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Original article

Localized fat or adiposity: therapeutic classification

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Abstract. White adipose tissue is essential for energy storage, endocrine communication, and insulin sensitivity. However, its distribution may present some alterations, as is the case of localized adiposity made up of normal adipose tissue, which is one of the conditions that represent the highest demand in aesthetic medicine. The most common causes for its development are an increased caloric intake and decreased energy demand due to a sedentary lifestyle. Localized adiposity is usually chronic and progressive; treatment therefore requires a substantial learning curve from a team of healthcare professionals. In addition, it can significantly impact the patient and lead to important psychological problems. The traditional classification of localized adiposity involves several measurements: a) waist circumference, measured at the midline level between the costal margin and the iliac crest; b) hip circumference, measured at the level of the greater trochanters of the femur. Based on these measurements and other considerations for diagnosing and classifying localized adiposity, we have developed an algorithm that includes the following criteria: i) body mass index; ii) adipose tissue location; iii) degree of alteration of the underlying tissues; iv) aesthetic impact on body harmony; v) level of emotional discomfort it causes the patient. This algorithm aims to help determine the best therapeutic approach for each patient. It identifies five types of localized adiposity, with three subtypes, depending on their location.

Key words: adipocyte, localized adiposity, fat distribution, leptin, lipogenesis

Introduction

Localized fat or adiposity (LA) refers to the accumulation of normal adipose tissue (AT) in defined anatomical areas, resulting in increased local volume and alteration of a person's body shape[1]. LA is one of the conditions that generates more demand in aesthetic medicine since it has a significant emotional impact on the patient and may lead to important psychological problems[2].

The most common -and yet insufficiently understood- causes for the development of this tissue are an increased caloric intake and decreased energy demand[3], alongside a genetic predisposition. Fat is usually concentrated in the belly, flanks, thighs, back, arms, and chest[1]. It is characterized by being resistant to strict diets and physical exercise regimes, regardless of the degree of obesity[4]. It may be accompanied by flaccidity, edematous fibrosclerotic panniculopathy, or cellulite, as well as by venous and lymphatic circulation and other alterations, as can be observed with AIDS.

The increase in AT results from adipocyte hypertrophy or hyperplasia. Adipocyte hypertrophy is caused by an increased cell volume. It is an adaptative response to the excess of nutrients which maintains the nutrient buffering capacity of AT and protects other tissues from lipotoxicity[5,6]. It is usually associated with being overweight, and mild obesity. Hyperplasia is an increase in the number of cells, and it is associated with genetic factors. It mainly develops in gluteal-femoral fat, although it can also be observed in child obesity or moderate or severe obesity[6].

Since the etiopathogenesis of LA is highly complex and poorly understood, its chronic evolution,

clinical management, and diagnosis are not related to the therapeutic approach or make it difficult to find one, frequently resulting in low patient and physician satisfaction. Traditional classifications of LA do not provide effective therapeutic solutions to address this condition. This article aims to outline a new classification method that allows for a more agile, effective, and satisfactory therapeutic approach, both for the patient, and the physician.

Adipose tissue types and characteristics

Historically, AT has been classified as white adipose tissue (WAT) and brown adipose tissue (BAT), both made up of adipocytes that can be visually distinguished by the color of the tissue[7]. WAT is essential for energy storage, endocrine communication, and insulin sensitivity, and it constitutes most of the volume of AT in humans. It is also responsible for the development of LA[7]. In WAT, adipocytes are white and larger (120 μm), generally spherical and contain a large single lipid droplet that pushes all other organelles, including the nucleus, to the cell's periphery. WAT adipocytes have a higher lipid storage capacity and can expand up to a diameter of almost 100 μm[8]. Their capacity to expand in number and size depends on the depot.

In terms of their origin, although white adipocytes of WAT have a mesenchymal origin in white fat, subcutaneous adipocytes have different developmental origins and metabolic properties compared to visceral adipocytes[9].

The first published citation mentioning AT dates back to 1837[10], and it was in the mid-1980s that the secretory functions of AT and the production of WAT adipocyte-specific proteins were first understood[11]. Although the functions of these secretory products lack in clarity, their discovery revealed adipocytes to be significant sources of protein products, including many endocrine hormones. Perhaps one of the most important of these discoveries was leptin[12], an adipocyte-derived hormone that acts not only as an afferent "adipostat" signal of fat mass to central brain centers in the regulation of body weight[12] but also has peripheral actions that impact glucose metabolism[13] and immune function[14].

Characteristics of White Adipose Tissue (WAT)

WAT is an example of the interaction between genetics and epigenetics, which is still poorly understood. Its pathology is usually chronic and progressive; thus, its treatment requires a significant learning curve from healthcare professionals.

The number and diversity of adipocytes increase with obesity and metabolic dysfunction. WAT can expand during adult life to accommodate a chronic excess caloric intake. This expansion is characterized by adipocytes that accumulate lipids and grow in size (hypertrophy) or number (hyperplasia or adipogenesis) or that increase in both ways (hypertrophy and hyperplasia). Besides adipocytes, WAT contains endothelial cells, blood cells, fibroblasts, pericytes, preadipocytes, macrophages, and several immune cell types[15].

A high caloric overload increases subcutaneous AT and leads to fat accumulation in ectopic tissues, such as the liver, skeletal muscle, and the heart, and visceral adipose tissue (VAT) depots, commonly known as "lipotoxicity"[16]. Excess ectopic lipid accumulation causes local inflammation and insulin resistance (IR)[17]. Adipocytes have a finite expansion and lipid storage capacity. Studies conducted in humans[18] suggest that the inability of adipocytes to store excess lipids in AT is a key feature that leads to metabolic dysfunctions[16]. Adipocyte number, size, and location depend on gender, age, genetics, hormonal factors, diet, and exercise.

White adipose tissue can develop in several locations. One can be superficial or areolar, giving way to superficial adipose tissue (SAT), accounting for ~80% of all AT, with a uniform body distribution higher in the hips, thighs, and belly area. This type of fat is where the condition known as cellulite or "orange skin" develops as a result of adipocyte lobules divided by vertical fibrous septa, usually associated with the hormonal effect on the shape of said fibrous septa. Another location the deep visceral area, where visceral adipose tissue (VAT) or steatometric tissue is found. This tissue accounts for about 20% of total AT and is separated from SAT by the infraumbilical fascia. This fat is comprised of horizontal lobules, which are difficult to move, with a larger number of insulin- and estrogen-sensitive lipogenic receptors and entail a higher metabolic risk (due to endocrine and paracrine factors), responding

to gender-differentiation patterns. It may also be located in the retroperitoneal area, where retroperitoneal adipose tissue (RPAT) is located along the dorsal abdominal wall, accounting for ~7% of total AT[19].

Adipocytes as energy reserves

Adipocytes store triacylglycerols (TAGs) under conditions of energy surplus and release fatty acids (FAs) to other tissues during fasting or high energy demand. For this reason, AT is essential to regulate systemic lipid metabolism and the nutritional and hormonal signals necessary to balance lipid storage and breakdown inner fat cells[7]. A critical balance between lipogenesis and lipolysis inside adipocytes is necessary to maintain whole-body insulin sensitivity and energy homeostasis.

Lipogenesis

Adipocytes accumulate lipids through two processes. The first one occurs under normal feeding conditions, when adipocytes take up circulating dietary lipids in the form of free fatty acids (FFAs) released from circulating TAGs through the action of lipoprotein lipase (LPL). Adipocytes also take up glucose, which is converted to glycerol, essential for the sequential esterification of FA and TAG formation. The second process by which adipocytes store lipids is de novo lipogenesis (DNL), which occurs inside adipocytes. DNL includes de novo synthesis of FAs from acetyl-coenzyme A (acetyl-CoA) and esterifying these FAs to a glycerol backbone that produces TAGs. DNL can occur in the fasting and fed states[20]. After food intake, especially a meal high in carbohydrates, excess glucose oxidation produces elevated levels of acetyl-CoA, which become a substrate to generate FAs.

Lipolysis

When metabolic fuels are low, or energy demand is high, such as during fasting, exercise, and exposure to cold temperatures, adipocytes mobilize and break down lipids from their TAG reserves through the catabolic process known as lipolysis, which supplies fuel to peripheral tissues[21]. It is a highly regulated biochemical process that generates glycerol and FFAs from TAGs through the action of lipases[22]. This process can occur in all tissues, although it is most prevalent in AT, where most TAGs are stored.

Adipocyte action in white adipose tissue for energy storage is summarized in Figure 1.

Endocrine properties of adipose tissue

Adipocytes and other AT cells secrete complex mediators, including exosomes, micro-RNA, lipids, inflammatory cytokines, and peptide hormones that act in paracrine and endocrine ways[23]. However, substantial progress has been made in studying three endocrine hormones produced in adipocytes and other AT cells, which regulate food intake, the reproductive

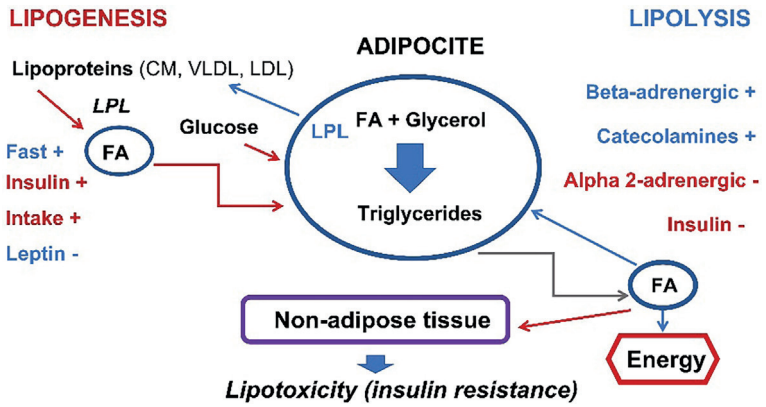

Figure 1. Adipocyte action in white adipose tissue for energy storage. Abbreviations: FA: fatty acids; LPL: lipoprotein lipase; CM: chylomicrons; VLDL: very low-density lipoproteins; LDL: low-density lipoprotein.

axis, insulin sensitivity, and the immune response. These hormones are leptin, adiponectin, and resistin. Androgens modulate the function of adipocytes, as well as the size of adipose tissue compartments[24].

Leptin

The first direct function observed from leptin was its effect on food intake[1,3,25]. It acts as a sensor of energy reserves, although in obesity, the negative feedback loop is disrupted due to the development of leptin resistance[26]. It has strong proatherogenic effects on multiple vascular cells, including macrophages, endothelial cells, and smooth muscle cells[27,28]. It has also been implicated in tumorigenesis[29]. Studies have shown that postmenopausal women with obesity have a 20-40% greater risk of developing breast cancer[30].

Adiponectin

Adiponectin is a hormone secreted by adipocytes, which has anti-hyperglycemic, anti-atherogenic, and anti-inflammatory effects[31], making it an attractive therapeutic target for the treatment of obesity and insulin resistance[32]. Receptors 1 and 2, called AdipoR1 and AdipoR2, have been identified[33]. Unlike leptin, adiponectin levels decrease with increasing fat mass[31] and are thus lower in obese individuals than in lean ones.

Resistin

Resistin is the most recently discovered hormone and, in AT, is mainly secreted by macrophages and, to a lesser extent, by adipocytes. Its main action, at elevated circulating levels, is to induce insulin resistance in patients who are obese or have type 2 diabetes[34,35]. It is involved in pro-inflammatory responses in atherosclerosis and acute pulmonary injury[34,36], and at high concentrations, it has been associated with other autoimmune inflammatory diseases[37–39].

Adipose tissue distribution patterns

As mentioned prior, androgens modulate the function of adipocytes, as well as the size of adipose tissue compartments. Body fat distribution patterns probably result from the balance between androgens and glucocorticoids active in the AT[24]. Its distribution is linked to health, regardless of gender, although the latter affects its location, as shown in Figure 2. In humans, fat deposition in the upper body area, mainly visceral but also subcutaneous abdominal depots, is linked to a higher risk of metabolic dysfunctions. In comparison, lower body adiposity in the subcutaneous gluteal and femoral regions is associated with a lower risk and might even have a protective effect[40].

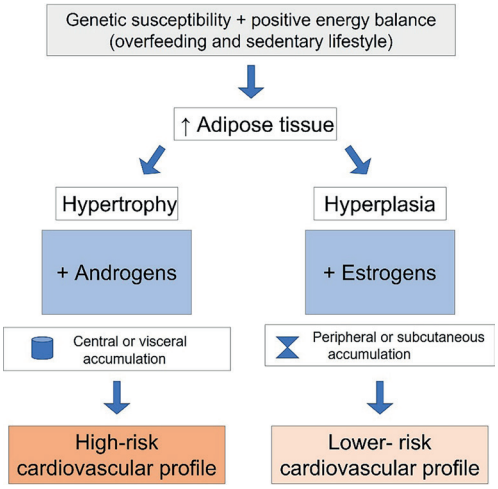

Figure 2. The influence of sex hormones on the distribution of body fat[41]

Abdominal depots are characterized by their quick fat uptake, mainly from the diet and a high lipid turnover stimulated by an adrenergic receptor activation[40]. Fat depots in the lower area of the body have a reduced lipid turnover, with fewer inflammatory signals, and can recruit additional adipocytes due to weight gain. Some studies suggest that functional differences between tissues in the upper and lower part of the body are controlled by development genes specific to the site under epigenetic control, such as HOXA6, HOXA5, HOXA3, IRX2 and TBX5 in SAT, and HOTAIR, SHOX2, and HOXC11 in the gluteal-femoral adipose tissue[42].

Gender differences

After puberty, women have around 10% more total fat than men, and the percentage increases with

age in both genders. Women have a lower percentage of VAT due to estrogens. However, as levels decrease with age, the amount of VAT in women increases. The highest concentration of SAT in women is in the gluteal-femoral area due to hyperplasia, and in the abdominal area, due to hypertrophy. In men, it is higher in the abdominal area. Furthermore, in men, the amount of SAT is lower than VAT in the abdominal region, resulting in a poorer metabolic profile. Women have a better metabolic profile than men regarding type 2 diabetes and atherosclerosis, although this difference disappears with age or when the waist/hip ratio is > 0.85. In addition, men have higher insulin sensitivity and higher post-uptake affinity of FFAs by SAT (gluteal-femoral). In women, exercise produces higher FFA oxidation, resulting in increased mobility, whereas, in men, it produces higher carbohydrate oxidation, which leads to increased stability[43]. In men, there is less inhibition of post-prandial lipolysis and higher direct uptake of FFAs towards VAT (abdominal).

Clinical diagnosis of LA

Diagnosis of LA is mainly clinical and should include at least the following parameters (Table 1): body mass index (BMI) (Table 2), body diameters, location of LA, assessing whether it is accompanied by other subcutaneous cellular tissue (SCT) alterations, such as cellulite, or muscle or skin flaccidity. The impact of said LA on body harmony and the patient's level of emotional discomfort should be assessed (Table 3). Other diagnostic and screening tests (insulin resistance and others) and ultrasound should also be considered, even though they are not included in the classification criteria.

Traditional classification

The traditional classification (Table 4) includes the following measurements: a) waist circumference, measured at the midline level between the coastal margin and the iliac crest. Values of 84 cm for women and

Table 1. Assessments for the new therapeutic classification proposed for the diagnosis and classification of localized adiposity.

Criterion	Assessment
Body mass index (BMI)	Based on SEEDO 2007 consensus (Table 2)
Location of adipose tissue	According to the traditional classification: • gynoid • central • upper
Degree of alteration of the tissues in the LA region	Presence of cellulite, skin or muscle flaccidity, or diastasis recti (abdominal region) • 0 no alteration • 1 mild • 2 moderate • 3 severe
Aesthetic impact on body shape	Since excess fat can be stored anywhere in the body, leading to highly localized aesthetic disharmony, independent from usual anthropometric measurements (waist, hip, arm, etc.) and the ratio between them, the aesthetic impact will be assessed by the physician, who will classify it into three degrees*: • low • medium • high
Emotional Discomfort	We propose the use of the AdipoQol scale (Table 3), based on the melasma-validated MelasQol scale, and adapting it to localized adiposity**.

* Even having an objective bias, we have not found a more objective assessment method in the literature, since the somatotype classification based on the Heath-Carter method could not be adapted effectively to this condition. ** We believe it to be perfectly adaptable, as it is an aesthetic problem that has similar emotional impact, and because it can be easily incorporated to the clinical practice.

Table 2. SEEDO criteria to define obesity in degrees according to body mass index (BMI) in adults[45].

Category	Limit values of BMI (kg/m^2)
Underweight	< 18.5
Normal weight	18.5 – 24.9
Overweight degree I	25.0 – 26.9
Overweight degree II (pre-obesity)	27.0 – 29.9
Obesity Class I	30.0 – 34.9
Obesity Class II	35.0 – 39.9
Obesity Class III (morbid)	40.0 – 49.9
Obesity Class IV (extreme)	≥ 50

Abbreviations: BMI: body mass index; kg: kilograms; m^2: square meter.

Table 3. Adipoqol emotional discomfort scale.

Adipoqol Questionnaire
Considering the unsightliness of your localized adipose tissue:
1. The presence of said adipose tissue ( )
2. Makes me feel frustrated ( )
3. Makes me feel ashamed ( )
4. Makes me feel depressed
5. Affects my relationships with others (friends, family, acquaintances)
6. Influences my desire to interact with other people (strangers)
7. Prevents me from showing affection to others
8. Makes me feel less vital
9. Makes me feel less productive
10. Is a condition that curtails my freedom (clothes, etc.)
Possible answers and score
a. It doesn't upset me at all (I never think about it): 1
b. It generally doesn't upset me: 2
c. It sometimes upsets me: 3
d. Neutral: 4
e. Sometimes upset: 5
f. Upset most of the time: 6
g. Upset all the time (I constantly think about it): 7
Emotional Discomfort Score:
0-14: low; 14-35: medium; 35-70: high

Table 4. Traditional classification of localized adiposity, based on waist circumference and hip circumference measurements, and on waist/hip ratio.

Traditional Classification of Localized Adiposity
1. Lower 1.a. Gynoid or gluteal-femoral Ccc <1 men; Ccc<0.9 women 1.b. Lower extremities: "Egyptian column" or lipedema
2. Central or abdominal: Ccc>1 men; Ccc>0.9 women
3. Upper: trunk, back and upper extremities (android)

Abbreviations: Ccc: waist/hip ratio.

94 cm for men are considered normal; b) Hip circumference, measured at the level of the greater trochanters of the femur.

New therapeutic classification proposed

Based on the previous measurements and other considerations for diagnosing and classifying LA, we have developed an algorithm (Table 5) to detect and classify LA, which includes the following five criteria: i) body mass index; ii) adipose tissue location; iii) degree of alteration of the underlying tissues; iv) aesthetic impact on body harmony; v) level of emotional discomfort it causes the patient. Based on these assessments, five types are developed: Type I or pure LA (Figure 3), Type II LA (Figure 4), Type III LA (Figure 5), Type IV LA (Figure 6), and Type V LA (Figure 7). The the aim for proposing this new classification was to develop a tool that would allow us to readily identify the best therapeutic approach to LA in each patient.

Differential diagnosis

One differential diagnosis for LA is lipomas, whose assessment should be conducted using ultrasound when they are superficial, and nuclear magnetic resonance (NMR), or computed axial tomography (CAT) when deep. Other diagnoses to be ruled out are soft tissue tumors, muscle hernias, large lipodystrophies, or diastasis recti, which should be assessed with exploratory exams or ultrasound. Cellulite should not affect adipose tissue volume. Flaccidity is excess

Table 5. New proposal for the classification of localized adiposity.

	BMI	Location	Degree of tissue alteration	Aesthetic impact	Emotional impact
Type I or pure	<28	Any	0-1	Medium-high	Medium-high
Type II	<28	IIa, IIb, IIc	1-2	Medium-high	Medium-high
Type III	<28	IIIa, IIIb, IIIc	2-3	Medium-high	Medium-high
Type IV	<30	IVa, IVb, IVc	2-3	Medium-high	Low-medium
Type V	>30	Va, Vb, Vc	2-3	Low-medium	Low-medium

Abbreviations: BMI: body mass index; a: lower; b: central; c: upper.

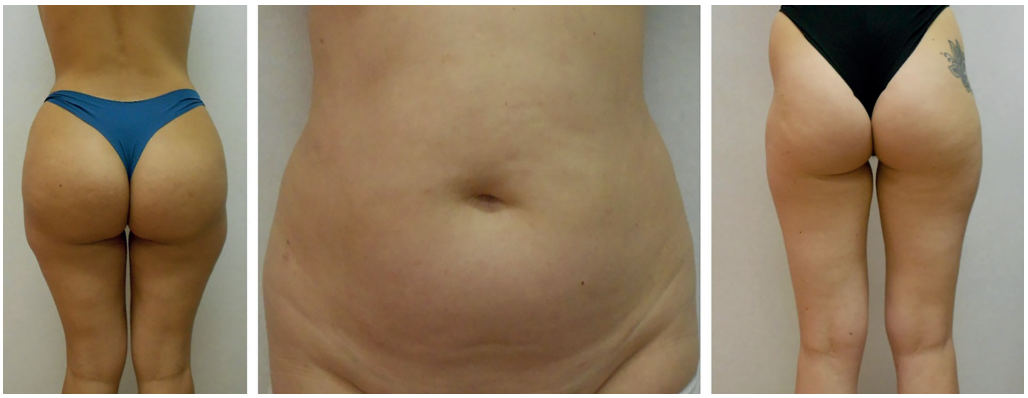

Figure 3. Examples of type I localized adiposity: BMI<28, any location, with no adjacent tissue local alterations, medium or high impact, medium or high discomfort.

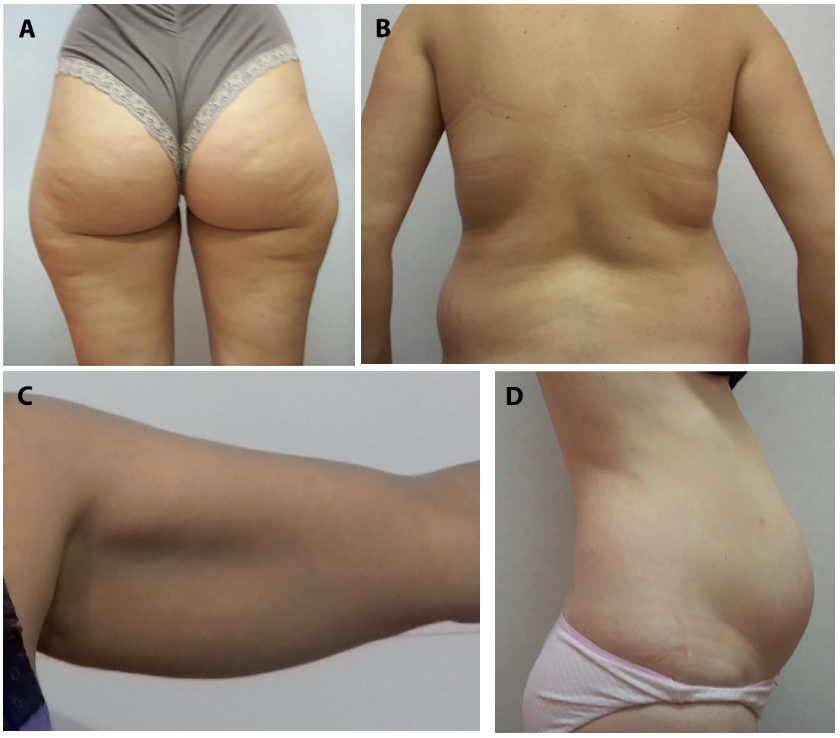

Figure 4. Examples of type II localized adiposity (LA): BMI<28, type I-II cellulite and/or mild flaccidity, medium or high impact, medium or high discomfort (a. Type IIa LA: lower; b. Type IIb LA: central, with/without diastasis recti; c. Type IIc LA: upper).

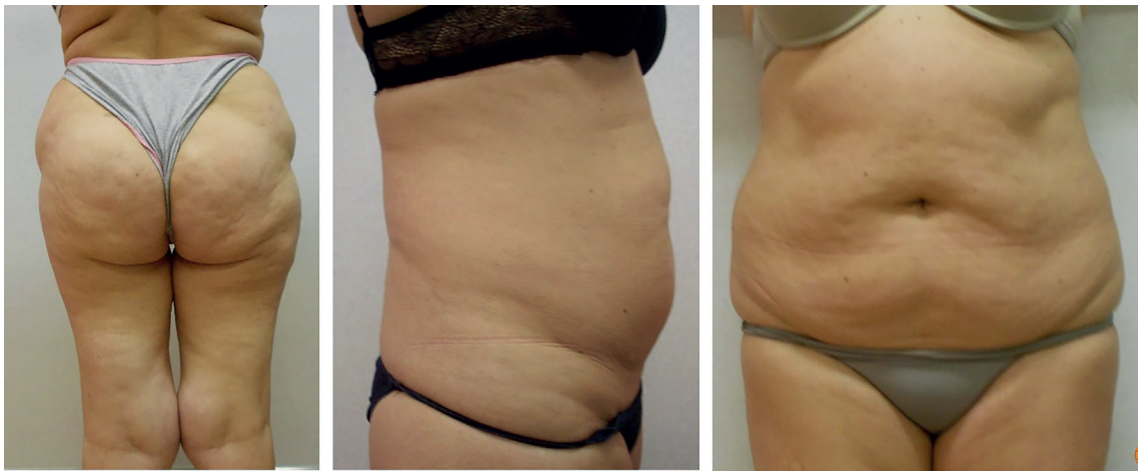

Figure 5. Examples of type III localized adiposity: BMI<28, type II-III cellulite and/or significant flaccidity; medium or high impact, low or medium discomfort.

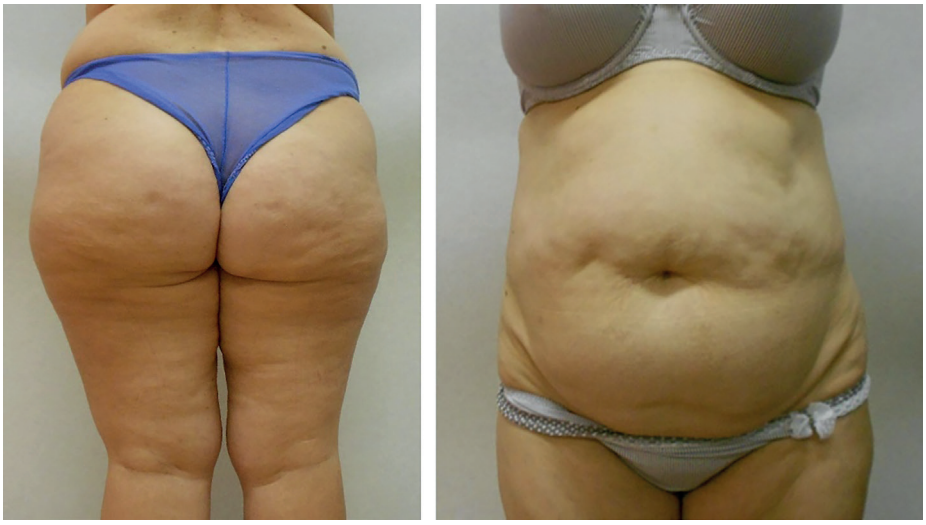

Figure 6. Examples of type IV localized adiposity: BMI 28-32, type II-III cellulite and/or significant flaccidity; medium or high impact, low or medium discomfort.

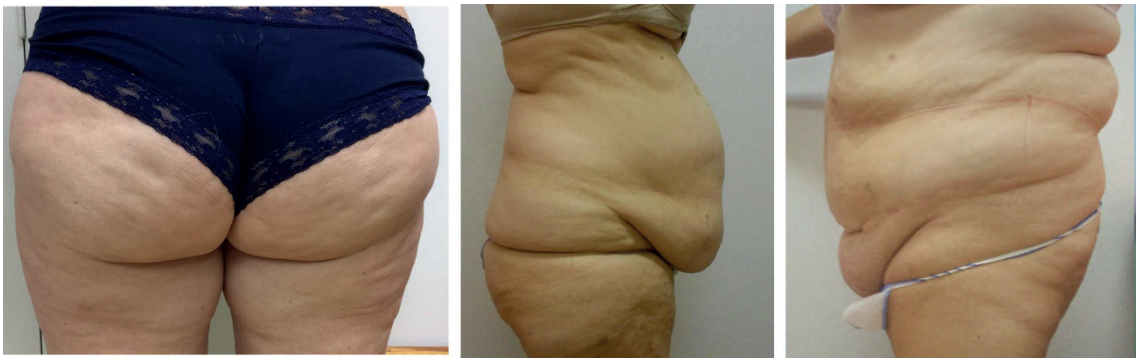

Figure 7. Examples of type V localized adiposity: BMI> 32, type II-III cellulite and/or significant flaccidity; low or medium impact, low or medium discomfort.

skin with a normal SCT. To diagnose obesity, especially of the gynoid type, the patient's BMI should be considered. Lipedema is chronic and hereditary and especially affects women; it develops in the fat tissue of the lower extremities, is bilateral, and does not occur on feet. Lymphedema is an organic lymphatic system condition characterized by stasis and cutaneous affectation (unilateral or otherwise) and does not spare the feet[44].

Treatment of LA

Any treatment for LA should include recommendations for the patient regarding adopting a healthy lifestyle (diet and exercise) to prevent metabolic problems and improve aesthetic results. There are different treatments for LA, depending on the mechanism of action. A distinction can be made between lipolytic treatments (which cause triacylglycerols and fatty acids breakdown without affecting the number of adipocytes) and adipocitolytic treatments (which cause rupture of the adipocyte membrane, extravasation of its content to the adjacent tissue, and its death, thus reducing the number of adipocytes). Lipolytic treatments include a) chemical treatments like mesotherapy and carboxytherapy; b) non-invasive physical treatments like carboxytherapy, endermologie, high intensity focused ultrasound (HIFU), radiofrequency (RF), microwave or laser lipolysis. In terms of adipocitolytic treatments, we can differentiate between invasive procedures (which remove adipocytes), the most relevant being classical or assisted liposuction (laser, ultrasound, RF) and dermolipectomy, and non-invasive treatments (which do not remove the adipocyte, but release its fatty acids to the surrounding tissue). These include intralipotherapy or chemical adipocyte lysis, lipoclasia, and cryolipolysis. Both lipolytic and adipocitolytic treatments, which do not entail the removal of adipocytes, require establishing subsequent therapeutic continuity guidelines with the patient (exercise, diet) to ensure that the released TGs or FAs are not used again. In the case of treatments involving adipocyte removal, patients should be informed that an excess caloric intake would result in fat storage in VAT or in ectopic tissues, which would lead to a poorer metabolic profile.

Table 6. Therapeutic approach proposed according to the new LA classification.

LA Classification	Proposed Treatment
Type I or pure	Adipocitolytic
Type II	Adipocitolytic
Type III a and c	Adipocitolytic and lipolytic (previously improving tissue alteration)
Type III b	Dermolipectomy
Type IV	Diet and lipolytic agents
Type V	Diet and lipolytic agents

Treatments based on LA Type

For the treatment of Type I or pure LA (Figure 3) and type II LA (Figure 4), invasive or non-invasive adipocitolytic treatments could be used. For treating Type III LA (Figure 5), lipolytic and adipocitolytic procedures may be used, always considering the level of tissue alteration, or improving them before resorting to interventionist techniques. In the case of Type IIIb LA, dermolipectomy would be highly effective. In the case of Type IV LA (Figure 6) and type V LA (Figure 7), physical or chemical lipolytic techniques should be initiated and combined with dietary guidelines. For Type IV LA (Figure 6), depending on the response to previous treatments, liposuction or dermolipectomy can be indicated based on its location. In the case of Type IVb LA, unless the patient manages to decrease their BMI to less than 30, a surgical treatment option should be considered, depending on the impact and discomfort of LA for the patient. This is summarized in Table 6.

Conclusions

Adipose tissue is a highly biochemically active organ that acts as a caloric reservoir and is a thermoregulator and an important hormonal regulator. Its highly complex physiopathology makes it difficult to study and develop treatments targeted to its function. Etiologies of localized adiposity are multicausal and have multiorgan effects, despite the prevailing view that it is only an aesthetic concern. Treatment success

is based on an accurate diagnosis and classification to ensure that the approach adopted does not lead to metabolic problems in the future.

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Conflict of Interest: The author has no conflicts of interest or financial ties to disclose.

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