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REVIEW ARTICLE

Cellulite: a review

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ABSTRACT

Gynoid lipodystrophy (cellulite) is an extremely controversial topic. A lack of knowledge regarding specific aetiopathogenic factors, as well as the opportunism of some professionals and the media, has fuelled debate regarding the scientific basis of this condition. This article reviews the clinical, epidemiological, histopathological and therapeutic aspects of cellulite.

Key words: cellulite, lipodystrophy, panniculopathy

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Concept and nomenclature

Cellulite is an alteration of the topography of the skin that occurs mainly in women on the pelvic region, lower limbs and abdomen. It is characterized by a padded or 'orange peel' appearance.

The term 'cellulite' was first used in the 1920s to describe an aesthetic alteration of the cutaneous surface. Since then, other more descriptive names have been suggested; these include nodular liposclerosis,[1] oedemato-fibrosclerotic panniculopathy,[2] panniculosis,[3] gynoid lipodystrophy (GLD)[4] and others. Etymologically, cellulite is defined as a localized metabolic disorder of the subcutaneous tissue which provokes an alteration in the female body shape.

Many authors confuse GLD with obesity. However, this is incorrect; in obesity, only adipocyte hypertrophy and hyperplasia are observed,[5] whereas in GLD, there are several structural alterations in the dermis, in the microcirculation and within the adipocytes. These, in turn, may be associated with additional morphological, histochemical, biochemical and ultrastructural modifications,[6–9] Clinically, these changes produce the padded and orange peel appearance of the skin.

Aetiopathogenesis and histopathology

In the first description of the disease, Alquier and Paviot (1920) described a 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.[4] The dystrophy was thought to be a reaction to traumatic, topical, infectious or glandular stimuli.

Currently, several observations suggest a physiological basis for GLD. These include abnormal hyperpolymerization of the connective tissue,[4] primary alterations in the fatty tissue[10–12] and microcirculatory alterations.[1,2,8,9,13–17]

GLD may be associated with chronic venous insufficiency. Both conditions share common signs and symptoms, including the presence of telangiectasias and microhemorrhages, paresthetic symptoms, such as heaviness, cramps in the lower limbs and pain to local palpation,[2] and decreased temperature of the skin surface on affected sites, as detected by thermographic and infra-red examination.

Analysis of the interstitial liquid shows an increased protein concentration (0.8–1.2 mg/mL; normal 0.2–5.1 mg/mL). The interstitial pressure is also increased (150–200 mm H_20; normal physiological pressure, 75–91 mm H_20), These microcirculatory alterations may be caused by insufficiency of the precapillary sphincters, whose blood flow regulating function is modified by the disease.[14] Some studies, performed using laser Doppler fluxometry, have shown that the blood flux mean in the areas affected by GLD is 35% lower than in non-affected regions.[17]

Biochemical analysis has demonstrated a significant difference in the composition of triglycerides and free fatty acids among the adipocytes of obese patients who have GLD.[9] According to Curri (1991), the pathophysiology of GLD can be divided into four evolutionary stages: 1) pre-capillary arteriolar sphincter alterations lead to modification of capillo-venular permeability, as well as to capillary ectasia, with pericapillary and interadipocyte transudation and oedema; 2) the oedema causes metabolic changes which result in hyperplasia and hypertrophy of the

reticular framework. This leads to the formation of an irregular framework of pericapillary and periadipocyte argentaffin fibrils. Anisopoikilocytotic adipocytes surrounded by reticular septae of irregular thickness are formed; 3) collagen fibres bind together around groups of adipocytes, forming micronodules; 4) sclerosis causes macronodules to form through the confluence of several micronodules.

Histopathologically, three evolutive phases may be recognized: 1) alteration of adipocytes (anisopoikilocytosis) which is associated with lymphatic stasis and proliferation of fibrocytes; 2) fibroplasia, collagenesis and capillary neoformation occur with focal microhemorrhage and follicular hyperkeratosis. There is mild dermal oedema. This causes the orange peel appearance; 3) the third stage includes the previous alterations, as well as sclerosis of the fibrous septae of the subcutaneous tissue and deep dermis, causing the padded appearance, The granular texture on deep palpation of the affected area corresponds to the nodules in the subcutaneous tissue seen histopathologically.[2]

Ciporkin and Paschoal[4] have reformulated the concept of 'operational units', originally proposed by Merlen[13] through which predisposing factors (genetic), hormonal factors (hyperestrogenism) and coexisting conditions (inactivity, food intake, associated diseases and iatrogenic factors) act on four functional units of the fatty tissue: the matricial–interstitial unit, the microcirculatory unit, the neuro-vegetative unit and the energy-fatty unit.

The matricial–interstitial unit

The matricial–interstitial unit is formed by cells (especially fibroblasts, which are responsible for the synthesis of the macromolecules of the cellular matrix) and by the extracellular matrix, which includes fibrous tissue (collagen, elastic and reticular fibres) and ground substance (proteoglycans, glycoproteins and hyaluronic acid). While the fibrous tissue is responsible for resistance and support, the ground substance allows for diffusion of nutrients, metabolites and hormones from the circulatory system through the interstitial tissues. Glycosaminoglycans have hydrophilic properties and help to maintain interstitial osmotic pressure. Proteoglycans play a role in the production of collagen by fibroblasts, as well as their tridimensional distribution.[18] They help to increase collagen storage and to rebuild the extracellular matrix.[19]

Electronic microscopic study of the proteoglycans, performed on specimens obtained from thigh skin of patients with GLD, have demonstrated precipitation of granular electrodense material in the dermal capillary walls and adjacent to the collagen and elastic fibres of the dermis; this is associated with oedema of the ground substance and may lead to structural alterations of the fibres followed by sclerosis.[20]

Proliferation and activity of fibroblasts is controlled by cyclic nucleotides. Hormonal activity is affected by receptors that either activate or inhibit the enzyme adenyl cyclase, which is responsible for the production of cAMP. Several factors may modify the matrix proteoglycans: (a) topographic variations (related to species, individual and regional characteristics); (b) age (a greater quantity is produced during the embryonic phase than during the senile phase); (c) oestrogens (which increases hyaluronic acid and chondroitin sulphate production); (d) pregnancy (which increases hyaluronic acid and glycosaminoglycan production); (e) hyperthyroidism (which increases hyaluronic acid and chondroitin sulphate production); (f) diabetes (associated with decreased production of glycosaminoglycans and an increase in heparin); (g) corticosteroids (hydrocortisone inhibits the production of hyaluronic acid, chondroitin sulphate and heparin; prednisone decreases the production of chondroitin sulphate and hyaluronic acid); (h) free radicals (super-oxide depolymerizes hyaluronic acid).

Fibroblast alterations, provoked mainly by oestrogen, cause glycosaminoglycans in the dermis and the perivascular connective tissue to undergo structural alterations, followed by hyperpolymerization, increasing their hydrophilicity and the interstitial osmotic pressure. This causes water retention (oedema) and an increase in viscosity, which causes cellular changes and, consequently, compresses the vessels, provoking tissue hypoxia.[4] The hypoxia leads to an alteration in aerobic glucose metabolism, which results in increased production of lactic acid, This activates proline hydroxylase, the enzyme that facilitates the conversion of the proline to hydroxyproline within procollagen, with a consequent increase in collagen production. When there is tissue inflammation, cytokines stimulate fibroblast metabolism, which leads to an increase in the rate of collagen synthesis and in the formation of incomplete and altered proteins. These proteins are not able to maintain normal physiological functions or structural connective tissue maintenance, or regulate their own synthesis feedback.[21]

The microcirculatory unit

The microcirculatory unit includes five components: arterioles, venules, capillaries, lymphatic and interstitial tissues. Normally, a balance exists between arterial capillary filtering and venous capillary absorption. A lack of this balance may occur due to an increase in capillary pressure, a decrease in plasma osmotic pressure, an increase in interstitial liquid pressure, or a decrease of the lymphatic flux, which leads to intercellular oedema. The factors which influence the microcirculation may be endogenous or exogenous. Among the former are the central nervous system (vasomotor centres, hypothalamus, renin-angiotensin-aldosterone system, afferent innervation – pain and temperature); adrenergic sympathetic nervous system, through the alpha (vasoconstriction) and beta (vasodilation) receptors; and humoral factors (catecholamines, acetylcholine, prostaglandins, dopamine, histamine, serotonin, amino acids, intestinal vasoactive polypeptides and chemical factors [calcium, magnesium,

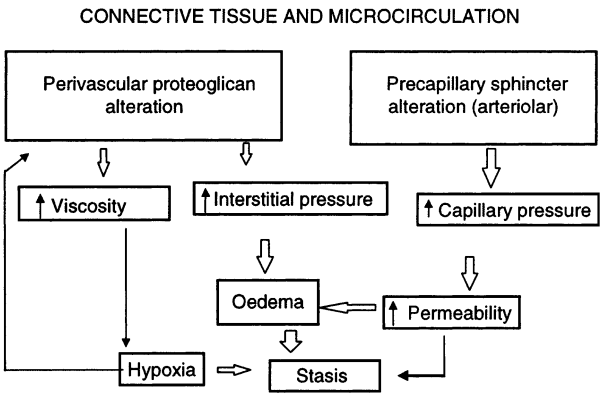

fig. 1 Interactions between the matrical–interstitial and microcirculatory units in cellulite.

oxygen, pH, carbon dioxide]), Pharmacological factors (beta-sympathomimetic adrenergetic and alpha blockers, beta-blockers, phosphodiesterase inhibitors, as well as veno-active and lympho-kinetic agents which act on membrane permeability) may also be important,

Merlen[22] has described an alteration of the arteriolar precapillary sphincter in the affected areas; this would provoke an increase in capillary pressure which, together with the elevation of interstitial pressure (provoked by the hyperpolymerization of glycosaminoglycans) and the decrease in plasma flux (provoked by vascular compression) could cause an increase in capillary and venular permeability and, consequently, lead to ectasia, as well as to oedema of the dermis and of the interadipocyte and interlobular septae. A decrease in venous tone would occur concurrently with increased capillary fragility resulting from perivascular connective tissue alterations, which provoke rupture and microhemorrhage.[1,3,23]

The complex interactions within and between the matricial-interstitial and microcirculatory units are illustrated in fig. 1.

The neuro-vegetative unit

The neuro-vegetative unit is formed by the sympathetic innervation of the dermis and subcutaneous tissue. This acts on the alpha and beta receptors to provoke a response through the adenyl cyclase system. This modifies the cAMP:cGMP ratio, which regulates fibroblasts (cellular proliferation and collagen and glycosaminoglycan turnover), the microcirculation (arteriolar vasoconstriction and vasodilation) and adipocytes (lipolysis and lipogenesis).

The adrenergic effects of the catecholamines are modulated by thyrotrophic stimulant hormone, 3,5,3-triiodothyronine, thyroxine, adenocortico-trophic hormone, T_3, T_4, ACTH, some prostaglandins, glucagon, prolactin and secretin.

The energy–fatty unit

The energy–fatty unit includes the collections of adipocytes. These comprise lobules, each of which is supplied by an arteriole and surrounded by connective tissue septae. Each adipocyte is associated with a glycoprotein layer, reticular fibrils and other cells (fibroblasts, mastocytes and macrophages), as well as an adjacent capillary. The adipocyte stores triglycerides. Fatty tissue has the most capacity to vary volume of any tissue within the body.

The topographical anatomy of the fatty tissue includes two layers separated by a superficial fascia. The more external layer (in contact with the dermis), called the areolar layer, is formed by globular and large adipocytes arranged vertically; here the blood vessels are numerous and fragile. Within the deeper layer, called the lamellar layer, the cells are fusiform, smaller and arranged horizontally; here the vessels are larger. This second layer increases in thickness when a person gains weight, mainly due to the increase in adipocyte volume which invades the fascia superficialis. The relative size of the two layers varies according to skin thickness (in thick skin, the areolar layer is thicker, while in thin skin, the opposite is true); region and body segment; and sex and age (women and children have a thicker areolar layer[24,25]).

The fatty tissue undergoes two periods of growth. The first occurs from the first quarter of intra-uterine life to 18 months of life, and the second occurs during puberty.[26,27] Fatty tissue development during puberty is much greater in women than in men.[28] This may be explained by the influence of oestrogen, as 17-beta-oestradiol stimulates the replication of adipocyte precursors.[29]

In women, lipid changes occur more slowly within the femoral region than within the abdominal region; the adipocytes within the femoral region are larger and are influenced by female sex hormones. They are metabolically more stable and resistant to lipolysis. The increase in the fatty tissue in the gluteofemoral regions characterizes gynoid feminine-type obesity.[30]

Several factors influence lipolysis or lipogenesis, and contribute to a decrease or increase in the thickness of the fatty tissue (fig. 2). Insulin stimulates lipogenesis which is enhanced by oestrogen and prolactin, and decreased by

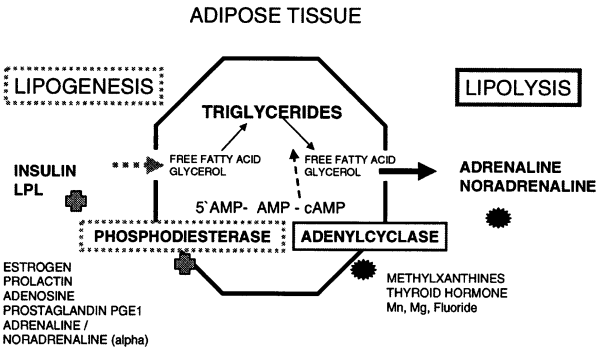

fig. 2 The influence of lipid metabolism on the pathophysiology of cellulite.

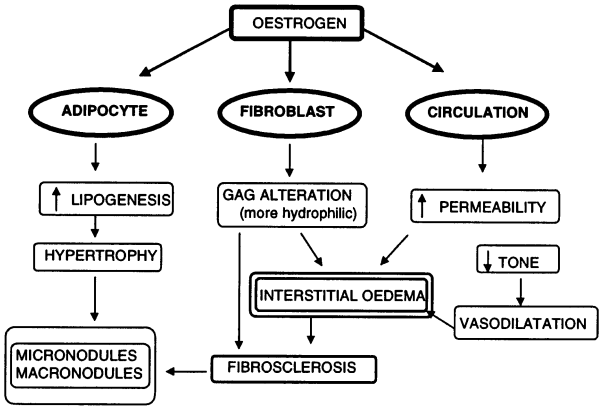

fig. 3 The influence of oestrogen on the pathophysiology of cellulite.

progesterone, luteinizing hormone (LH), testosterone and glucocorticoids. A hypercalorific diet rich in carbohydrates stimulates lipogenesis, because it increases lipoprotein lipase (LPL) activity. Physical exercise decreases the plasma concentration of insulin. Catecholamines stimulate lipolysis through the activation of adenyl cyclase. MethyIxanthines, papaverine and tiratricol also increase lipolysis through the inhibition of phosphodiesterase.

In GLD the stimulus to lipogenesis provokes adipocyte hypertrophy. The increase in viscosity of the ground substance and the microcirculatory alterations make metabolic changes and oxygenation difficult, increasing lipolytic resistance and provoking anisopoikilocytosis. An interstitial-mesenchymous reaction ensues followed by hypertrophy and hyperplasia of the pericapillary and periadipocyte reticular fibres forming the micronodules and macronodules.[1,4,23,31]

Hormonal factors

Hormonal factors may play a predisposing or aggravating role in the pathophysiology of GLD. They may be especially important during adolescence. Oestrogen is the most important hormone and may initiate, aggravate and perpetuate GLD. Evidence for oestrogen involvement includes: (a) the presence of GLD in the vast majority of women; (b) the onset of the disease after puberty; (c) aggravation of the condition during pregnancy, nursing, menstruation and oestrogen therapy; and (d) the interaction of oestrogen with other hormones. Absolute or relative hyperoestrogenism may occur. Absolute hyperoestrogenism involves an increase in ovarian secretion or oestrogen intake (e.g. hormonal contraceptives). Relative hyperoestrogenism may occur because of an abnormal oestrogen: progesterone ratio or may be due to an increased number of oestrogen receptors, especially within adipocytes.[4]

Within the amorphous ground substance, oestrogen acts via cyclic nucleotides, stimulating proliferation of fibroblasts and influencing macromolecule turnover and, at the same time, provoking alterations in glycosaminoglycans and collagen. The increase and hyperpolymerization of hyaluronic acid provokes an increase in interstitial osmotic pressure and oedema. The alteration in collagen provokes fibrosclerosis in the interlobular connective tissue septae (fig. 3).[32,33]

Oestrogen increases the response of the adipocyte to the antilipolytic alpha receptors and stimulates lipoprotein lipase (LPL), the main enzyme responsible for lipogenesis. The increase in lipogenesis provokes adipocyte hypertrophy and anisopoikilocytosis which, together with the fibrosclerosis, leads to the formation of micronodules and macronodules (fig. 3).

Other hormones also participate in the pathophysiology of GLD. Insulin stimulates lipogenesis and inhibits lipolysis through activation of LPL. Catecholamines (adrenaline and noradrenaline) may either stimulate or inhibit lipolysis depending on the activated receptor (beta or alpha). In low concentrations, beta receptors are more sensitive than alpha receptors, The opposite occurs with high concentrations.

Thyroid hormones increase lipolysis within the fatty tissue by stimulating adenyl cyclase synthesis. In addition, they decrease the activity of phosphodiesterase and the antilipolytic alpha receptors. They also participate in the synthesis of hyaluronidase, which is responsible for the depolymerization of glycosaminoglycans. A peripheral relative hyperthyroidism causes myxedematous changes of the ground substance and decreases lipolysis and collagen turnover through a reduction in oxygen consumption. Prolactin increases water retention within the fatty tissue.[33]

Predisposing factors

A genetic and inherent predisposition is necessary for GLD, to develop. Important hereditary factors include: (a) sex (GLD affects, in its classical pattern, almost exclusively women); (b) race (white women tend more to GLD than Asian or black women); (c) biotype (Latin women develop GLD on the hips, while Anglo-Saxon and Nordic women develop GLD, on the abdomen); (d) fatty tissue distribution; (c) number, disposition and sensitivity of hormone receptors on the affected cells; and (f) predisposition to develop peripheral angiopathy (or susceptibility to circulatory insufficiency).[33] As discussed below, other factors may also play a role.

A non-balanced diet with excessive intake of fats and carbohydrates provokes hyperinsulinemia and an increase in lipogenesis. Excessive salt intake provokes fluid retention. A fibre-poor diet leads to constipation and increases venous resistance within the lower limbs; this leads to stasis and an increase in capillary permeability. The ideal diet must be established for each individual; however, in general, the protein contribution must not be less than 12% of the total calorie intake. The intake of fast absorbing carbohydrates (starch) must be reduced, and at least 20% of dietary lipids must be polyunsaturated.[33,34]

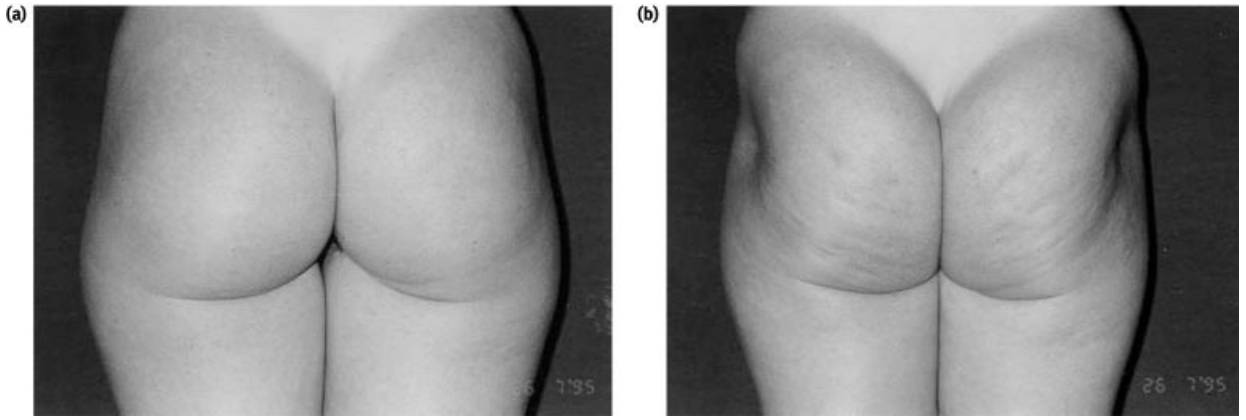

fig. 4 GLD grade II (**a**) at rest and (**b**) after gluteal contraction.

A sedentary lifestyle contributes to the aggravation of GLD, through the following mechanisms[4]: (a) a decrease in muscle mass, followed by an increase in fatty mass; (b) increased flaccidity of tendons and muscles; and (c) decreased muscular pumping mechanism in the lower limbs, inhibiting venous return and, consequently, increasing stasis. Wearing tight clothes also may make venous return difficult, as may high heeled shoes, which may also provoke calf muscle dysfunction, causing damage to the muscular pumping mechanism. Long periods in a single position (sitting or standing) also lead to stasis, Smoking provokes alterations in the microcirculation and decreases tissue oxygenation; in addition, it increases the formation of free radicals. Alcohol evokes an increase in lipogenesis.

Emotional disturbances lead to an increase in catecholamines (adrenaline and noradrenaline) which, under high concentrations, stimulate lipogenesis. Some authors classify GLD as a psychosomatic disorder, and suggest that modifications (circulatory, hormonal) within the hypothalamic centres provoke metabolic alterations. These centres could be affected by frustration, anxiety, depression and stress.[1,3]

Coexisting disorders may be important. These include hormonal, circulatory, metabolic, gynecological, nephrotic and gastrointestinal alterations. Some treatments, such as oestrogens, antihistamines, antithyroid treatments and beta-blockers, also may contribute to the development of GLD.[4]

Pregnancy is associated with an increase in certain hormonal levels (prolactin, insulin), In addition, the pregnant uterus itself acts as a mechanical barrier to venous return, increasing circulatory stasis in the lower limbs as well as the presence of nodules on deep palpation are recorded. Palpation with increased pressure may provoke appearance of a fovea (through dermal and subcutaneous oedema) and, rarely, of an ecchymosis (a sign of increased capillary fragility). The classical 'Ricoux tetrad' includes four signs which are detected when palpating GLD. They are: (a) an increase in the thickness of the subcutaneous tissue; (b) increased density; (c) increased pain and sensitivity; and (d) decreased mobility.[1,6,35,36]

Classification

GLD may be classified into four grades or stages according to the histopathological and clinical changes.[1]

Grade I

The patient is asymptomatic and there are no clinical alterations. On histopathological evaluation, there may be increased thickness of the areolar layer, increased capillary permeability, adipocyte anisopoikilocytosis, diapedetic microhemorrhages, capillary ectasia, and fusiform microaneurysms within the postcapillary venules.

Grade II

After skin compression or after muscular contraction (fig. 4a,b), there is pallor, decreased temperature and decreased elasticity. There are no relief alterations at rest. Histopathologically, hyperplasia and hypertrophy of the periadipocyte and pericapillary argentaffin fibril framework occurs along with capillary dilatation, microhaemorrhages and increased thickness of the capillary basement membrane.

Grade III

A padded skin and/or an orange peel appearance is evident at rest; palpable sensation of thin granulations in the deep levels; pain to palpation; decreased elasticity; pallor and decreased temperature (fig. 5a,b). Histopathologically there is: fatty tissue disassociation and rarefaction (due to neoformation of collagen fibrils) followed by encapsulation of small collections of degenerated adipocytes, forming micronodules; sclerosis and thickening of the internal layer of small arteries; dilation of venules and small veins; formation of numerous microaneurysms and haemorrhage within the fatty tissue; neoformation of capillaries; obliteration of the border between the dermis and subcutaneous tissue, followed by an increase in the volume of the fatty micronodules, which are usually dysmorphic; and sclerosis with inclusion of adipocytes within the connective tissue of the deep dermis.

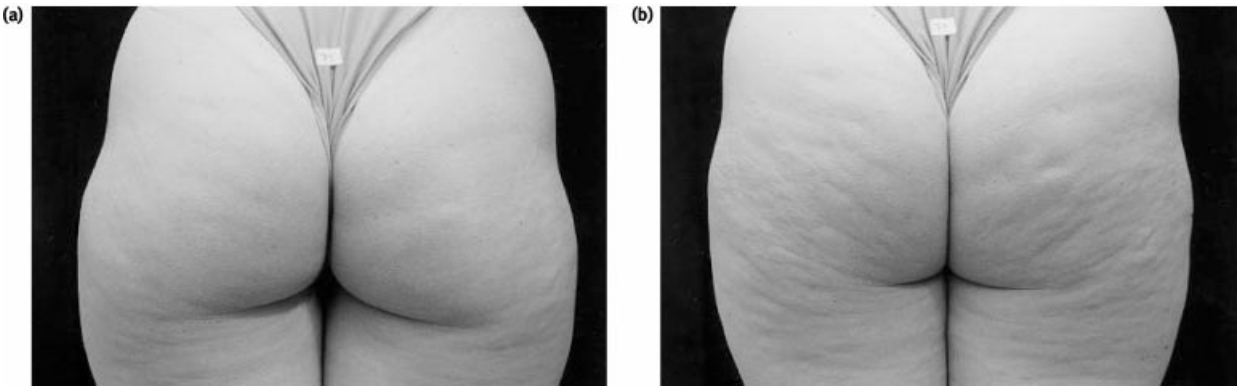

fig. 5. GLD grade III (**a**) at rest and (**b**) after gluteal contraction.

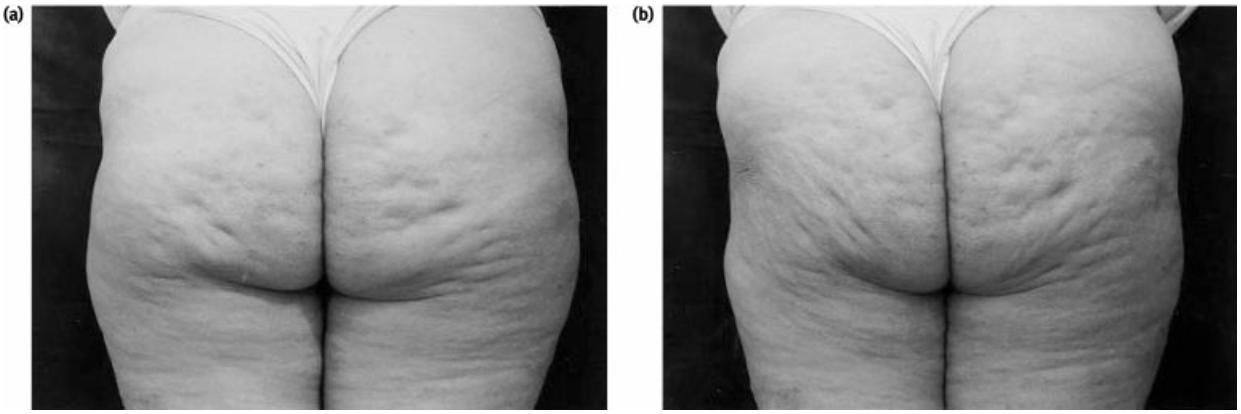

fig. 6 GLD grade IV (**a**) at rest and (**b**) after gluteal contraction.

Grade IV

There are the same characteristics as in grade III with more palpable, visible and painful nodules, adherence to the deep levels and an obvious wavy appearance of the skin surface (fig. 6a,b). Histopathologically, the lobular structure of the fatty tissue has disappeared and some nodules are encapsulated by dense connective tissue. Diffuse liposclerosis (followed by important microcirculatory alterations), telangiectasias, microvarices and varices, and epidermal atrophy complete the microscopic picture.

Clinical changes

GLD may also be classified by skin consistency: hard, flaccid, oedematous or mixed.[37]

Hard

Hard GLD is observed in young women who perform regular physical activity. The appearance is compact, firm and it does not change according to position (standing or lying), On palpation, the surface is attached to the deep levels and, when pinching, the peel orange aspect is evident. This pattern is frequently associated with stretch marks and it is the most common pattern found among teenagers.

Flaccid

Flaccid GLD is found in inactive women. It is associated with muscular hypotonia and flaccidity. It also occurs in women who have lost weight suddenly. The padded surface is evident, the skin shakes with movement and changes according to position. There may be circulatory disturbances (telangiectasias and varices). Occasionally, the flaccid form of GLD, which is frequent after the age of 40, occurs if the hard form of GLD is not treated appropriately.

Oedematous

Oedematous GLD manifests as increased volume of the entire lower limbs and a positive Godet sign (depression of the tissue to fingertip palpation, which persists when the finger is removed). The skin is bright and thin. A sense of heaviness and sore legs are common complaints. It is the most severe and, fortunately, the least frequent of the GLD patterns.

Mixed

Mixed GLD occurs most often. Here, more than one kind of GLD can be observed on different sites in the same patient.

Evaluation methods: complementary examinations

In order to correctly classify GLD, and to evaluate the response to therapy, it is necessary to perform some complementary examinations.

The anthropometrical examination is most often used because of its simplicity and low cost. It consists of measuring weight, height, and calculating the body mass index [using the formula: weight (kg) divided by height (m), squared] and calculating the body circumference, which is done with a tape measuring. It is a quantitative method, which can be utilized as an indirect measurement of the thickness of the panniculus. Thus, it is a good way to evaluate obesity and localized fat, but it does not accurately assess GLD, as there may be weight loss, with a consequent reduction in the diameter, without any improvement in the condition.[38,39]

Bioelectric impedance measures the apparent resistance of a circuit through the flux of an alternating electrical current. An interpolar electrode is placed on the upper and lower limbs to gather information about body composition, The percentage lean mass (bones, muscles and viscera), fat mass (fatty tissue) and water can be determined. However, this technique does not provide data on the rnicrocirculatory connective tissue alterations.[40]

Xerography consists of irradiation of the skin with X-rays, utilizing an electromagnetic field modified by the use of electrostatically charged selenium. As radiation courses through the tissues, different thicknesses form different images, depending on the density of the connective tissue, muscles and subcutaneous tissue. Although this method offers the possibility of identifying the limits of the epidermis, dermis, subcutaneous and muscular tissue, and allows for measurement of the thickness of each of these layers, it does not evaluate microcirculatory alterations, Also, the technique itself is not harmless, because of the X-ray irradiation risk.

Bidimensional ecography (B scan), with transductors of 7.5–10 MHz frequency, allows evaluation of the subcutaneous tissue. It identifies the presence of nodules and their diameter, as well as the texture of the connective tissue that surrounds them and their thickness. After the introduction, more recently, of 20–40 MHz transductors, it also became possible to visualize the papillary and the reticular dermis, as well as to identify oedema in this region. The use of the ecography with the Doppler permits evaluation of the local circulation as well.[41] Thus, this is a non-invasive method which identifies alterations in the subcutaneous tissue, the connective tissue and the circulation. Its major limitation is the need for specific equipment and specially trained individuals (radiologists/dermatologists).

Anode thermography is a method to evaluate the temperature of the skin surface using a flexible anode made up of thermosensitive cholesterol crystals. After a few seconds of contact, a 'map' of colours appears, which is determined by the different temperatures on the skin surface and the basal temperature of the anode (28–31 °C). According to the thermographic image, the grade of GLD can be determined. Generally, a homogenous and uniform thermographic image, with a green or rosy colour, indicates grade I or absence of GLD, while stained images, with hypodermal dark areas ('black holes' and 'leopard skin'), indicate a more advanced grade.[1] This method has the advantage of being harmless, but it has some disadvantages, such as the necessity of having the temperature and humidity of the room consistently stable. Factors that provoke circulatory alterations of the body surface temperature (such as solar exposure, fever, smoking and menstrual cycle) may alter the results.

Computerized tomography and magnetic resonance imaging measure only the thickness of the fatty tissue and do not allow evaluation of the dermis or microcirculation. They are used, mainly, to evaluate obesity.[42]

The histopathological examination is a direct and accurate method of evaluation, despite the inconvenience of being invasive. It may be performed through 4 mm punch biopsies of affected sites.[16] Useful stains include: haematoxylin-eosin for routine histological examination; Alcian blue for polysaccharides; periodic acid-Schiff for basement membranes; Weigert–Van Gieson (fuchsin-resorcin and acid fuchsin), which demonstrates elastic, collagen and flat muscle fibres; and Masson trichromic (Weigert ferric haematoxylin, Biebrich bright red and dye blue), which shows good contrast between collagen fibres and dermal muscles.[21,43]

Therapy

Due to the multifactoral pathogenesis of GLD, there are numerous therapeutic approaches. These include attenuation of aggravating factors, physical and mechanical methods, and pharmacological agents.

Aggravating factors

Regarding attenuation of aggravating factors, it is of fundamental importance to monitor diet, exercise regularly and use non-hormonal contraceptives. Anxiety and stress control are also of considerable benefit.

Physical and mechanical methods

Iontophoresis

The interstitial fluid, as well as the blood, contains electrolytes. This allows it to act as an electrical conductor, in contrast to the stratum corneum, which acts as a non-conducting barrier.

By applying a galvanic current with a stable potential difference on the skin surface, an electromagnetic field is created. This allows a drug to pass through the horny layer into the dermis. The current must be in an ion pattern (dissociated) and it is important to know the polarity, the structure and the molecular size of the drug that is used. Currents of 4–16 mA are generated. The galvanic current itself has a vasomotor action (vasoconstriction, followed by vasodilation) which may have a positive effect on the metabolic changes.[34,44]

Ultrasound

High frequency vibrations, which have a thermic and vasodilator effect, help in the penetration of active drugs, Recently, ultrasound has been used to cause hydrolipoclasia, a form of degeneration of the adipocyte. This provokes lipolysis, followed by lipoaspiration, and is used during liposculpture procedures. Ultrasound acts only on the subcutaneous tissue, with fair results regarding the localized fat.

Thermotherapy

This technique uses heat or cold to obtain vasodilation. Its effectiveness is questionable, as vasodilation itself may aggravate GLD, and the high temperatures may lead to protein denaturation.

Pressotherapy

This is a physiotherapy method which utilizes a pneumatic massager to perform sequential compression. This is done in the direction of the circulatory flow, activating the venous return, and is used to treat lymphatic, venous or mixed oedema of the limbs. It is also used as a adjunctive therapy for GLD.[45]

Lymphatic drainage

This is a massage technique, described for the first time in 1936, which consists of pumping movements using gentle and rhythmic pressures, which stimulate lymphatic flux. This reduces oedema. It must be performed in the direction of the lymphatic return, and thus good anatomic knowledge of the local lymphatic circulation is necessary.[1,3]

Electrolipophoresis

This consists of the application of several pairs of thin (0.3 mm) long (5–15 cm) needles which are connected to a low frequency current generator. An electromagnetic field is created which modifies the interstitial tissue, aiding circulatory drainage and promoting metabolic changes and lipolysis.[1,3]

Pharmacological agents

Certain drugs act on the fatty tissue and connective tissue and on the microcirculation. They can be used topically, systemically, or transdermally.

Drugs that have a lipolytic effect on fatty tissue include the methyIxanthines (theobromine, theophylline, aminophylline, caffeine), which act through phosphodiesterase inhibition, isoproterenol and adrenaline (beta-adrenergic agonists), and yohimbine, piperoxan, phentolamine and dihydroergotamine (alpha-antagonists). *In vitro* studies have demonstrated that beta-adrenergic agonists, as well as the methylxanthines, stimulate lipolysis and a reduction in the size of adipocytes through an increase in intracellular cAMP inhibition of phosphodiesterase.[46,47] A double-blind placebo-controlled study, which utilized a topical beta-agonist (isoproterenol), a methylxanthine (aminophylline – a phosphodiesterase inhibitor) and an alpha-antagonist (yohimbine), demonstrated a statistically significant reduction in the anthropometric measurement of the medial thigh, This reduction was greatest when all the active drugs were used together, 3–5 times a week, during a 4-week period. Used separately, the drug that showed the best results was aminophylline.[48]

Coenzyme A and the amino acid l-carnitine enhance the effects of the methyIxanthines by stimulating the mobilization and destruction of free fatty acids and inducing their active transport through the mitochrondral membrane. This is important because free fatty acids may saturate the system, leading to negative feedback of lipolysis. Additionally, this process releases ATP, which increases lipase activity, enhancing hydrolysis of triglycerides.[49]

Among the drugs which act on the connective tissue, the most studied are sillicium and Asiatic centella. Sillicium is a structural element of the connective tissue. It regulates and normalizes cellular metabolism and cellular division. Studies performed using fibroblast cultures have demonstrated that silanols (groups of hydrogen and sillicium compounds, similar to the hydrocarbides) provoke the formation of bridges between the hydroxylated amino acids of the elastic fibres and collagen fibres protecting them from non-enzymatic glycolysation and decreasing their degradation rate. Sillicum acts as a coenzyme during interstitial matrix macromolecule synthesis and reorganizes structural glycoproteins, as well as proteoglycans of the ground substance, by stimulating polar amino acid grouping and normalizing hydrophilic capacity. In the microcirculation, it modifies venous capillary and lymphatic permeability and, in the fatty tissue it stimulates cAMP synthesis as well as triglyceride hydrolysis, probably by activating adenyl cyclase in the cellular membrane.[1,5,49]

Asiatic centella extract has a vegetable origin; chemically, it consists of asiaticosideo (40%), madecassic acid (30%) and Asiatic acid (30%), triterpenic derivatives which act *in vitro* on fibroblasts, stimulating collagen and mucopolysaccharide synthesis.[52,53] A histological study using epidermic cell cultures has demonstrated stimulation of the keratinization process by asiaticosideo.[54] Both topically and systemically, an effect on the microcirculation has been observed. This effect includes increased lower limb perfusion, which has been

demonstrated through capillaroscopy in patients with chronic venous insufficiency[55] who were being treated for chronic venous ulcers.[56–59] Toxicity tests, as well as cutaneous hypersensitivity tests, have shown these compounds to be harmless when used either systemically or topically.[60]

Centella extract has been used systemically in several studies of GLD. Analysis of the results is made difficult by the varied methodologies, as well as the different and non-standardized evaluation criteria. Another confounding factor is the absence of controls in most of the studies.[37,61–66] A histopathological, double-blind study has evaluated adipocyte size (diameter average of 200 adipocytes) in the gluteofemoral region, compared with the deltoid region, in 35 patients. Twenty patients were treated with 60 mg of dry Asiatic centella extract orally once a day for 90 days, There was a significant reduction in the diameter of adipocytes in both regions in the patients who received centella compared to those who received placebo; this reduction was more apparent on the gluteofemoral region ($P < 0.001$). There was also a decrease in interadipocyte fibrosis.[67]

Drugs which act on the microcirculation include the ivy and Indian chestnut vegetable extracts, which are rich in saponines, ginkgo biloba and rutin, which contain bioflavonoids. These compounds decrease capillary hyperpermeability and increase venous tone by stimulation of proline hydroxylase and inhibition of prostaglandin PGE2.[68] They also decrease platelet aggregation, thereby inhibiting microthrombus formation. Experimental studies (using oscillometry, Doppler, haemodynamic methods and capillaroscopy) have demonstrated that ginkgo biloba extract is antiedematous (by decreasing capillary hyperpermeability) and improves venous return and arterial circulation.[69,70]

Pentoxifylline is a methylxanthine; it improves microcirculatory perfusion through its effect on haemorrheological factors, including erythrocyte shape, platelet aggregation and plasma fibrinogen concentration. It also has immunomodulatory activity.[71] It has been utilized for peripheral vascular disease treatment (chronic venous insufficiency, stasis ulcers) with significant benefit.[72–74] There are no reports of its systemic administration for GLD although it has been used transdermally together with other drugs, which makes evaluation of its effectiveness difficult.[23]

As suggested above, many of these drugs may be used topically as well as systemically. When using topical treatments, the concentration and pharmacological/pharmacokinetic characteristics of the active drugs must be considered, as well as the nature of the vehicle. The interaction of the drug with the vehicle and the skin, the way the drug is applied, and other biological and environmental factors may also affect the response to treatment.[75–77]

Because the stratum corneum is the main barrier to drug penetration,[78,79] formulations for topical use may include so called skin enhancers, substances which, when included in the formulation, significantly increase cutaneous penetration.[76,80] Skin enhancers can be common solvents (water, alcohol, methyl alkyl sulphoxide) or surfactants. They may also be phytosomes, phospholipid molecules which, when attached to the active drug, increase their liposolubility, or liposomes – lipid vesicles filled with active drugs.[4,81,82]

Intradermotherapy (mesotherapy), a therapeutic method in which the drug is administered directly into the dermis, was described by Pistor in 1958 and it has been used for treating GLD since 1964. It involves the infusion of a small amount of the 'active drug' directly to the affected site with 4-mm needles, bypassing the resistance of the epidermal barrier. The 'ideal' drug used must be hydrosoluble, isotonic, have an adequate pH, be physically and chemically stable, be well tolerated after dermal administration, and have low allergenic potential.[4,51]

As there is no data available concerning the pharmacokinetics (absorption, distribution, metabolism, elimination, systemic possible adverse events) and no clinical controlled studies with any drug with this kind of administration, the risks for the patient and the efficacy of this method are unknown.

The use of topical retinol to improve cellulite was proposed by Kligman *et al.*,[83] based on the capacity of all-trans-retinoic acid (tretinoin) to promote the synthesis of glycosaminoglycans in normal skin and increase the deposition of collagen in the photodamaged dermis. Hypothetically, these effects could lead to an increase of the thickness and firmness of the dermis, putting a 'cap' over the more mobile fat which can easily change its shape without any change in volume. The proposal of retinol instead of tretinoin was based on the better tolerability and the evidence that retinol is metabolized to retinoic acid in the skin. Twenty patients were included in an intra-individual controlled preliminary study. Retinol 0.3% or its vehicle was applied to opposite lateral thighs twice daily for 6 months and the patients were evaluated clinically by the investigator, and by laser Doppler velocimetry. Nineteen patients completed the study. In the instrumental evaluation the retinol-treated thigh showed better results than the vehicle-treated thigh (in spite of the large variance), in 12 patients the clinical improvement was higher with retinol than with vehicle and in seven patients there was no difference between the retinol side and the vehicle side. Despite the fact that there was a statistically significant difference in the retinol-treated thighs, the small number of patients included does not allow the extrapolation of results and more studies are required to confirm this treatment option.

Conclusion

GLD is a skin alteration of multifactorial aetiology. It is aesthetically undesirable, hence the untiring search for new therapies. A number of products for systemic and topical use have been developed. Most have little scientific basis. The absence of research in this area may be due to the lack of a standardized reproducible methodology to evaluate the

treatment response. The influence of other factors which may affect GLD (diet, physical exercise, weight loss) makes evaluation of the treatment response even more difficult.

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