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Review Article

Cellulite: nature and aetiopathogenesis

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Abstract

Only a limited number of studies on cellulite have been published in the international literature and many of them reach somewhat antithetical conclusions. Consequently, it is not yet possible to reconcile the extreme differences of opinion which have lingered on for years concerning the nature of this disorder, as well as its origin and even the most basic aspects of its histopathological classification. It does not even have a recognized name: in fact, the term 'cellulitis' is used in scientific English to indicate a spreading gangrenous infection of the subcutaneous cellular tissue. The other terms used from time to time [panniculitis, lipodystrophy, edematofibrosclerotic panniculitis (EFP), liposclerosis, lipoedema, etc.] have quite different morphological and pathogenetic connotations in general. Over the last few decades, three major conflicting theories have emerged in relation to the ethiopathogenesis of cellulite. These indicate, respectively, the following causes:

1. Oedema caused by excessive hydrophilia of the intercellular matrix.
2. A homeostatic alteration on a regional microcirculatory level; this pathogenetic theory is summarized in a synthetic and self-explanatory denomination: EFP.
3. A peculiar anatomical conformation of the subcutaneous tissue of women, different from male morphology.

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These theories must all now be updated in the light of recent advances on the sophisticated and composite physiopathology of the adipose organ – which acts not only as a control device which regulates the systematic equilibrium of energy and modulates the food intake and the metabolism of other tissue substrate through a multiple glandular secretion of hormones and parahormones.

Résumé

Seulement un nombre limité d'études sur la cellulite a été publié dans la littérature internationale et beaucoup de ces articles arrivent à des conclusions plutôt antithétiques. Par conséquent, actuellement il est impossible de reconcilier les opinions extrèmement différentes concernant la nature de ce désordre, ainsi que son origine, de même que les aspects les plus basilaires de sa classification histopathologique. Le nom même de cette affection n'est pas reconnu: en fait le terme '' cellulite ''est utilisé dans le language scientifique pour indiquer une inflammation du tissu cellulaire sous-cutané, d'origine infectieuse. Les autres termes employés de temps an temps tels que panniculopathie, lipodystrophie, panniculopathie oedémato-fibroscléreuse, liposclérose, lipoedème etc. ont en general des connotations morphologiques e pathogénétiques tout à fait différentes. Au cours des dernières décennies, trois principales théories contradictoires ont émergé pour ce qui concerne l'etiopathologie dela cellulite. Chacune théorie indique respectivement les suivantes causes:

1. Oedème causé par excessive hydrophilie de la matrice intercellulaire.
2. Altération parcellaire de l'homeostase au niveau microcirculatoire ; cette théorie pathogénétique est résumée à l'intérieur de la synthétique et explicite dénomination: panniculopathie oedémato-fibroscléreuse.
3. Particulière conformation anatomique du tissu sous-cutané chez la femme, différente par rapport à l'homme.

Ces théories doivent toutes être mises à jour, à la lumière des recents développements concernant la sophistiquée et composée physiopathologie de l'adipocyte, qui n'agit pas seulement comme entrepôt de stockage du matériel calorique en excès mais aussi comme dispositif de régulation de l'équilibre énergetique systémique, avec la capacitè de moduler l'ingestion d'aliments et le métabolisme d'autres substrats tissutaires. La révision de ces théories doit être faite aussi sur la base des nouvelles acquisitions concernant la modalitè attravers laquelle cet organe règle les multiples sécrétions hormonales et parahormonales.

Introduction

Cellulite affects millions of women over the world. All the media channels targeting the young female population concentrate heavily on this problem and its various remedies: numerous methods and procedures (surgical, pharmacological, phytotherapeutic, homeopathic, electro-medical, cosmetological, physio-massotherapeutic, etc.) have all achieved a fleeting moment of triumph [1], before proving ineffective. Of course, this does not prevent beauty clinics and health farms from continuing to gain astronomical sums of money based on their relentless pushing of improbable cures.

Given such a heartfelt problem, medical science appears to have made incredibly mediocre progress in resolving it: a search of *Medline* reveals that international journals have published only a small number of studies on the subject, all of which reach rather antithetical conclusions. Even more surprising is the disinterest displayed towards the 'cellulite problem' not only by University Institutes, but also by the research laboratories belonging to the major companies within the cosmetics sector, which nonetheless provide a valuable contribution to our increasing knowledge in relation to the physiopathy of the skin. Consequently, it is not yet possible to reconcile the substantial differences in opinion which for years have lingered on the nature of this disorder, as well as on the origin and even on the most basic elements of its histopathological aspects. It is still lacking a recognized name: in fact, the term 'cellulitis' [2] is used in scientific English to indicate an altogether different condition: a spreading gangrenous infection of the subcutaneous cellular tissue. The definitions of *panniculitis* [3] and *lipodystrophy* [4] include morbid forms which are clearly in a different category to common cellulite. In short, the other terms used from time to time [edematofibrosclerotic panniculitis (EFP), liposclerosis, lipoedema, etc.] have quite different morphological and pathogenic connotations in general.

There are many possible reasons for the lack of thorough investigation on the subject. On the one hand, the huge amount of pseudo-scientific nonsense circulating in relation to cellulite makes the subject less than attractive to any serious study group. On the other hand, in Anglo-Saxon countries, where a large proportion of biomedical research is carried out, a theory has prevailed that does not consider cellulite worthy of nosological study, considering it to be a 'normal' expression of female peritrochanteric adiposity.

The first attempt to define cellulite and the origin of the term itself both date back to the French doctors Alquier and Pavot who, in 1922, described a dystrophy of the mesenchymal tissues, without any phlogistic elements, which was characterized by interstitial fluid retention. Alquier and Pavot considered the disorder to be an elementary reaction of the connective tissue resulting from *noxae* of various natures (traumatic, toxic, infective and disendocrine).

Over the last few decades, three main contrasting theories have emerged on the aethiopathogenesis of cellulite, with mixed fortunes. These theories indicate, respectively, the following causes of the problem:

1. oedema resulting from excessive hydrophilia of the intercellular matrix;
2. a microcirculatory alteration;
3. a different anatomical conformation of the subcutaneous tissue in women compared to men.

These are discussed in greater detail below.

Excessive hydrophilia of the intercellular matrix

In 1964, Bassas-Grau and Bassas-Grau [5] described the phenomena of hyperpolymerization of

acid mucopolysaccharides in the connective matrix of the subcutaneous tissue of patients suffering from cellulite. They attributed the cause to an abnormal increase in tissue hydrophilia, provoking a chronic oedema, resulting in fibrosclerosis. Although not confirmed by other authors [6–8], this observation exerted a lengthy influence over therapeutic approaches, justifying the topical or mesotherapeutic administration of hyaluronidase and other agents known to have a lithic action on proteoglycans.

More recently, Lotti *et al.* [9], using ruthenium fixation techniques in electronic microscopy, examined the dermis of the skin covering the areas of adipose tissue affected by cellulite; there was a marked increase in the presence of glucosaminoglycans, together with signs of fibroblast activation, alterations in microvessel walls, as well as rarefaction of subepidermal collagen and elastic fibres. According to the authors' theory, repeated in a more recent re-evaluation [10], the histochemical scenario indicates an anomalous connective response which, through the retention of liquids in the interstitial matrix, can result in new collagen deposition in the subcutaneous tissue.

Microcirculatory alteration

The most popular theory, at least in Europe, explains cellulite as the consequence of a primitive dysfunction of the tissue microcirculation. Indeed European researchers have mainly contributed substantially towards the development of this theory.

Binazzi [11] set a milestone in the interpretation of the histopathological aspects of cellulite thanks to a series of observations which enabled him to develop a pathogenetic theory which is still adhered to today, and to summarize it with a synthetic and self-explanatory term: EFP [12].

According to Binazzi, the initial stage is often associated with adiposity and is clinically characterized by irregularity of the cutaneous surface on the buttocks, thighs, abdomen and shoulders, the so-called 'mattress' effect. Histological examination reveals only an extreme variability in the size and form of the adipocytes (anisopoichilocytosis), together with oedema of the dermis, dilation of the lymphatic vessels and patches of follicular hyperkeratosis (orange peel skin).

The subsequent stage is distinguished by the presence of nodular lesions on palpation, which are mobile and painful, varying in diameter between 1 and 5–6 mm; histological sections indicate a profound subversion of the subcutaneous tissue, with connective bands encircling adipose lobules, creating nodular formations, which become sclerotic; there are also haemorrhagic or thrombotic vessel alterations. Several authors linked these regressive processes in a pathogenetic interpretation which identifies the *primum movens* in the compromission of the delicate homeostasis at a microcirculatory level [13–18].

Curri takes the cue for his observations from a thorough anatomical–physiological study of the terminal branches of the circulatory system: the functional base element is the *microvascular-tissue unit* [19], formed by the regional distal vessels (afferent arteriole, metarteriole, precapillary sphinters, arteriovenous anastomosis, capillary network, efferent venules and initial lymphatics) and by the perivascular connective matrix. The latter, provides mechanical support to the delicate capillary wall (mucopolysaccharide sleeve [20]), and also acts as a dynamic filter in the metabolic exchanges between the blood and the parenchyma [21].

The motor of the haematic microcirculatory current is known as *vasomotion*, the rhythmic contracting action of the arteriolar myocells [22], with a frequency varying between three and 20 cycles per minute, in relation to local conditions (interstitial pressure, PO_2, etc.). The vasomotion determines, on a capillary level, the undulatory variations of the flow (*flowmotion*) [23].

Recent advances have clarified that endothelium is key to the microcirculatory homeostasis. Endothelium does not just perform a purely mechanical role function of endoluminal coating; it also modulates blood–tissue exchanges and, through a complex biosynthesis action resembling a diffuse glandular function, manages the equilibrium between many phenomena (pro and anti-coagulant, fibrinolitic and anti-fibrinolitic, vasodilatory and vasoconstrictive) in order to regulate, in real time, the local functionality of the microcirculation according to the changeable demands of the cells [24].

Curri and Merlen [25] clarified the morphological peculiarities of the microvascular-tissue unit of the subcutaneous tissue, which is characterized by:

- capillary network with very close together branches, in near proximity to adipocytes and reducing the 'diffusion space' to the minimum;

- absence of arterio-venous anastomosis: it leads to the deduction that the continuity of apidocyte perfusion is a condition which cannot be sacrificed;
- branches connecting the arteries and veins of adipose tissue to the vascular plexus of the dermis and muscular tissue: these form cylindrical units, arranged perpendicularly to the surface of the skin and reaching from the latter to the hypodermis [26]. This justifies the fact that the microcirculatory deficits of panniculopathy are often associated with alterations in the blood flow extending to the skin and regional musculature, where they cause both clinical (hyperkeratosis, cramping pains) [27] and instrumental effects [28, 29].

The presence of oestrogen receptors in the endothelial cells and smooth muscle [30] explains the functional differences of the female microcirculation [31, 32], especially in relation to vascular tone [33] and permeability [34].

On the basis of these suppositions, together with a thorough analysis of histological and clinical–instrumental data, Curri constructed his theory on the genesis of EFP.

The causal factor is identified as a chronic *microcirculatory maldistribution*, which is in turn due to a primitive defect of the arterial device modulating the blood flow or to an inadequacy of vasomotion. The consequences of this condition, which can be classified within the sphere of hypotonic phlebopathy (the preclincal stage of venous insufficiency), are as follows:

- slowdown of blood circulation;
- erythrocytic sludge phenomena;
- compromission of the hydrostatic capillary equilibrium;
- reduced parietal and tissue oxidation;
- endothelial damage (endothelial swelling, microanneurisms, microhaemorrhaging);
- abnormal capillary-venular permeability;
- increase in the hydrostatic pressure of the interstitial liquid and in its protein content [35];
- recurring episodes of inter-adipocyte oedema.

The damage caused to the adipocytes manifests itself initially with an anisopoichilocytosis, followed by ruptures of the plasmatic membrane and leakage of lipidic material. The fine interweaving of delicate fibrils which serve as the framework for the adipose lobule, enveloping each individual cell (we now know that each adipocyte is coated with a basement membrane [36]), thickens due to hypoxia and the consequent oxidative stress [37]. Bands of young connective tissue form, creating the lobule by encircling clusters of degenerate adipose cells [38, 39]. Subsequently, the micronodules formed in this way tend to merge due to the further apposition of collagen material which becomes sclerotic, leading to the production of palpable macro nodules, which cause the irregularity of the skin's surface.

Curri identifies four stages to this process [40]:

Clinical classification	**Pathogenesis**	**Histology and histochemistry**
Stage I		
Pale, pasty skin	Microcirculatory maldistribution, defective vasomotion	Lipoedema, anisopoichilocytosis, membrane ropture
Stage II		
Cutaneous hyperelasticity and hyperthermia, paresthesia	Stasis, sludge, microvessal ectasia, abnormal hypovoloemia, and zonal hypoxia	Regressive adipocyte manifestations, massive microvessal dilatation, fibrillopoiesis
Stage III		
Orange peel skin (patches of hyperkeratosis), palpable small lumps	Reduction in capillary flow, increase in the areas of relative hypoxia	Neoflibrillogenesis, degenerate adipocytes encapsulated in micronodules
Stage IV		
Painful nodules	Stasis, hypovoloemia, teleangectasia and microvaricosity	Sclerotic connecting collagen bundles surrounding macronodules. Local dystrophic phenomena of the dermis and the epidermis

Bartoletti *et al.* have provided significant contributions to the definition of cellulitic dystrophy. The first contribution was of a nosological nature. Curri, attributing to the pannicular perfusion deficit the capacity to increase the lipidic deposit [41], associated the pathogenesis of EFP with that of regional subcutaneous tissue thickening. Bartoletti made a more clear-cut distinction between panniculopathy and localized peritrochanteric adiposity in females, and reclassified the latter within the sphere of morphological and physiological normality, albeit without negating the possibility of intermediary forms [42].

In fact, the presence of oestrogen receptors on adipocytes [43, 44] explains the typical female fat distribution, which is a consequence of the modulation exerted by these hormones on the lipase [45, 46] and lipoprotein-lipase [47, 48] activities.

Furthermore, Bartoletti *et al.* [49, 50] completely re-examined the semiological and clinical classification, codified the diagnostic procedure[51] (identifying as the salient points, the general examination, the phlebological study, the postural evaluation and the ecographic investigation [52–55]) and developed the most followed therapeutic protocols at the present time [56, 57].

Anatomical peculiarities of female subcutaneous tissue

Numerous authors, such as Cambar *et al.* [58], Braun-Falco and Scherwitz [6], Ribuffo *et al.* [59] and Calvieri *et al.* [60], have denied that, in areas where the clinical aspects of cellulite appear, it is possible to discern, with an optical and electronic microscope, histological modifications different to those commonly observed in the zones of macroscopically 'normal' adipose tissue accumulation.

These observations lead to the widely held conception, especially in Anglo-Saxon countries that views cellulite as a simple manifestation of lipidic accumulation [61]. This provides a stark contrast to the microangiopathic theory.

Clearly, the existence of differing opinions within the realms of science is not unusual. However, the fact that this controversy is based on the expression of profoundly different histopathological assumptions produces a certain amount of perplexity: it seems surprising the persisting of such wide margins of disagreement on the definition of morphological aspects in structures which are easily accessible by means of bioptic examination. If cellulite is simply the expression of a localized excess of adipose tissue, then why is the appearance of this unsightly problem limited almost exclusively to the female gender, and only to certain areas of the body?

Two German doctors, Nürnberger and Müller [62], referring to the results of histological examinations carried out on a wide range of cases (150 samples from corpses and 30 from live subjects), deny having encountered any phenomena of oedema or of fibrosis. In fact, they attribute the manifestation of cutaneous irregularity in typical female areas to the combination of two causal factors:

- excessive lipidic deposit (there is no cellulite without adiposity);
- the peculiar architecture which, in women, characterizes the subcutaneous tissue in these areas, where fibrous branches perpendicular the skin's surface separate voluminous lobules in rectangular sections; their peaks press against dermis and push outwards, in the form of 'adipose lobes'.

The dermo-hypodermic border is therefore characterized, in 'cellulitic areas', by a 'hill' profile which, in the case of perfect normality, can be proved with the 'pinch test'. This action, which places in traction the non-stretchable connective tissue bands, highlights surface undulations even in very slim subjects. Women who develop a thickening of the subcutaneous panniculus in the areas typical of gynoid adiposity have enlarged lobules. These are held back along the sides by the bands, however, at the centre they stretch out into the dermis, with hypertrophic adipose lobes, thus creating an unattractive alternation of bumps and troughs which are first evident only when standing upright, but are subsequently also visible when lying down.

On the other hand, in male subcutaneous tissue, the bands take a different course, crisscrossing and thus forming smaller polygon-shaped lobules which, even in cases of lipidic hyper-accumulation, do not tend to protrude towards the dermis. In hypogonadic males, the adipose tissue assumes a feminine morphology, demonstrating androgen activity is the causal factor of any gender-related differences. Numerous reviews on the subject of cellulite have confirmed the opinions expressed by Nürnberger and Müller [62].

Amongst these, Marenus theorized that the projection of the adipose lobes towards the dermis is

brought about by the degeneration of the collagen component of the latter, resulting from the action of certain proteases [65].

Rosenbaum *et al.* [66] also noted an individual variability in addition to gender-related differences; the subcutaneous tissue in women with cellulite is characterized by a more irregular and broken subdermal layer, which is the factor enabling the adipose lobes to protrude.

Querleux *et al.* [67] employed, in over 70 subjects, magnetic nuclear resonance (MNR), using both imaging and spectroscopy techniques. The former recorded the indented profile which the adipose lobes make on the dermo-epidermic border, and confirmed the different orientation of the connective bands in males compared with females (although the difference did not appear to be as extreme as that indicated by Nürnberger and Müller). According to the authors, the MNR spectrometry data ruled out the possibility of an inter-adipocytary oedema occurring in cellulite. An even more recent study, using magnetic nuclear resonance imaging (MRI) to examine the morphology of subcutaneous adipose tissue, has provided further evidence of the structural differences relating to gender [68]. It proved once again the pathogenetic significance of the 'herniation' of adipose lobes in the reticular dermis in female subjects suffering from cellulite. Furthermore, it brought to light two interesting pieces of data: the first relates to the absence of a direct correlation between the body mass index (BMI) and the appearance of irregularities of the cutaneous surface: amongst the women whose BMI is over 30, it is possible to distinguish women with no signs of cellulite and subjects who are more or less severely affected by this dysmorphism. This demonstrates that other factors, in addition to localized excess adipose tissue, play a part in the dislocation of adipose hernias. The second piece of data relates to the fibrous component of the subcutaneous tissue affected by cellulite: the MRI showed that its overall size did not increase but, on the contrary, appeared to have reduced substantially in comparison with the controls. The authors therefore identify one of the pathogenic elements of cellulite as a constitutional thinness and laxity in the fibrous interlobular bands [68]. Further confirmation of this theory is provided by a recent study in which the visco-elastic properties of skin affected by cellulite were compared with those of unaffected skin [69].

In short, on the basis of the study of 39 post-mortem samples, Pierard *et al.* [70], although confirming the presence of adipose lobes in the female sex, concluded that these formations were too small to be capable of producing the coarse combination of convexity and depression typical of cellulite. However, this case would be due to the progress of the adiposity, which cause a stretching of the interlobular branches; some of these would undergo to retraction phenomena (due to reactive thickening and to the appearance of myofibroblasts), whilst others would suffer partial lacerations, similar to stretch marks, causing irregular protrusions of adipose lobules. This observation led the authors to try a therapeutic approach with retinol, although this produced only a modestly beneficial result [71].

Cellulite: new developments and new questions

Clearly, the debate surrounding the topic of cellulite remains unresolved, confined by the limited number of studies and the lack of resources devoted to addressing the subject. Moreover, the *impasse* which still exists due to the lack of solutions to relatively basic questions runs the risk of being overtaken by the advances of by other branches of medicine in relation to the comprehension of the physiology of the adipose tissue and endothelium, the two key cellular elements associated with the development of cellulite.

In particular, new developments are bringing to light a limitation which is shared by the two main theories on the origin of cellulite. According to the ideas of Curri as well as those of Nürnberger and Müller, adipose tissue, the area of distortion, does not play a significant role in the onset of cellulite: it participates only with a purely physical function, producing mechanical tension through its hypertrophy. Such claims carry traces of an idea which is now outmoded, which sees within the adipose tissue a cellular element with limited capacities, used only for the storage of excess calorific substrates. Given the illogical aspect of attributing extensive pathogenetic 'responsibilities' to such an apparently banal cytotype, the causal factors of cellulite were sought elsewhere.

Today we know that the adipose organ performs sophisticated and composite functions[72], acting as a:

- device controlling the systemic energy balance, able to modulate the food intake and the metabolism of the substrata of other tissues;
- glandular system for multiple hormonal and para-hormonal secretions[73–76], not only capable of carrying out the bio-conversion of circulating steroid hormones, but also able to synthesize *de novo* regulation elements of a proteic nature (adipokine).

The following substances released by the adipose tissue are known to have an endocrine and/or paracrine actions:

- leptin [77, 78];
- adiponectine [79, 80];
- resistin [81, 82];
- interleukin-6 [83];
- tumour necrosis factor (TNF)-α [84–87] and soluble receptors for TNF-α [88];
- fasting-induced adipose factor [89];
- acylation-stimulating protein [90];
- adipsin [90];
- prostaglandin [91, 92];
- lipoprotein lipase [93];
- angiotensinogen and angiotensin II [94];
- FGF (*fibroblast growth factor*) [95];
- transforming growth factor-beta [96];
- plasminogen activator inhibitor-1 [97];
- vascular endothelial growth factor [98, 99].

The apparent significance assumed by excess adipose tissue, especially the visceral type, in the pathogenesis of insulin resistance and diabetes [100, 101], similarly to that of atherosclerosis [102] and cardiovascular diseases in general [103], explains the huge amount of studies devoted in recent years to the biology of adipose tissue. Amongst other observations, one factor which has been highlighted is the significant plasticity of the adipose tissue, due to the presence of undifferentiated mesenchymal elements which are capable, when necessary, of converting themselves into adipocytes [104, 105]. Apoptosis phenomena counteract the neoadipogenesis; these can reduce the number of adipocytes in a certain area [106–108]. The extraordinary capabilities of the adipose tissue which are recognized nowadays cannot fail to have repercussions concerning the physiopathology of cellulite. For example, the theory suggesting that the subcutaneous tissue passively suffers the consequences of a microcirculatory dysfunction must, in all probability, be reviewed in light of new developments which identify, between the vessel and adipocyte components, an interweaving of far more dynamic connections, with a bidirectional course [109, 110]. In fact, we know that adipose tissue is able to modulate, directly or indirectly, the blood flow which passes through it in accordance with the demands exerted on it [111]. Furthermore, the adipocytes secrete neoangiogenetic elements [112] and numerous other substances with the ability to regulate the activity of the endothelial cells [98, 99].

The most recent studies inform us that, in obese subjects, amongst the functional alterations encountered by the adipocytes, as they become hypertrophic, is an increase in the release of phlogogenic cytokines [113, 114]. This cause systemic effects and at the same time induce, in the apparently 'normal' adipose tissue as a whole, a macrophagic infiltration proportional in size to the average adipocytaric volume[115–117]. Therefore, adiposity entails the activation, on a regional level, of biochemical–cellular mechanisms of a phlogistic nature. Paradoxically, these remain subclinical in the area of production, whilst causing metabolic repercussions from a distance, on the organism as a whole, contributing to the development of insulin resistance and cardiovascular diseases [118, 119].

At this point, it is not unreasonable to hypothesize that inflammatory processes (similar or different?) can also occur in dystrophic adipose accumulations of cellulite, where they could play quite a plausible role in its pathogenesis, rendering them responsible, for example, for the endothelial alterations and the oedema described by Curri. Cellulite could therefore prove worthy of its name, rightfully winning back its distinguishing features as a disorder originating primarily from inflammation. Unfortunately, no studies have been published to date to prove or disprove this theory. Similarly, on a more general level, no data are available to clarify whether, and if so in what way, the recently identified functional properties of the adipose tissue are involved in the pathogenesis of this problem.

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