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Original Article

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Lipedema: friend and foe

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Abstract:

Background: Lipedema is a chronic disorder presenting in women during puberty or other times of hormonal change such as childbirth or menopause, characterized by symmetric enlargement of nodular, painful subcutaneous adipose tissue (fat) in the limbs, sparing the hands, feet and trunk. Healthcare providers underdiagnose or misdiagnose lipedema as obesity or lymphedema.**Materials and methods:** The benefits (friend) and negative aspects (foe) of lipedema were collected from published literature, discussions with women with lipedema, and institutional review board approved evaluation of medical charts of 46 women with lipedema.**Results:** Lipedema is a foe because lifestyle change does not reduce lipedema fat, the fat is painful, can become obese, causes gait and joint abnormalities, fatigue, lymphedema and psychosocial distress. Hypermobility associated with lipedema can exacerbate joint disease and aortic disease. In contrast, lipedema fat can be a friend as it is associated with relative reductions in obesity-related metabolic dysfunction. In new data collected, lipedema was associated with a low risk of diabetes (2%), dyslipidemia (11.7%) and hypertension (13%) despite an obese average body mass index (BMI) of $35.3 \pm 1.7 \text{ kg/m}^2$.**Conclusion:** Lipedema is a painful psychologically distressing fat disorder, more foe than friend especially due to associated obesity and lymphedema. More controlled studies are needed to study the mechanisms and treatments for lipedema.**Keywords:** gynoid fat, hypermobility, lipedema, lymphedema, women**DOI:** 10.1515/hmbci-2017-0076**Received:** November 9, 2017; **Accepted:** December 28, 2017

Introduction

Lipedema (lipoedema in Europe) is a chronic condition of painful fat transmitted in an autosomal dominant manner with a sex preference for women [1] that manifests as symmetrical enlargement of the limbs, sparing the hands, feet and trunk [2]. Men with lipedema have been reported in the literature only as case reports and tend to have conditions associated with higher estrogen and lower relative testosterone levels, such as male hypogonadism and liver disease [3], [4], [5]. What makes lipedema fat unique is that it is resistant to reduction by diet and exercise called “persistent fat”; in fact loss of non-lipedema fat can result in a dramatic size disparity between the trunk and enlarged fat on the limbs.

Lipedema fat was first described by Drs. Allen and Hines in 1940 as offering “*abnormally poor resistance to the passage of fluid into the tissue from the blood thus permitting edema to occur*” [6]. This definition suggests lipedema is a connective tissue disorder where loss of elastic recoil in adipose tissue allows fluid to collect rather than exit into lymphatics. This loss of recoil is seen when dye is injected into lipedema tissue; instead of forming a small rounded spot before entering lymphatics, the dye seeps into the tissue forming flame-like structures [7]. A 1.5 million base pair deletion of chromosomal 7q11.23 resulting in the loss of a series of genes including *ELN* for elastin, an important component of connective tissue, results in Williams syndrome, a constellation of signs and symptoms including a lipedema phenotype in both males and females [8]. The association of lipedema tissue with loss of elasticity supports lipedema as a connective tissue disorder, though because of the complexity of adipose tissue, other connective tissue mutations or mutations affecting connective tissue structure are likely important in lipedema as well. Consistent with loss of elasticity, aortic stiffness develops in Williams syndrome [9] and in lipedema [10]. Increases in fluid and fat in the area of lipedema can result in deformations of the tissue (Figure 1) hindering ambulation and self-care.

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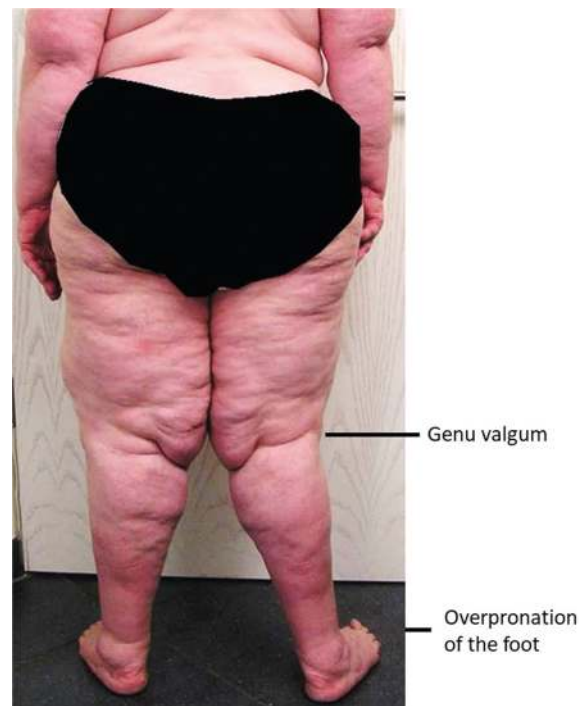


Figure 1: Woman with Stage 3 lipedema and genu valgum of the right knee and overpronation of the right foot. The medial thigh and knee lipedema fat tissue likely contributed to stress on both legs. Photo by Dr. med. Josef J. Stutz.

Lipedema is underdiagnosed by healthcare providers and is often misdiagnosed as obesity or lymphedema. The name, lipedema, sounds like lipidemia or lipemia, alteration of blood fats, increasing confusion when patients bring up lipedema and providers hear a different diagnosis. The prevalence and incidence of lipedema are unknown though it is thought to be common; lymphedema and lymphatic and vascular clinics report a prevalence rate for lipedema of 6.5–18.8% in their patients [1], [11], [12], [13], [14], [15], [16], [17]. A small study in Germany of 62 women in a single company resulted in a prevalence rate for lipedema of 9.7% [18].

Lipedema generally manifests during puberty, although it can appear at other times of hormonal change such as childbirth or menopause. This evidence plus the predominant occurrence of lipedema in females suggests importance of sex hormones in the development of this disorder. Indeed, the distribution of lipedema fat is in the female gynoid distribution (lower abdomen, hips, buttocks, thighs and lower leg), resulting in disproportion between the upper and lower body with a waist to hip ratio <1 . Lipedema fat is present on the arms in 80% of women with lipedema [2], but the gynoid distribution of lipedema fat dominates. There are three stages of lipedema and four types (Figure 2). The skin in lipedema can be smooth but the underlying fat is increased and contains pearl-sized nodules (Stage 1); or the skin can be indented over pearl-sized fat nodules and larger fat masses (Stage 2); or the skin can contain divots and folds over pearl-sized fat and larger fat masses with characteristic deforming fat lobules (Stage 3). Stage 4 is characterized by the development of lymphedema with lipedema better known as lipolymphedema and can occur with any stage [2]. Approximately 80% of women with lipedema have lipedema fat on their arms (Type IV) therefore this type of lipedema occurs jointly with lipedema affecting the legs. Lipedema fat can occur around the hips and buttocks (Type I), waist to knees like riding breeches (Type II) or waist to the ankles (Type III). It is rare to see lipedema fat dominate on the lower legs (Type V) [19].

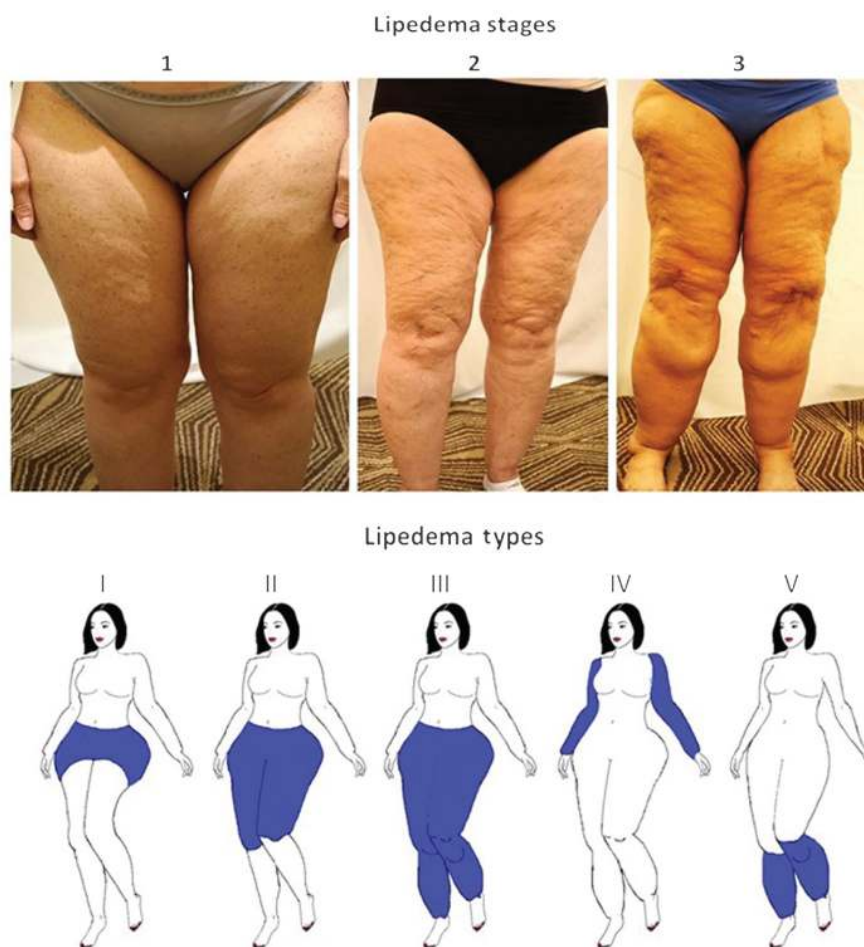


Figure 2: There are three stages and five types of lipedema.

In Stage 1, the skin is smooth but there are pearl-sized nodules in the fat underneath. In Stage 2, there is retraction of the skin due to fibrosis of connective tissue fibers surrounding fat lobules and pearl-sized and larger masses in the fat tissue. In Stage 3, there are pearl-sized nodules, larger masses and lobules of the skin and fat. The fourth Stage in lipedema is not shown, as it is the development of lymphedema that can occur at any stage. Lymphedema occurs in Stage 3 more than Stage 2 or Stage 1 and is known as lipo-lymphedema [20]. Five Types describe the location of lipedema fat. Type IV is found often combined with Type II or III.

This paper will highlight the benefits and the downsides, the friend and foe aspects, of lipedema.

Methods

This study was approved by the University of Arizona human subjects protection program. The following benefits and downsides of lipedema were collected from discussions during clinic visits with women with lipedema on benefits (friend) and downsides (foe) of lipedema, a review of medical charts of women with lipedema at Banner University of Arizona Medical Center over 6 months from 12 April 2017 to 12 October 2017, and using search terms “lipedema” and “lipoedema” in the database National Center for Biotechnology Information (NCBI) [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; [1988] – [cited 2017 Oct 01]. Available from: <https://www.ncbi.nlm.nih.gov/>.

Hypertension was noted for blood pressure $\geq 140/90$ mm Hg or use of antihypertensive medication. Diabetes was identified by hemoglobin A_{1C} (A_{1C}) or history of diabetes (including gestational) with use of anti-diabetic medication. Pre-diabetes was identified by A_{1C} 6.5% or higher, history or use of medication for pre-diabetes, specifically metformin [21] as no other medications were used. Data are presented \pm standard error of the mean. Differences between means were analyzed by non-parametric analysis of variance (ANOVA) and the Kruskal-Wallis test followed by a Dunn’s multiple comparison test.

Friend: the upside of lipedema fat

Women with lipedema report little if any benefit in having lipedema. The following are potential benefits of lipedema.

1. **Low risk of diabetes despite higher body mass index (BMI):** A study of 160 participants with lipedema showed a low prevalence of diabetes of $6 \pm 0.2\%$ despite an average BMI of $39 \pm 12 \text{ kg/m}^2$ [20] compared to 10.7% of women with diabetes with a similar age range. The risk of diabetes was even lower at $2 \pm 0.1\%$ in a smaller study of 51 participants with lipedema who had a similar average BMI of $38 \pm 2 \text{ kg/m}^2$ [22]. Gynoid fat has been shown to be negatively correlated with insulin resistance after total fat adjustment, whereas the opposite was found for abdominal fat, suggesting that lipedema fat may have a protective effect against diabetes [23]. Data tabulated for this study also suggests that the risk of diabetes is low in lipedema ($\sim 2\%$) for an average BMI of $35.3 \pm 1.7 \text{ kg/m}^2$; the risk of pre-diabetes increased in Stages 2 and 3 (Table 1), suggesting that the risk of diabetes may increase with stage. Research on insulin sensitivity in women with lipedema is needed preferably using the gold standard glucose clamp procedure.
2. **Normal blood pressure despite obese BMI:** In this study, hypertension was present in less than 30% of women with Stages 2 and 3 and not present in women with Stage 1 lipedema (Table 1). National data suggests hypertension rates in women of any BMI age 40–59 year was 32.4% [24]; higher hypertension rates of 60% were reported for obese Caucasian women mean age 63 year [25]. The presence of hypertension in women with Stages 2–3 is concerning and larger populations should be studied to better understand the risk of hypertension with lipedema stage.
3. **Gynoid shape and cardiovascular disease (CVD):** Lipedema fat in the absence of abdominal obesity confers a gynoid shape with a greater amount of fat in the gynoid area, hips, buttocks and legs, compared to the upper body [26]. The presence of gynoid fat confers lower cardiovascular disease (CVD) risk compared to android fat (abdominal obesity) [27]. The use of body shape along with weight has been shown to provide a better estimate of risk of morbidity than weight alone [28]. Women with lipedema may therefore have lower CVD risk due to gynoid fat (Table 1). The presence of CVD in women with lipedema should be studied to better understand any risk of lipedema fat.
4. **Resistance of lipedema fat to loss by lifestyle changes:** Lipedema fat resists loss by extreme dieting and/or over-exercise [6], [29]. This persistent fat is especially frustrating for women *with* lipedema, when women *without* lipedema can lose weight by less extreme measures. What is concerning is that women with lipedema find it difficult to lose weight prior to a needed surgery or other procedures. This aspect of lipedema is a foe, but there may be an evolutionary benefit to a woman having lipedema fat [30]. For example, in times of famine, women with lipedema could have retained fat maintaining fertility and the ability to breast-feed their children, passing on their genes within the population.
5. **Normal lipid panel despite higher BMI:** Women with gynoid fat had lower fasting triglyceride-rich lipoprotein, and lower triglyceride levels and smaller chylomicron particle size after a mixed test meal providing 40 g triglycerides than women with android obesity [31], suggesting that gynoid fat protects against abnormal blood lipids that would confer a cardiovascular risk. The majority of women with lipedema in the current study had a normal lipid profile (Table 1), where only 11.7% had high total cholesterol $\geq 240 \text{ mg/dL}$ (considered high) compared to 33.5% of females in the general population [32] and even higher percentages when females were obese [33].
6. **Buoyancy:** Lipedema fat offers dramatic buoyancy in water making water activities enjoyable. Women who cannot swim to the bottom of a swimming pool or scuba dive without a very heavy weight belt do not find this beneficial.
7. **Compassion:** Women with lipedema, recognizing the existence of persistent fat, have developed compassion for people who are overweight and obese and their struggles with weight loss. This compassion is important in our society that is rampant with fat bias [34], [35].
8. **Soft skin:** Many women with lipedema have joint hypermobility or possibly Ehlers-Danlos hypermobility type (EDS-HT) syndrome [2], [20]. Individuals with EDS-HT are well-known to have soft skin [36].
9. **Beautiful face:** Women with lipedema state that they have fewer wrinkles and a more youthful face than women without lipedema.

10. **Healthy lifestyle:** As women with lipedema journey through life trying multiple diets to try and diminish lipedema fat, they might become very educated about food and aware early on in life how to eat nutritiously; this benefits not only women with lipedema but their children who are at risk for lipedema due to the autosomal dominant heritage pattern of lipedema [1].

Table 1: Demographics and metabolic parameters of women with lipedema by stage.^a

Demographics/parameters	Lipedema stages		
	1	2	3
Number	12	24	10
Age, years	40.7 ± 4.3 ^b	54 ± 2.2	54 ± 3
BMI, kg/m ²	26 ± 1 ^b	33 ± 0.9 ^c	51 ± 5 ^b
Race	11 Caucasian 1 African American	22 Caucasians 1 Alaskan Indian 1 Multiracial	9 Caucasian 1 African American
Ethnicity	0 Hispanic	3 Hispanic	0 Hispanic
SBP, mm Hg	120.8 ± 3	129 ± 4	142 ± 4.5 ^c
DBP, mm Hg	76 ± 2	80 ± 2	83 ± 3
TC, mg/dL	145 ± 16	190 ± 11	178 ± 10
TG, mg/dL	72 ± 17	121 ± 22	122 ± 18
HDL, mg/dL	63 ± 11	59 ± 5	54 ± 5
LDL, mg/dL	68 ± 4 ^b	109 ± 8	93 ± 5
Diabetes	0	0	1
Pre-diabetes	0	3 (12.5%)	3 (30%)
Hypertension	0	6 (25%)	2 (20%)
Smokers	0	4 Former	1 Smoker 1 Former

^aBanner University of Arizona Medical Center Chart Review. ^bp < 0.05 vs. Stage 2. ^cp < 0.05 vs. Stage 1. BMI, Body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein.

Foe: the downside of lipedema fat

1. **Lipedema fat resists diet and exercise:** Despite over-exercise and extreme dieting, lipedema fat (shape) remains while normal or obese fat can be lost. Published studies on different diets may shed more light on this aspect of the disease. In general, women with lipedema reduce non-lipedema fat with diets low in processed carbohydrates either with anti-inflammatory foods high in fruits and vegetables [37] or with protein and fats to induce ketosis. Failure to lose weight with dieting results in eating disorders, and in one study, increased risk for suicide in lipedema patients [38].
2. **Pain:** Women with lipedema have fat pain that commonly occurs after the tissue is pressed or palpated but also in the absence of contact. The pain is definitely associated with lipedema fat, as suction assisted lipectomy (liposuction) significantly reduces the pain [39]. Joint pain is not uncommon in lipedema especially the knees and low back, the latter due to lordosis and changes in the structure of the spine (especially degenerative disc disease), tendons and ligaments. Hypermobility may also contribute to joint damage and pain in women with lipedema.
3. **Obesity:** Women with lipedema are at elevated risk for developing morbid obesity. Obesity is itself a risk factor for lymphedema [40] which can exacerbate lipedema [41] (Figure 1 and Figure 3). Lymphedema is the retention of fluid in tissues causing swelling due to congenital or acquired damage to the lymphatic system. The term “lipedema” is defined as “fluid in fat”, therefore, excess tissue fluid from lymphedema not only adds to the fluid already present in lipedema fat, but induces additional fat growth [41] adding to the burden of fat in lipedema.
4. **Gait abnormalities and leg joint issues:** Excess lipedema fat on the buttocks, hips, thighs and lower legs changes the gait of women with lipedema, resulting in stress on the joints, especially the knees [42] often causing genu valgum (knock knees), an antalgic gait and overpronation of the feet (Figure 1). These issues

can be caused, enhanced and exacerbated by hypermobility. Gait disturbance and knee pain reduce the desire and ability to ambulate, which can lead to further risk of obesity.

5. **Gynoid fat and lymph flow:** Lymph flow is inhibited and lymphatic [43] and blood capillaries leak in gynoid fat [44]. Though studies on gynoid fat have not specifically focused on lipedema, it is likely that if lipedema does affect millions of women worldwide, then many of the women in these studies likely had lipedema. Women with Stages 2 or 3 lipedema are more likely to develop lymphedema compared to women with Stage 1 [2].
6. **Lower resting energy expenditure (REE):** Women with lipedema were found to have lower REE than expected calculations [6]. These studies need to be repeated because the methods were not clearly defined. The lower REE may represent a lower metabolism in lipedema fat such that women with more lipedema fat per body weight should have lower REE than matched women with less lipedema fat. This localized lower metabolic rate in lipedema fat could partly explain the failure of lipedema fat to reduce with diet and exercise, in addition to increasing the risk for obesity.
7. **Psychosocial distress:** The impact of lipedema on the life of a woman with lipedema has been well documented [45]. This includes relief felt when finally getting a diagnosis, followed by feelings of frustration and despair when realizing that treatment may not improve symptoms as much as they had hoped; difficulty in self-care; a social stigma attached to increased body size and physical restrictions; anxiety; depression; self-loathing; discrimination especially not fitting into seats in public spaces such as airplanes or toilets; lack of understanding and fear expressed by family, friends and colleagues; verbal abuse from members of the public; failure to form relationships; all of which can result in social avoidance, withdrawal and isolation.
8. **Aortic disease:** Women with lipedema were found to have higher mean systolic and diastolic aortic diameters and aortic stiffness index, while aortic strain and distensibility were significantly lower compared to controls by transthoracic echocardiogram [10]. These aortic parameters may be present due to hypermobility and the resultant connective tissue changes in the aorta. While these parameters are thought to increase the risk for CVD, metabolic risks such as blood pressure and dyslipidemia may confer less cardiovascular risk in women with lipedema. These data again support the need for targeted studies on CVD in women with lipedema to determine if lipedema fat is protective or not.
9. **Fatigue:** In one study, ~75% of women with lipedema complained of fatigue [2]. Women do report higher levels of fatigue than men and fatigue increases with chronic disease [46]. As comparator populations, up to 45.8% of women in the workforce report fatigue [47], while fatigue was present in 38.6% of women with chronic musculoskeletal pain and inflammatory joint disease [48]. Brain fog or difficulty with cognition can also accompany fatigue [49].
10. **Hypermobility:** Hypermobility appears to be prevalent in the lipedema population. In one study over half of 160 patients with lipedema, average age 50 year and BMI 39 kg/m² had hypermobile joints [20]. Hypermobility confers risk for additional joint damage and alteration of gait in women with lipedema (Figure 1). Skin changes including thin skin and tattoos that leak into the skin can be found in women who are hypermobile. Hypermobility may change the structure of the lipedema tissue affecting how much fluid fat can accommodate, leakage of fluid from vessels, dilation of vessels and dysfunction of capillaries. Women with lipedema also have higher aortic distensibility and strain, reliable characteristics of arterial elasticity [10], also suggestive of connective tissue changes consistent with hypermobility, and possibly risk for cardiovascular mortality.

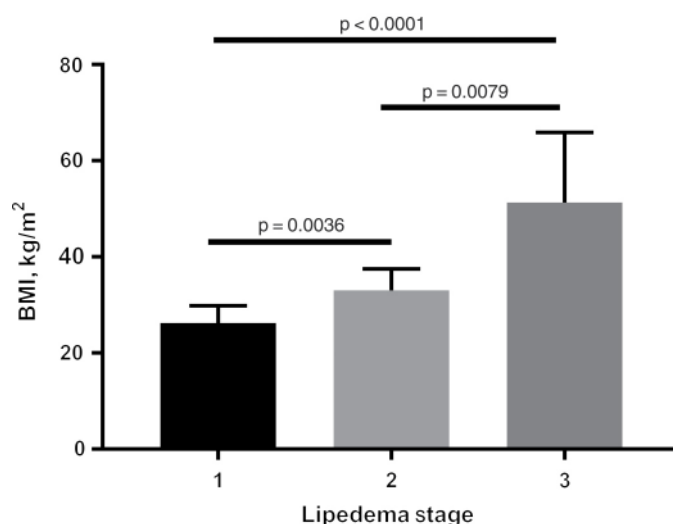


Figure 3: Body mass index increases with stage of lipedema.

Women with lipedema Stage 1 (n = 12), Stage 2 (n = 24) and Stage 3 (n = 10).

The majority if not all of women with lipedema in our practice agree that foe wins over friend with reference to lipedema. While persistent fat may be evolutionarily beneficial in times of famine, today when food is plentiful throughout the lifetime of a woman with lipedema, the true evolutionary benefit of this fat is unclear.

Reducing the foe aspect of lipedema fat

A multi-pronged approach is needed for women with lipedema. Standard treatment recommendations for lipedema are (1) healthy low carbohydrate eating plans to keep obesity at bay; (2) increasing metabolism through exercise by activating the muscle pump to improve venous and lymphatic flow and muscle fitness; (3) complete decongestive therapy to include manual lymphatic drainage; (4) skin care to reduce dryness and cracks that increase the risk for infection (cellulitis) especially when lymphedema is present; (5) recommendations for compression garments; (6) a sequential pneumatic compression pump and (7) psychological care. Additional treatment recommendations include:

1. **Medical support:** Care from family, friends, primary care providers including gynecologists who may have the ability to diagnose the development of lipedema at puberty and educate early to prevent progression, orthopedic surgeons willing to operate on the knees of women with lipedema, healthcare providers with expertise in lymphedema, physical and occupational therapists with knowledge and training about the lymphatic system who are also not afraid to treat deeper into the tissue and reduce fibrosis [50], professionals who can provide psychological services and compression garment fitters are needed to improve the quality of life for women with lipedema.
2. **Groups:** Internet groups but also national and local groups are useful for women with lipedema to share resources, provide comfort and support, allow for spiritual strengthening and self-love.
3. **Suction-assisted lipectomy:** The removal of lipedema fat by suction-assisted lipectomy (liposuction) has improved quality of life and reduced pain for women with lipedema [51], [52], [53].
4. **Subcutaneous adipose tissue therapy:** Manual lymphatic drainage therapy as a part of decongestive therapy with or without sequential pneumatic pump therapy has improved capillary fragility in women with lipedema [54], [55]. Deep manual treatment into the lipedema fat has improved pain and quality of the lipedema fat [50]. Other techniques such as Astym® therapy and Graston Technique® have in practice been shown to reduce fibrosis in lipedema fat and also improve blood flow in tissue [56] as well as joint, tendon and ligament issues associated with hypermobility [57].

Treatments can have an economic impact on the patients with lipedema as doctor visits, clinical imaging, pain medication, surgeries, exercise equipment and healthier food alternatives and definitely, liposuction, are often expensive and not covered by insurance or are accompanied by large co-pays.

Conclusion

Lipedema is a foe for women reducing quality of life, inhibiting their ability to lose weight from areas of persistent lipedema fat and putting them at risk for the development of mobility issues, joint deformations and lymphedema. Despite lipedema fat causing overweight and obesity, lipedema can be a friend metabolically until later stages. Treatments can reduce pain and quality of lipedema fat but only liposuction to date has reduced lipedema fat.

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Author Statement

Conflict of interest: None of the authors declare a conflict of interest.

Informed consent: A waiver of consent for access to Banner health records for this study was received by University of Arizona Human Subjects Protection Program.

Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies and was performed in accordance with the tenets of the Helsinki Declaration and has been approved by the University of Arizona Human Subjects Protection Program.

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