tissue on cellulite.[7] Losing weight was found not only to decrease the fat percentage and the diameter of the thighs, but in 17 of the 28 women studied, it also reduced the severity of the cellulite, dermal density and skin stiffness, and increased the laxity by enhancing compliance and elastic deformation. Dermal thickness and dermis–hypodermis interface remained unchanged. By contrast, for nine of the subjects, weight loss was accompanied by increased severity of the cellulite. These findings appear to be coherent with those of Mirrashed[41] and Piérard[24]as the first group had initially higher values of BMI and greater cellulite severity than the second.

The author observed how dimples depth did not necessarily change with weight loss, concluding that '*dimple pattern*' might be a permanent pattern, typical of the structure itself, which does not vary with weight loss,[5] in agreement with the indications of Piérard.[24]

Vascular changes

Merlen & Curri[45,46] described the vascular component of adipose tissue as a classic pattern of arteries, arterioles, capillaries, venules and veins, without the co-occurrence of arteriovenous anastomoses, as other authors had suggested. The capillary network is far more abundant than in the dermis, and the vessel walls are thinner. There is a close relationship between these vessels and the adipocytes, with a minimal interstitial space, thus favouring substances exchange. There is poor presence of mast cells or fibroblasts, but more of glycosaminoglycans (GAGs), collagen fibres and elastin.[47,48]

The authors identified the occurrence of endoarterial or endovenous mechanisms, '*dispositifs de blocage*', that regulate blood flow. Their contraction causes the lumen of the vessel to expand, and their relaxation makes it close to a greater or lesser degree. In cellulite, these mechanisms have become sclerotized altering the fluid balance.[47,48]

Authors argue that blood stasis and excessive plasma permeability are neither due to nor necessarily accompanied by lymphatic failure. In the case of lymphatic stasis, this would be due to a quantitative rather than a qualitative disorder of the fluid balance and lymphatic system, as that system can only facilitate, complicate, or accelerate the process, but never trigger it,[45] and support these claims with findings that show how the lymphatic system is not extensively present in adipose tissue; there is also no dilation lymph vessels in cellulite tissue, an aspect that was confirmed years later by Piérard.[24]

According to Ryan & Curri,[48–50] in normal conditions fat is deposited in the adipocytes, with the absence of lymphatic drainage possibly being required for this to occur. It is thus unnecessary for lymphatic drainage to exist in normal fat tissue. However, lymphatic drainage becomes essential in an oedematous environment, especially in one that is rich in macromolecules, and its sparse, even though normal presence will lead to the establishment of a lymphedaema that will foster the onset of fibrosclerotic processes.

As these authors admit, although the precise mechanisms that regulate capillary permeability once, it increases in adipose tissue are still poorly understood, there are various factors that perpetuate the situation and prevent interstitial oedema elimination. Of particular relevance are the absence of effective lymphatic drainage, the action of estrogens[27] and the increased deposition of mucopolysaccharides.[30] This last increase, although not especially significant in itself, is sufficient to establish the oedema and stimulate the fibroblasts to synthesize GAGs and collagen, as in normal conditions they do not exist in large amounts in the interstices of the adipose tissue.[48–50] The result of all this, is an excessive CT deposition, which evolves into a fibrotic process that makes it even more difficult to eliminate the oedema.

These changes were identified by Lotti & Ghersetich[30] who described the presence of oedematous CT and increased GAGs, principally in the extracellular matrix, at the elastic and collagenous fibres periphery and among these fibres. They observed signs of fibroblast activation, alterations in the walls of blood microvessels and numerous fibrous granules joined to each other by filamentous projections attached to the collagen fibres throughout the extracellular matrix.

Piérard[24] also noted the increased presence of myofibroblasts in the cellulite tissue, impoverished development of vascular tissue in the subcutis and alteration in the shape and layout of elastic fibres. Besides, he found no alteration of the lymphatic component or signs of inflammation.

According to Rossi & Vergnanini,[27] the action of oestrogens would be one of the principal factors inducing these changes expressed.

Chronic inflammation

In 1999, Gruber & Huber[51] pointed out that ovarian hormones have many extragenital functions and are responsible for the differences between men and women in the incidence of certain disorders. One of their most relevant aspects is their influence on collagen integrity and the distribution and storage of adiposity.

Draelos[34] subsequently took up this theory in which a chronic inflammatory response secondary to the hormonal activity characteristic of a woman's menstrual cycle is the cause of the dermal collagen mesh deterioration, making it prone to indentations of the hypodermis. Citing other authors, she argues that the changes that the endometrium undergoes in each menstrual cycle are mediated by, among other substances, metalloproteases, such as collagenases and gelatinases, to produce the corresponding bleeding. These collagenases destroy the collagen triple helix at neutral pH, an action that also extends to the dermis. Gelatinase B is associated with an influx of polymorphonuclear leukocytes, macrophages and eosinophils. These contribute to the inflammatory process, one of whose characteristics is the synthesis and proliferation of dermal GAGs that increase the water content, thus worsening the appearance of the cellulite and favouring mucoid oedema. The repeated occurrence of these phenomena with each menstrual cycle triggers a chronic inflammation that causes the continuous collagen destruction. Reticular and papillary dermis is thus weakened, favouring the subcutaneous adipose content intrusion. Summing up, Draelos concludes that the process represented by cellulite is not pathological.

Pugliese[52] maintains that changes in the estrogens and metalloproteases levels, whose target is the principally collagenous endometrial tissue, also attack cutaneous Type-I collagen, thus considering cellulite as a '*connective tissue disorder*'. It has to be noted that this theory is closely related to the previous ones.

Genetic influence: a recent contribution

Recently, Emanuele[36,37] published two studies, which describe how (i) polymorphisms angiotensin converting enzyme(ACE)-rs1799752 and HIF1A-rs11549465 are significantly associated with cellulite presence; and (ii) adiponectictin mRNA expression in subcutaneous adipose tissue in the gluteal region in women with cellulite is significantly reduced.

Emanuele[36,38] found that women who carry the D allele of the ACE increase the risk of developing cellulite, which is related to the rise of production of angiotensin II in the subcutaneous adipose tissue. This growth provokes blood flow dysregulation, and facilitates adipocyte hypertrophy, increased deposition at the extracellular matrix and the formation of a complex mesh of subcutaneous fibrous tissue.

Stavroulaki & Pramantiotis[53] have recently found a significant synergism between this ACE I/D polymorphism and smoking for the risk of cellulite, thus demonstrating for first time that smoking may be a leading aetiological and/or modifying factor in its development.

Continuing with Emanuel,[36,38] the increased presence of the rare T allele of HIF1A (alpha subunit of hypoxia-inducible factor 1) detected in women without cellulite is associated with their reduced risk of developing this condition. High levels of HIF1A promote not only angiogenesis, but also fibrotic processes in the fatty tissue and a local inflammatory response. However, in slim women without cellulite, the author detected a rare mutation of this allele (T allele) that slows down this fibro-inflammatory process.

Finally, citing Emanuel,[37] local reduction on adiponectin production in areas with cellulite may cause vascular microcirculation impairment, and the suppression of local anti-inflammatory action and anti-fibrotic effects of adiponectin, supporting the potential role of adiponectin to develop changes that have been found in cellulite by previous researchers.

Conclusions

We must take an eclectic position concerning the different theories discussed above. One accepts cellulite is a physiological phenomenon, or at least, that it has a physiological base, characteristic of women, with a multi-causal origin, and in which many factors coexist that trigger, perpetuate, or exacerbate it. Of particular relevance among these factors are the architecture of CT, the action of oestrogens, microvascular alterations and certain genetic and hormonal characteristics, which could explain the previous aspects. It is, therefore, necessary to take some or all of these factors into account in developing an effective therapy and providing us with future and novel clues to cellulite treatment.

However, we consider the importance of further investigation with the aim of clarifying the questions, which still remain unanswered, as regards cellulite nature and the impact of new concepts of adipose tissue biology on cellulite (patho)physiology.

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