endocrines

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Review

Lipedema: From Women's Hormonal Changes to Nutritional Intervention

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Abstract: Lipedema is a chronic disease of the subcutaneous adipose tissue that mostly affects women. The etiopathogenesis of the disease is still poorly understood. Lipedema typically develops after major hormonal changes, such as puberty, pregnancy, and menopause. Alongside genetic susceptibility, the pathophysiological mechanism involving hormonal changes is mostly linked to aberrantly expressed estrogen receptors in adipose tissue. Lipedema has no known cure, and current therapies aim primarily to reduce symptoms, avoid complications, and slow the disease progression. Achieving or maintaining a healthy body composition, preserving or regaining mobility and functionality, preventing the progression of disease, and reducing pain and other symptoms are all possible outcomes of proper nutrition and weight management. Since nutrition may provide a long-term solution to control almost constant inflammation, it should be a major part of lipedema treatment. Despite the lack of a specific, scientifically supported diet for lipedema patients, several dietary approaches have been suggested. In this comprehensive narrative review, supported by published revisions and peer-reviewed studies following scrutiny of digital medical databases, the current state of knowledge and theories regarding the hormonal etiopathogenesis of lipedema are presented, as well as the role of nutritional intervention in reducing its symptoms and progression.

Keywords: nutrition; anti-inflammatory diets; lipedema; estrogen; adipose tissue

Academic Editor: Alessandro Genazzani

Received: 17 February 2025
Revised: 5 May 2025
Accepted: 13 May 2025
Published: 19 May 2025

Citation: Tomada, I. Lipedema: From Women's Hormonal Changes to Nutritional Intervention. *Endocrines* **2025**, *6*, 24. https://doi.org/10.3390/endocrines6020024

1. Introduction

Lipedema is a chronic, painful disease of adipose tissue (AT) that primarily affects women and significantly weakens their quality of life (QoL) [1,2]. Although the exact etiology of lipedema is largely unknown, a complex interaction of factors, including genetic and hormonal influences, is probably involved [3]. The hallmark of this disease is a disproportionate symmetrical accumulation of painful fat that affects the upper and/or lower leg (the so-called pillar-shaped leg), or upper arm and/or forearm uniformly, or just the upper or lower leg. Head, neck, trunk, feet, or hands are not affected [1,3,4]. Common characteristics of lipedema include the change in diameter with respect to the nearby healthy region and the painful increase in AT above and/or below the knees, in the triceps region of the upper arm, and on the forearms [1].

The diagnosis of lipedema is made clinically based on the patient's medical history and familial history, visual inspection, and physical examination. Medical professionals make the diagnosis using a set of precise criteria that characterize the time of change in fat distribution, diet resistance, and the regionalization of fat accumulation and pain. These criteria include a bilateral, symmetrical distribution of subcutaneous AT (SAT), primarily

in the legs (but not the hands or feet), a negative Stemmer's sign (i.e., the skin fold between the second and third toe can be pinched and lifted), and minimal pitting edema [5–8]. Additionally, bruising following minor trauma (hematoma formation), pressure, tension, heaviness, pain on palpation, and spontaneous pain are very common complaints from patients [1]. Psychological distress, lack of body acceptance and self-acceptance, and weight gain and obesity are also frequent accompanying manifestations that can exacerbate pain [1]. Through inflammatory mediators, psychological symptoms can exacerbate the pain, which, in turn, increases mental stress, creating a vicious cycle [9].

Different classification systems are used to describe fat distribution in lipedema. The World Health Organization's International Classification of Functioning, Disability, and Health (ICF) system was an early approach to classifying lipedema based on patient functionality and body composition [10]. Yet, the type (I–V) and stage (1–4) classification systems are the most widely accepted and recognized by lipedema organizations (Table 1) [11]. Type describes the distribution of symmetrical AT deposition, while stage indicates changes in the shape, consistency, texture, and level of swelling [5–8,11].

Table 1. Characterization of lipedema type and stages.

Types of Lipedema (According to the Area Where Adipose Tissue Is Accumulated)	
1	Fat accumulates in the pelvis, buttocks, and hip
2	Fat spreads from the buttocks to the knees (with formation of folds of fat around the inner side of the knee)
3	Fat extends to the hips and ankles (feet are not affected)
4 a–c	Fat is increased in the upper arms sparing the wrist (a: upper arm; b: lower arm; c: whole arm)
5	Fat accumulates in the lower legs (knees to ankles)
Stages of Lipedema (According to the Progression of Fat Accumulation and Changes to Skin and Lymphatic System)	
1	Normal skin surface with enlarged subcutaneous tissue; fat tissue is soft with noticeable small nodules
2	Uneven skin with enlarged subcutaneous tissue; larger fat nodules present
3	Large extrusions of tissue cause deformations, especially on the thighs and around the knees; fat nodules of varying sizes are palpable
4	Development of lipolymphedema with large overhangs of tissue

Lipedema is frequently misdiagnosed and mistreated because of its clinical presentation, which is particularly similar to that of obesity (Table 2 summarizes some characteristics that are helpful in the differential diagnosis of these two conditions) [7]. However, lipedema is neither caused by obesity nor is a cause of obesity [1]. Lipedema remains clinically stable with weight maintenance, but progressive weight gain is associated with increased limb volume and disease progression. In addition to weight gain, hormonal factors may be implicated in the development of lipedema, increasing the volume of the affected areas and pain symptoms [1].

Lipedema affects 11–19% of women worldwide, an estimated prevalence certainly underestimated [6,7,12–16]. The condition has been reported in familiar clusters (up to 60% of patients have a first-degree relative with lipedema), suggesting that the inheritance pattern is either X-linked dominant or autosomal dominant with incomplete penetrance [11,17–19]. Although the precise genetic determinants of lipedema remain unidentified, a recent review compiles a list of genes that have been linked to lipedema, making them prime candidates for future research [18].

Lipedema mostly develops or worsens in periods of hormone changes, such as puberty, pregnancy, menopause, or even when using oral contraceptives. This suggests that estrogen and estrogen signaling contribute to the pathogenesis of lipedema by directly impacting

adipocytes and immune cells and/or indirectly affecting brain control centers [6,7,12–15]. Despite the autosomal dominant inheritance, it has been also proposed that lipedema is caused by a polygenically mediated alteration in the distribution pattern of alpha- and beta-estrogen receptors (ERα, ERβ). It has been observed that there is a reduction in ERα expression and an increase in ERβ expression in the white AT of affected areas [13].

Table 2. Differential diagnosis of lipedema and obesity (adapted from van Esch-Smeenge et al., 2017).

Characteristics	Lipedema	Obesity
Gender	Female	Male and Female
Onset	Puberty Pregnancy Menopause	Any time over life span
Causal effect of diet	None	Present
Effect of legs elevation on symptoms	Minimal	Ineffective
Bilateral	Always	Always (android or gynoid)
Affected areas	Lower limbs and arms	Whole body
Retromalleolar fat pad	Present	Absent
Tissue consistency upon palpation	Soft-firm	Soft
Easy bruising of affected skin areas	Very common	Absent
Tenderness of affected skin areas	Very common	Absent
Stemmer's sign	Negative	Negative
Pain/Painful skin sensitivity to touch or pressure	Yes	No

In recent years, both medical professionals and the public have become more aware of lipedema. The growing visibility of the condition is largely attributable to the expanded dissemination of information via digital platforms and the increasing recognition it has garnered within medical and scientific communities. Although a genetic predisposition has been established, and hormonal, environmental, and epigenetic factors are known to play a significant role, lipedema is a chronic and likely progressive condition. Early identification of the factors that trigger and perpetuate the disease is essential to improving outcomes and mitigating its impact on patients' QoL.

In this comprehensive narrative review, the current state of knowledge and theories regarding the hormonal etiology and pathogenesis of lipedema are presented, as well as the role of nutritional intervention in reducing its symptoms and progression. The main goal is to increase the awareness of healthcare professionals of early diagnosis and treatment.

2. Methodology

A comprehensive literature search was developed for publications addressing lipedema etiology and pathophysiology, and its management through nutritional interventions and diets, was conducted in December 2024 and January 2025. The search was conducted across multiple databases, including MEDLINE (via PubMed), Web of Science, Scopus, and Cochrane Library, without date restriction, using the following search terms: "lipedema" AND ("female hormones" OR "estrogens" OR "nutritional intervention" OR "diet" OR "inflammation").

Reviews, systematic reviews, meta-analysis, and clinical trials published in English, Spanish, or Portuguese were initially screened by title and then by abstract, and those that were pertinent to the theme were accessed in full for assessment and inclusion. Reference

lists of all relevant publications were examined and used to identify additional articles for inclusion. Duplicated studies, as well as studies performed in animal models were excluded. More than 500 articles were identified, of which 93 articles were included in this review.

3. Estrogens, Inflammation, and Lipedema

3.1. Reproductive Milestones

In women, it seems to be hormones, rather than genetics, that determine how the body modifies its fat distribution over the course of its life. The physiological hormonal changes that occur in women from puberty to menopause, influenced by variations in follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) and their effects on the regulation of both gonadal and extra-gonadal steroidogenesis, affect how fat is distributed throughout the body and can substantially contribute to both the onset and clinical course of lipedema [20].

Estrogens have a strong impact on body fat distribution, highlighting their significance in the pathophysiology of lipedema [20]. In fact, evidence shows that estrogen specifically facilitates AT accumulation in the lower body depots, including the hips, thighs, and buttocks [21,22], which are common areas of excessive fat deposition in the majority of lipedema types.

In puberty, the onset of reproductive activity, characterized by cyclical elevations in estradiol and progesterone, determined the distribution of fat, particularly SAT, with a gynoid predominance, notably in the gluteofemoral region, the anatomical area most frequently impacted by lipedema. Since most of women with lipedema report that their symptoms started during or after puberty, this stage may be a significant turning point in the history of the disease [20]. The impact of reproductive hormones is further highlighted by studies that support the notion that lipedema can emerge or progress during pregnancy. Estrogen and progesterone levels significantly rise during pregnancy, making hormonal changes even more noticeable than during puberty. The preferential storage pattern of gluteofemoral fat becomes amplified with increased fat storage and lipolysis resistance [23]. The physiological decrease in insulin sensitivity observed in pregnancy, particularly from the second trimester onward, also promotes fat deposition and inhibits lipolysis [23,24]. Prolactin, a hormone produced by lactotrophs in the anterior pituitary gland, also plays a role during pregnancy and lactation. Interestingly, the development of lipedema during pregnancy and lactation may be partially explained by the increase in prolactin receptor expression in AT, which controls adipogenesis and inhibits lipolysis [23]. Lastly, the production of estrogen and progesterone gradually declines during the menopausal transition and menopause, while FSH and LH levels rise. The distribution of body fat and the function of AT are both impacted by this hormonal shift. Once the ovaries stop performing this function, AT undergoes changes to take over steroidogenesis, which may influence the development of lipedema. Although lipedema is most frequently diagnosed in women of reproductive age, around 20% of cases are identified during menopause [25]. Furthermore, approximately 67% of women with lipedema experience symptom exacerbation upon the onset of menopause, underscoring the critical need to elucidate the role of extra-gonadal steroidogenesis in modulating the pathophysiology and clinical trajectory of the disease during this endocrinological transition [20,25].

3.2. Estrogens, Estrogen Receptors, and Adipose Tissue

Estrogens are steroid hormones with pleiotropic effects, exerting regulatory functions across multiple organs throughout the body. In AT, estrogens promote adipogenesis (differentiation of pre-adipocytes into mature adipocytes), regulate lipogenesis (storage of fatty

acids), and influence body fat distribution [26,27]. While physiological levels of estrogen promote hyperplastic expansion of SAT, reduced estrogen levels favor hypertrophic growth of metabolically detrimental visceral AT [27].

Estrogens facilitate energy storage in part by enhancing insulin secretion, increasing insulin sensitivity in target tissues, and possibly preventing fatty acid oxidation. Along with its many other intricate effects, insulin facilitates the storage of metabolic fuels and suppresses the lipolysis of stored triglycerides [28]. Therefore, the physiological sensing of negative energy balance brought on by elevated insulin levels may increase appetite and food intake, ultimately resulting in weight gain.

The human body synthesizes estrogens in three distinct endogenous forms: estrone, estradiol, and estriol. Estradiol, the main product of estrogen synthesis and the one that has been extensively studied, is essential for the functioning of the reproductive phase and a wide range of chronic illnesses. Estrogens exert their function through the ERα and ERβ, and the expression of both receptors varies with age and body fat mass. For instance, the expression of both is noticeably elevated on SAT of pre-menopausal women [12,25]. In contrast to their normal-weight counterparts, post-menopausal women and clinically obese women treated with estradiol have lower levels of ERα expression on SAT [29,30]; whereas ERβ, which serves an antagonistic role on ERα-mediated gene expression, is highly expressed in post-menopausal women [26]. It is interesting to note that ERs content is different in abdominal than gluteal SAT of overweight-to-obese pre-menopausal women [31]. As previously mentioned, fat accumulates in the lower extremities of lipedema patients, supporting the hypothesis that ERs are involved in disease development. The contribution of estrogenic activity to site-specific adipose deposition in the context of lipedema is supported by the noteworthy finding that acute estrogen administration to post-menopausal women lowers basal lipolysis on SAT, especially in the proximal thigh area [32]. Lastly, the third ER, the G protein-coupled ER (GPER), has several significant effects, including the control of body weight, inflammation, insulin sensitivity, and metabolic dysfunction, even though it is expressed at lower concentrations on the adipocyte membrane [32]. Even though the exact mechanisms by which estrogens affect GPER are still unclear, analyzing estrogen–ER signaling pathways could provide insight into their involvement in lipedema development.

Preadipocytes express ERα, supporting the involvement of estrogen in adipogenesis independent of the antagonistic mechanisms of ERα and ERβ [33]. Given that regionalized AT deposition is one of the main features of lipedema, the distribution of preadipocytes and adipocytes as well as the expression of ERs on differentiated adipocytes may contribute to the pathophysiology of this condition. Activation of ERα, ERβ, and GPER on adipocytes initiates intranuclear signaling that can either up- or downregulate the expression and activity of key regulatory proteins, such as leptin and lipoprotein lipase (LPL), thereby influencing AT homeostasis [28]. Estrogen contributes to the regulation of body weight and the balance between lipogenesis and lipolysis, in part through this modulation of protein expression.

The dysregulated AT observed in lipedema may be related to ERα and ERβ. There are two possible mechanisms for this dysregulation. Compared to adipocytes without lipedema, those in this region exhibit a higher ERα–ERβ ratio [14]. As reviewed by Katzer and colleagues [14], there are several consequences of this imbalance, including an increased influx of free fatty acids into adipocytes for triacylglycerol synthesis driven by elevated LPL activity, and a reduction in lipolysis mediated by ERα-induced upregulation of the anti-lipolytic α-adrenergic receptor. Additionally, in lipedema, adipocytes from the affected areas may produce more steroidogenic enzymes; paracrine signaling would occur among these adipocytes, activating ERα [14]. Taking together, these effects would raise the

regionalized aberrant lipid deposition in adipocytes, leading to an increase in AT mass and enhancing the pathological features typical of lipedema.

Any changes in estrogen signaling or the absence of ER lead to SAT accumulation, a pattern also observed in individuals with lipedema [12,29,34]. Yi et al. [35] provided evidence supporting the hypothesis that lipedema is hormonally mediated, demonstrating that estrogen modulates the expression of leptin, a hormone that controls hunger and body weight. According to Szél et al. [13], this may be the reason why lipedema patients have difficulty losing weight with diet and exercise, and for their ongoing weight gain. Nevertheless, despite the underlying mechanisms remaining incompletely understood, leptin levels in individuals with lipedema tend to remain within normal ranges, contrasting with the hyperleptinemia generally observed in obesity [36,37].

AT is a vital organ that can produce and metabolize steroid hormones in addition to being an energy storage site [20]. Adipocytes express enzymes involved in the synthesis of sex steroids from precursor molecules (such as cholesterol, the primary substrate in the steroidogenic pathway leading to sex steroid hormones production, including estrogens), contributing to female hormone regulation without requiring systemic production in the ovaries or adrenal glands. The capacity of AT to produce sex steroids locally, impacts numerous physiological processes, including the menstrual cycle, fertility, body composition, and women's metabolic health. However, in lipidemic AT, modifications in the local expression and activity of steroidogenic enzymes could play a critical role in disease progression. For instance, a reduction in healthy fat storage capacity due to impaired estrogen production in lipidemic adipocytes may cause pathological fat accumulation and the hypertrophy of pre-existing adipocytes [27].

Aromatase is an enzyme expressed by adipocytes that convert androgens to estrogen. Chronic low-level inflammation of AT, which is frequently seen in lipedema [35,38,39], can have a detrimental effect on estrogen metabolism, since the most common increased pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6, downregulate aromatase expression, leading to a reduction in local estrogen production [35]. This mechanism may play a role in disrupting hormonal homeostasis and contributing to lipedema progression by worsening the abnormal fat accumulation (hypertrophy), increasing insulin resistance and exacerbating local inflammation [35,38,40]. In turn, inflammation promotes the recruitment and infiltration of immune cells around adipocytes, particularly macrophages, raising inflammatory cytokines production and perpetuating inflammation and metabolic dysfunction [41]. Concerning macrophage infiltration, it is important to note that gene expression analysis of lipedema biopsies reveal an increased macrophage polarization towards an M2-like (anti-inflammatory) phenotype [37,42]. These macrophages, in opposition to type M1, synthetize IL-10 and transforming growth factor-β (TGFβ), which help to resolve inflammation and prevent excessive immune responses. In the early stages of the disease, anti-inflammatory M2-like macrophages, as evidenced by overexpression of CD163, predominate. However, this predominance is progressively lost in more advanced stages, suggesting a transition toward a pro-inflammatory macrophage phenotype [37,38,42]. The presence of M2-like macrophages distinctly differentiates lipedema from primary obesity and may play a pivotal role in the pathophysiology and symptomatology of lipedema across various stages [38,42]. Finally, it is important to emphasize that CD163-expressing M2 macrophages have been regarded as the principal mediators of lipid accumulation in lipedema [42].

3.3. Estrogens and Inflammation

Estrogen also regulates the immune system through ER-dependent and independent pathways [43]. These effects can be either positive or negative, depending on a variety

of factors, including estrogen levels, ERs expression, cell types, and environment [44]. Lipedema AT is characterized by adipocyte hypertrophy, increased activation of immune cells, and the rearrangement of the extracellular matrix [39]. Several studies have shown that when estrogen levels fall, as in women undergoing menopause or oophorectomy, the expression of pro-inflammatory cytokines, such as IL-6, IL1-β, and TNF-α, increases [45]. Women with lipedema may experience heightened discomfort and inflammation during menopause. In fact, the decline in hormone levels, particularly estrogen, can influence the inflammatory response in AT and alter fat distribution, worsening lipedema symptoms. Additionally, insulin resistance and metabolic shifts associated with menopause may further contribute to the exacerbation of fat accumulation and inflammatory processes within the affected tissues, potentially accelerating the progression of the condition [20]. On the other hand, suppressed immune responses have been observed in pregnant women and those taking exogenous estrogens [39]. Therefore, as estrogen levels fluctuate throughout the lifetime of lipedema patients, inflammatory signals in the tissue may also vary.

The influence of the inflammation found in this diseased AT can be challenging to understand, as it is currently unknown if it is the inflamed AT that generates more local estrogen or if it is the local estrogenic changes that generate more inflammation. Indeed, the relationship between estrogen and inflammation is extremely complex and depends on the type of inflammation stimulus, cell type, reproductive status (pregnancy, pre- and post-menopause), total estrogen load (total, serum and tissue estrogen concentrations), ER expression, local estrogen metabolism, estrogen effects on the hypothalamic–pituitary–adrenal axis and on the peripheral nervous system, and sympathetic activation [46].

It is crucial to remember that inflammation can be seen as both an adaptation to continuous, possibly chronic painful stimuli, and a response to stressful stimuli. It is interesting to note that at present, there are no clear and systematic methods for reporting this type of inflammation, in which classical markers often remain unchanged [47]. In effect, unlike obesity, individuals with lipedema typically present normal levels of adipokines (e.g., adiponectin and leptin) and C-reactive protein (CRP) [48]. However, a recent study by Patton et al. [25] involving 360 women with lipedema—both obese and non-obese—found that CRP levels were significantly elevated in more advanced clinical stages, even after adjusting for age and BMI. Moreover, in participants with obesity, CRP levels increased progressively across higher BMI categories. Additional studies are required to gain a deeper understanding of the mechanisms behind these findings.

3.4. The Role of "Leaky Gut"

The loss of selective intestinal permeability, called "leaky gut", is frequently caused by dysbiosis or other intestinal barrier disorders. This condition generates chronic low-grade inflammation, due, in part, to the translocation of LPS (lipopolysaccharides), which are components of the outer membrane of Gram-negative bacteria, from the intestine into the systemic circulation [49,50]. When LPS circulates through the bloodstream, it also reaches adipocytes, which then produce pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, that alter adipocyte functions and cause a significant local inflammatory response [49,51]. Sustained upregulation of these inflammatory mediators perpetuates a chronic, subclinical inflammatory state, possibly a major pathophysiological mechanism implicated in lipedema [49]. This chronic inflammation may aggravate lipedema by interfering with normal AT metabolism.

Inflamed adipocytes are implicated not only in the onset of insulin resistance, but also in the perturbation of endocrine homeostasis, with a particular emphasis on the dysregulation of local estrogen metabolism. The expression and activity of aromatase can be adversely affected by LPS-induced chronic inflammation [34]. Hormonal imbalance

resulting from altered estrogen production within AT may exacerbate fat accumulation, promote an environment favorable to adipocyte hypertrophy, and aggravate AT fibrosis. Fibrosis can hinder lymphatic drainage, aggravate edema, and cause additional pain and discomfort [20]. The fibrotic component is likely responsible for the disproportionate volumetric reduction observed in the affected limbs, even following significant weight loss achieved through nutritional interventions, physical exercise, or bariatric surgery [52].

The gut microbiota plays a pivotal role in this process. Alterations in microbiome composition, driven by diet, antibiotic exposure, or other factors, can modulate LPS production and compromise intestinal barrier integrity. Probiotics, prebiotics, exercise, and healthy diet are examples of therapeutic strategies that have been shown to reduce LPS translocation and systemic inflammation aiming to restore the intestinal barrier [53]. Although this is a promising area of research, there is currently limited direct scientific evidence connecting intestinal permeability to lipedema.

4. Nutrition and Nutritional Supplements

Lifestyle changes, including diet and exercise, are crucial to improving the QoL of lipedema patients [16]. Dietary modifications play an important role in weight management and control for women with lipedema. Although weight loss programs demonstrate limited efficacy in reducing abnormal fat distribution or lipedema-associated AT (weight loss does not result in fat reduction in the affected areas and may even further accentuate the disproportion between the upper and lower body), adequate nutrition remains essential for enhancing patients' sense of autonomy, mitigating the risk of obesity-related comorbidities and promoting overall health and wellbeing [3].

4.1. Body Composition and Weight Management

Obesity increases the risk of lipedema, and conversely, being overweight exacerbates lipedema symptoms [16,19]. Although lipedema is frequently linked to obesity, it can also occur in normal weight women, particularly in younger women [47].

Lipedema is resistant to conventional diet and exercise interventions [7,54]. In fact, among patients diagnosed with lipedema and presenting with an elevated body mass index (BMI), the obesity component will respond to dietary changes, but the disproportionate leg shapes will not; the lower body maintains its shape from the waist to the ankles, while the upper body mass decreases [7,17,55]. Interestingly, some studies have shown that women with lipedema have lower resting energy expenditure (REE) than expected [7]. These findings may indicate diminished metabolic activity within lipedema-associated AT, suggesting that women with a higher proportion of lipedema fat relative to total body mass would demonstrate a lower REE compared to body weight-matched counterparts with a lesser extent of lipedema fat. In addition to raising obesity risk, the localized reduction in metabolic rate within lipedema fat may partially account for the limited efficacy of diet and exercise in reducing lipedema-associated AT [7].

Lipedema is not limited to SAT. Compared to women with obesity, those with lipedema had a notably lower muscle strength and a clinically relevant lower exercise-endurance capacity [55]. Nonetheless, it remains uncertain as to whether the observed muscular weakness constitutes an intrinsic feature of the underlying pathology or arises secondarily from reduced physical activity, which is frequently constrained by the severity of the clinical condition [55]. Patients with lipedema in later stages have an elevated BMI due to excess of SAT and decreased muscle function, thereby increasing their risk of developing severe obesity with metabolic complications, which, in turn, exacerbates lipedema symptoms [54].

According to Bertsch and Erbarcher [56] and Child et al. [17], over 85% of cases of lipedema and obesity were reported to co-occur. This highlights the need for an effi-

cient intervention that addresses both conditions. Due to the co-occurrence of obesity and lipedema, the distinction between these two conditions poses substantial diagnostic challenges [57] (Table 2). Most patients with lipedema have elevated BMIs, which can cause lipedema to be mistakenly diagnosed as a lifestyle-induced disorder like obesity. Poojari et al. [58] observed a vicious negative cycle attributed to the coexistence of lipedema, obesity, and low-grade inflammation. The authors observed that in individuals presenting with both obesity and lipedema, persistent low-grade chronic inflammation severely reduces lymphatic function, which, in turn, exacerbates AT accumulation [58]. It is not yet entirely clear whether, in lipedema, the subcutaneous fat cells increase in number (hyperplasia) or simply enlarge in size (hypertrophy) [58,59]. However, very recently, Pagani et al. [60], referring to single-cell RNA-sequencing analysis, identified three distinct adipocyte populations at play in lipedema. Each of these subpopulations of adipocytes has distinct genetic profiles and can be classified as follows: a *lipid-generating adipocyte* (adipocyte cluster A, which is primarily found in lipidemic fat and possesses a genetic profile indicative of active participation in adipogenesis, lipid transportation, and metabolism); a *disease catalyst adipocyte* (adipocyte cluster B, which expresses genes that affect the structural integrity of the tissue by simultaneously inhibiting phagocytosis of dead cells, causing a collapse of the micro-lymphatic system in the area, and facilitating the binding of high-density lipoproteins to the microenvironment; this is linked to the regulation of the complement pathway, lymphatic dysfunction, and lipid storage, possibly suggesting a role in the progression of disease within lipedema tissue); and a *lipedemic adipocyte* (adipocyte cluster C, which is almost exclusively present in lipedema AT and exhibits a genetic profile consistent with large, hypertrophic cells with sustained metabolic activity; this subgroup of cells is influenced by types A and B adipocytes, retaining large lipid stores while simultaneously maintaining viability) [60]. Although further exploration is needed, the authors concluded that the interplay between these adipocyte subtypes offers important insights into the intricate pathophysiology of lipedema [60].

At the time of diagnosis, patients must be informed about the negative impact of obesity on lipedema, as well as the importance of maintaining a healthy diet and an active lifestyle. In cases of overweight or obesity, leg volume may also be reduced through weight loss achieved by following a healthy diet. Diet, exercise, and, if required, behavioral therapy techniques should always be the cornerstones of weight loss in cases of coincident obesity. Achieving or maintaining a healthy body composition, preserving or regaining mobility and functionality, preventing the progression of disease, and reducing pain and other symptoms, are all possible outcomes of proper nutrition and weight management [1,6].

4.2. Particularlities of Anthropometrical Evaluation

The standardized anthropometric measurements that should be a part of routine clinical follow-up, both to assess the spontaneous course of the disorder and to monitor its response to treatment, include body weight, BMI, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and the circumference and volume of the limbs [7,17].

The accentuated increase in AT in the extremities frequently results in falsely high BMI values, making it useless for differentiating lipedema from obesity and inconclusive for classifying patients with lipedema as overweight [1,61]. Therefore, a comprehensive nutritional follow-up requires the combination of anthropometric measurements with other methods for body composition assessment, such as dual-energy x-ray absorptiometry (DEXA) and bioelectrical impedance (BIA) [57,62]. Segmental-BIA (S-BIA) is greatly helpful in clinical settings since it allows for the monitoring of body composition changes at limb level during nutritional treatments [57]. According to recent data, the SAT area,

determined by magnetic resonance imaging (MRI), may be a useful imaging biomarker for differentiating lipedema from obesity [63].

Due to the disproportionate fat distribution in the lower extremities compared to the upper body, BMI and overall body weight are considered inaccurate tools for assessing obesity prevalence in lipedema patients [10]. Waist circumference is regarded as a more effective measure for managing lipedema [10]. However, the distribution of lipedema fat (lower abdomen, hips, buttocks, thighs, and lower leg) results in disproportion between the upper and lower body with a WHR < 1 [7]. An even more accurate assessment of the disproportionate fat distribution is achieved by WHtR (an index independent of total body weight that provides insights into body fat distribution and the risk of cardiovascular diseases; a WHtR cutoff of 0.5 can be used in different sex and ethnic groups and is generally accepted as a universal cutoff for central obesity) [1,61]. Therefore, it is important that biometric data for weight, height, and waist and hip circumferences should be collected at the time of initial documentation and during follow-up [1]. Depending on the extremities involved, supplementary measures and indices should be incorporated. To describe disproportionality, the lipohypertrophy quotient (LipQ) based on Herpertz can be used (LipQ = circumference at the thickest point of the thigh, in cm/height, in cm; 32–35% = slight; 36–40% = moderate; 41–45% = severe; 46–51% = massive; ≥52% = gigantic) [1]. However, any body-circumference-based measure presents the same limitation: it fails to differentiate AT from fat-free mass, as well as to specify the type of tissue undergoing reduction during follow-up.

4.3. Food and Special Diets

At present, there is no specific, scientifically supported diet for patients with lipedema. Current dietary strategies, which are mostly based on empirical data, aim to reduce body weight through a hypocaloric diet and to inhibit systemic inflammation using antioxidant and anti-inflammatory nutrients [16]. Whenever possible, dietary changes should be made under the care of a psychologist because many lipedema patients also suffer from eating disorders [7].

Dietary changes cannot prevent disproportionate fat distribution in patients with lipedema but can greatly enhance their overall health and prognosis [6,59]. According to research on dietary interventions for lipedema, customized diets that are low in calories and rich in anti-inflammatory nutrients can effectively slow the disease progression by reducing symptoms, such as inflammation and pain, and improve QoL [2,41,64–68]. To prevent frustration, healthcare professionals must explain to patients that the primary objective of nutritional treatment is symptoms relief rather than improving the appearance of the extremities [16].

Eating patterns affect insulin and blood glucose levels, which, in turn, affect lipogenesis and inflammatory processes. Therefore, patients should be counseled to avoid short-term diets and encouraged to permanently alter their eating habits to a healthy, individually tailored diet [1]. For instance, since elevated insulin levels have pro-inflammatory effects and promote lipogenesis and water and sodium retention [69], blood glucose spikes should be avoided (via an iso- or low-glycemic index diet), and adequate time between meals should be observed [70].

The failure of some nutritional schemes to alleviate the symptoms of lipedema may be explained by the presence of a strong inflammatory component in the condition, thereby triggering the production of free radicals. Many lipedema patients adhere to low-energy, restrictive diets, which frequently fail to control hunger and result in unsustainable weight loss attempts [68,71,72]. Furthermore, these regimens may also lead to poor adherence and decreased compliance with dietary interventions, often resulting in eating disorders,

such as compulsive eating, and ultimately leading to weight gain [71]. Despite the lack of official guidelines regarding an appropriate diet suitable for lipedema, a variety of dietary recommendations are given to patients. It is recommended to avoid gluten and milk, even though there is no evidence linking them to inflammation. It makes sense to abstain from soy and foods with estrogen-mimetics (given the hypothesis of estrogen dependence). Additionally, saturated fat-rich foods (animal-based products) and refined carbohydrates (white bread, pasta, sugars, and ultra-processed foods) should be avoided due to their pro-inflammatory effects. Conversely, it is recommended to include unprocessed foods (mainly plant-based) to increase the intake of foods with anti-inflammatory properties, such as foods rich in DHA and EPA (omega-3 fatty acids), colored fruits and vegetables (rich in polyphenols and other antioxidants), and whole-grain products [73]. Furthermore, some foods, when combined with regular exercise and adequate hydration, may promote lipolysis by stimulating metabolic activity and suppressing appetite [73]. Good fats, meat and dairy proteins, and medium-chain triglycerides (MCTs) are all components of fat-burning foods. Lipids from a variety of foods, including avocados, nuts, fish and vegetable oils, are considered good fats [73]. They are rich in β-sitosterol, oleic acid, and omega-3 polyunsaturated fatty acids and can accelerate fat burning and decrease triglycerides and LDL-cholesterol levels [74]. MCTs, whose main natural source is coconut oil, are readily digested and absorbed, being promptly converted into energy. Foods enriched with MCTs, or the prescription of 100% MCT oil supplements, help reduce appetite and promote fat loss [75]. Finally, proteins from meat and dairy undergo complex digestion and absorption processes that consume energy. Furthermore, they enhance satiety and require energy for their conversion and storage as fats [73].

Overall, the guidelines underscore the significance of adopting a healthy lifestyle, developing individualized dietary plans aligned with specific caloric balance objectives, and implementing a structured, progressive exercise regimen to enhance overall health, without endorsing any particular dietary approach [3]. Nonetheless, due to the elevated BMI levels associated with the condition, various dietary strategies have been proposed. These strategies include the Mediterranean diet (MedD), intermittent fasting, and Ketogenic diets (KDs) like the very-low-calorie Ketogenic diet (VLCKD), the medium-fat medium-carbohydrate (MFMC) diet, and the low-carbohydrate high-fat (LCHF) diet [43,65,76–79]. Table 3 outlines the main dietary strategies, as well as their potential benefits and limitations in the management of lipedema.

The idea that pro- and anti-inflammatory factors might affect lipedema symptoms has led some authors to concentrate on inflammation treatment and suggest anti-inflammatory and/or KDs. Several case series and studies have demonstrated that KDs are superior to other diets in terms of reducing weight and fat mass, improving the appearance of the extremities, and reducing lipedema symptoms [2,3,43,47,57,64,68,78–81]. The KD intervention has been indicated to notably decrease inflammation in comparison to MedD and intermittent fasting regimens [82].

Recently, Lundanes et al. [2] have investigated the effect of an 8-week low-energy low-carbohydrate diet and an isoenergetic, low-fat control diet on pain intensity and QoL in women with lipedema. Even though both groups experienced improvements in several QoL aspects, the low-carbohydrate diet produced the strongest benefits, including greater weight loss and larger reduction in pain [2].

The KD is a dietary strategy that severely limits carbohydrate consumption (<30 g per day, or less than 10% of the daily total calories), with a varying proportion of protein and fat [46]. According to research by Keith et al. [71], a KD may be used as a treatment for lipedema. It involves limiting carbohydrates to induce ketosis and promoting fat utilization for energy, which produces ketones and maintains the body in a state of ketosis (defined as a blood

concentration of beta-hydroxybutyrate greater than 0.5 mmol/L) [71]. The metabolic changes induced by ketosis may lower insulin plasma concentrations enough to promote lipolysis of lipedema adipocytes [62], which contribute to weight loss and lessen lipedema symptoms, including fat deposition, pain, inflammation, and edema [8,68,71]. One explanation for the anti-inflammatory effect of KDs is the reduction of pro-inflammatory cytokines secretion, such as IL-6 and TNF-α, as a result of elevated ketone bodies concentration, such as beta-hydroxybutyrate [83]. Interestingly, as KD enhances leptin (the AT hormone that signals satiety) sensitivity in the brain, satiety increases, which may be beneficial for patients with obesity and lipedema [71].

Table 3. Overview of some dietary strategies, potential benefits, and limitations in lipedema management.

Diet Type	Main Features	Potential Benefits in Lipedema	Considerations/Limitations
Ketogenic Diet	Very low carbohydrate (<50 g/day); high fat; moderate protein	Enhanced fat oxidation (may lead to rapid fat loss, primarily in non-lipedema areas); reduced inflammation; appetite control; possible reduction of lipedema-related adipose tissue	Long-term safety unclear; may be restrictive and unsustainable; potential nutrient deficiencies
Low-Carbohydrate, High-Fat Diet	Restricts carbohydrates; increases fat intake; moderate protein; often calorie restricted	Weight reduction; improved insulin sensitivity; improved lipid and glucose profiles; reduction in pain and edema	Long-term adherence may be challenging; potential nutrient deficiencies; requires monitoring
Calorie-Restricted Diet	Focus on overall reduction in daily caloric intake	General weight and fat loss	Lipedema fat is often resistant to calorie restriction alone
Mediterranean Diet	Emphasis on whole grains, vegetables, legumes, fish and olive oil; eliminates processed foods, sugars and processed fats; rich in antioxidants and omega-3 fatty acids	Anti-inflammatory effects; cardiovascular and metabolic health; supports gradual weight loss	Effectiveness depends on adherence; may be less effective for fat redistribution
Modified Mediterranean Ketogenic Diet	Combines principles of Mediterranean and Ketogenic diets; low carbohydrates; rich in unsaturated fats	Potential anti-inflammatory and metabolic benefits; more palatable and sustainable than classic Ketogenic diet	Limited evidence in lipedema; needs further clinical validation

The KD has been demonstrated by Cannataro et al. [80] to have an anti-inflammatory effect in addition to facilitating significant and healthy weight loss in obese subjects. Conversely, a low-carb diet (less than 100 g of carbohydrates per day, with particular attention to the glycemic peaks) only permitted moderate weight loss and the maintenance of the anti-inflammatory state. The authors concluded that KD has a more potent anti-inflammatory effect, especially because it completely avoids glycemic peaks, which are known to promote the synthesis of advanced glycation end-products (AGEs) (pro-inflammatory action), with a consequent production of free radicals [80,84]. Although patients with lipedema usually have normal insulin sensitivity, limiting or completely avoiding glycemia spikes, choosing complex carbohydrates over simple ones, prioritizing fiber, and pairing carbohydrates with protein and healthy fats most likely form the cornerstone of a successful diet in this context. Other inflammatory factors should be assessed individually. For instance, in the case of gluten sensitivity, gluten should be almost entirely removed from diet [85].

Similarly, if there is lactose intolerance, this may affect intestinal microbiota and thus serve as a pro-inflammatory stimulus [86].

More recently, Amato et al. [87] conducted a systematic review and meta-analysis aiming to evaluate the effects of KDs on women with lipedema. The authors found that following LCHF for nearly 16-weeks resulted in notable reductions in BMI, total body weight, waist and hip circumferences, and WHR [87]. The patients enrolled in this study also reported an important decrease in pain sensitivity [87], which has been attributed to decreased inflammation, the prevention of fibrosis, a reduction in edema or total body water levels (probably as a result muscle glycogen depletion dehydrating lean tissue), and/or changes in metabolism and hormonal milieu [2,71]. These findings support the possible advantages of LCHF KDs for lipedema management [87]. It should be noted that in contrast to what is typically observed with energy-restricted diets, LCHF combined with an appropriate protein intake may mitigate the loss of fat free mass [62].

It is crucial to emphasize that regarding lipedema, KDs have pros and cons of their own. Unquestionably, they reduce inflammation and oxidative stress and aid weight loss without incurring the risk of sarcopenia commonly associated with hypocaloric dietary interventions [71,88]. KDs reduce leptin levels (suppressing appetite), adipocyte size, and plasma insulin levels low enough to allow for lipolysis [71]. However, these diets carry potential risks, especially with long-term adherence or improper implementation. KDs are associated with potential nutrient deficiencies (e.g., low intake of fiber, B-complex vitamins, vitamin C, magnesium and potassium), restricted food options that may lead to poor adherence over time, and in some cases, it may promote disordered eating patterns or social isolation due to dietary limitations [88]. Furthermore, KDs are associated with a possible increase in LDL cholesterol, extra renal and hepatic burden (especially with high protein consumption), constipation, and a rare but serious risk of ketoacidosis [88]. For these reasons, MedD presents as a reasonable dietetic approach since it offers a nutrient-rich strategy that promotes cardiovascular health and has anti-inflammatory properties. Nevertheless, it may have limited effects on weight loss in lipedema patients.

In line with this, the modified MedD is a further suggested dietary strategy focused on hypocaloric intake, emphasizing the consumption of healthy foods rich in antioxidants and anti-inflammatory compounds, while limiting the intake of sugars and processed fats. Studies conducted by Di Renzo's research group showed substantial weight loss in the upper and lower limbs of individuals with lipedema following a modified MedD compared with controls [43]. More recently, this research group performed another study, in which all the selected lipedema patients received modified a Mediterranean ketogenic diet (MMKD): 20% calorie restriction of daily energy requirements; <10% of total kcal/day of carbohydrates (<30 g day); 15 g of fiber; 20–25% of total kcal/day of protein (of which 20% was of vegetable origin); and 70% of total kcal/day of lipids (of which 48% comprised polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA)) [89]. This diet is based on the food choices of the MedD but follows a ketogenic approach due to its low content of carbohydrates, salt, and simple sugars. Seasonal vegetables; foods rich in MUFA and PUFA, such as virgin olive oil, nuts, seeds, avocado, oily fish, and fresh cheese with reduced saturated fat content; lean meat of organic origin; and the use of herbs and spices to reduce the amount of added salt are the main features of MMKD. All these foods are particularly rich in antioxidant and anti-inflammatory nutrients. Processed and preserved foods, such as frozen ready meals, cured meats, canned products and sausages, simple carbohydrates and sugars, sugary alcoholic beverages and soft drinks, and fresh fruits (except for red fruits), were not included. After 10 weeks of MMKD, the authors observed statistically significant reductions in body weight, waist and hip circumferences, and total fat mass, while maintaining lean mass, reducing pain, and improving sleep quality

and fatigue [89]. Glycemic control or eating a diet low in carbohydrates and high in fiber, as well as the concurrent consumption of vitamins and polyphenols, which are common in the MedD and have a demonstrated epigenetic effect, are probably the main reasons why MMKD works so well for lipedema patients [77]. Moreover, long-term nutritional management must not be overlooked in lipedema patients to prevent the yo-yo effect and ensure lasting outcomes.

Although larger randomized clinical trials are needed to confirm all these findings, nutrition should play a major role in the management of lipedema. Diet may eventually be a useful strategy to lessen the low-grade inflammation that is nearly always present in this condition. It is also essential to continue studying this disease and its pathophysiology to develop focused therapeutic approaches.

4.4. Nutritional Supplements

The MedD and KD have been proposed for lipedema treatment [43,77]. Nevertheless, as part of the lipedema plan, appropriate nutritional supplements should be considered [54]. Several nutritional supplements are designed to optimize metabolism, boost fat burning, support lean mass growth, and aid weight loss. Individual needs and treatment response should always be considered when choosing supplements [8].

N-acetylcysteine (NAC), a rich blend of polyphenols and anthocyanins shown to be highly effective in enhancing the response to free radicals, should be included as support, along with any nutritional supplements that enhance the antioxidant state, such as vitamin C [90,91]. In addition to DHA and EPA, which can regulate the production of prostaglandins, which, in turn, reduce inflammation, fiber supplements would be helpful in preventing dysbiosis and subsequently limiting inflammation [92]. Lipedema patients can benefit from long-term use of curcumin, a strong natural anti-inflammatory, and the flavanone glycosides from citrus fruits, diosmin, and hesperidin, prescribed to reduce discomfort and swelling, as they improve microcirculation and lymphatic drainage [8].

Dietary supplements that promote AT reduction and muscle development may represent a supportive strategy in the clinical management of lipedema, potentially contributing to improved body image, pain reduction, and enhanced functional mobility [54]. Metabolic enhancer supplements can be categorized into several classes based on their mechanism of action: energy enhancers (catechins, caffeine); protein and amino acid supplements (whey protein, casein); adrenergic enhancers (7-keto dehydroepiandrosterone, yohimbine); and lean mass enhancers (chitosan, pyruvate, L-carnitine, chromium, CLA) [54,73]. This group of supplements promotes weight loss through a variety of molecular mechanisms, primarily by increasing metabolism and decreasing appetite [54]. They can increase the oxidation of fats during exercise, as well as energy expenditure, and can alter metabolic pathways over time to improve fat metabolism. In patients with lipedema, weight loss-induced by diet and by these supplements can be noticeably greater than weight loss from diet alone [54]. Nonetheless, healthcare professionals should remain cautious of the limitations and potential risks linked to the use of such supplements. As previously reported, weight loss does not selectively reduce adipose tissue in lipedema-affected regions and may, in fact, exacerbate the morphological disproportion between the upper and lower body segments.

Overall, despite the promising results, human research is required to confirm the effectiveness of these supplements and to determine which dietary supplements are most effective in treating lipedema.

5. Closing Remarks and Future Perspectives

Lipedema is a severe chronic AT disorder that affects women worldwide. Although first described in 1940 by Allen and Hines [93], just recently, in 2022, lipedema was included

in the International Classification of Diseases (ICD-11) of the World Health Organization as a distinct clinical entity in the category "Certain noninflammatory disorders of subcutaneous fat" (code EF02.2). According to the ICD-11 description "Lipedema is characterized by non-pitting diffuse 'fatty' swelling, usually confined to the legs, thighs, hips, and upper arms" [57].

Accumulating evidence indicates that estrogen dysfunction may be a key factor in the development of lipedema, even though the pathophysiology of the disease has not been fully understood, and some aspects are still debatable. It is reasonable to believe that estrogen signaling in AT is critically involved in lipedema development, which primarily affects women during periods of hormonal change. Furthermore, the correlation between hormones and adipogenesis leads us to consider lipedema as a hormonal disease.

Unfortunately, there is no cure for lipedema; instead, the main goals of current treatments are to lessen inflammation, alleviate subjective symptoms, avoid complications, slow down the progression of the disease, and enhance QoL [16,64]. Lipedema management encompasses both conservative and surgical strategies. Conservative interventions typically involve lifestyle modifications, individualized nutritional counseling, manual lymphatic therapy, the use of compression garments, pneumatic compression devices, and structured exercise programs. Although surgery is a very invasive treatment, it may be an option in selected cases when conservative measures are insufficient [3,64]. However, surgery is neither a cure for lipedema nor is it free from complications. As surgical options become more common, conservative treatment, which includes nutritional therapy, is used as an adjunct in both pre- and post-operative care [71].

Regardless of BMI, as soon as lipedema is diagnosed, it is recommended to start dietary modifications to avoid obesity or, if necessary, lose weight [89]. Finding a dietary plan that reduces the mass of the afflicted limbs while simultaneously minimizing pain from orthostatic edema and the growth of inflamed AT is unquestionably crucial to improving the QoL for these patients [89]. Strict glycemic control (at least in part with KDs protocols), special attention to food intolerances (gluten, lactose, milk protein, etc.), and the use of nutritional supplements that reduce pro-oxidant and inflammatory activity are all essential components of nutritional management of lipedema [47]. The Mediterranean and LCHF diets improve overall QoL and reduce perceived pain, notwithstanding weight loss. Even though the exact mechanisms underlying the effects of KDs are still unknown, several hypotheses have been proposed, including weight loss, ketosis, anti-inflammatory effects, and the potential effect of a decrease in total body water [57]. Although further research is needed to confirm the effectiveness of KDs in treating lipedema, the study by Jeziorek et al. [81] represents a notable advance in this area. In their study, the authors assessed the effects of a calorie-restricted LCHF diet over 7 months on anthropometric and blood parameters in women with lipedema, as well as those with overweight or obesity. Their findings suggest that the LCHF diet may be a valuable nutritional strategy for lipedema and overweight/obese women, showing beneficial effects on body weight, glucose metabolism, liver function, and lipid profile, with no adverse impact on kidney and thyroid functions [81]. Nevertheless, determining the best nutritional approaches will be aided by larger studies with longer-term follow-up. Findings from randomized controlled trials evaluating distinct nutritional interventions or dietary patterns, with or without nutritional supplements, alongside mechanistic studies exploring estrogen–AT crosstalk, may lay the groundwork for evidence-based nutritional recommendations and enhance the clinical guidance for healthcare professionals facing routine challenges in this area.

Currently, lipedema is underdiagnosed, but as healthcare providers become more aware of this condition, the number of women who receive a diagnosis may rise in the future. Since lipedema is a chronic, progressive condition, women should always receive

enough information about how to adopt a healthy lifestyle and eat nutritiously as soon as they are diagnosed. This will benefit not only the women with lipedema but also their daughters or grand-daughters who are at risk of the disease due to the autosomal dominant heritage pattern of lipedema.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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