Insights on the Pathophysiology, Diagnosis and Treatment of Lipedema

Lipedema can cause chronic pain and increases patients' risk for conditions such as lymphedema and venous disease. This author explores how lipedema affects the body, why its effects are disproportionate in the lower body, and how to diagnose and manage the condition.

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Body fat functions to store and deliver energy to our bodies and at the same time, provides our body shape. Sex hormones drive where fat cells (adipocytes) establish themselves on our body. In men, this is usually on the abdomen or android area, and in women, it is on the hips, thighs, and buttocks or gynoid area. Gynoid fat tends to be cardioprotective and android fat tends to be metabolically unhealthy. When excess fat deposits on the body in the gynoid area out of proportion to the trunk, causes pain and dysmobility, and cannot be lost by diet or exercise, we call this condition lipedema.

Fat tissue is not just adipocytes. Within fat are fibroblasts that make collagen and elastin fibers, forming a net-like extracellular matrix (ECM) that provides shape to fat tissue, stem cells including preadipocytes that generate new adipocytes, and immune cells that survey and repair fat tissue when it is wounded. Macrophages are immune cells that engulf necrotic adipocytes and are present when excess fluid pools within tissue. Fat cushions and mechanically protects and connects nearby tissues such as muscles, tendons and ligaments. Fat is therefore a connective tissue. The softness and pliability of fat makes it loose rather than dense connective tissue.

Fluid, nutrients and cells from blood vessels enter loose connective tissue (LCT), flow between and interact with cells and then exit along with cell waste though lymphatic vessels. LCT communicates with the body by secreting proteins called adipokines, which also exit through lymphatic vessels. The structure of LCT facilitates flow through the binding of ECM fibers to cells and surrounding tissues, pushing fluid out through lymphatic vessels. A breakdown in the structure of the ECM by inflammation reduces pressure and therefore flow, allowing fluid to stagnate and expand in the ECM, inducing the further growth of fat tissue (**Figure 1**).[1–3]

LCT can act as a sponge to sop up excess fluid by upregulating proteoglycans in the ECM. Proteoglycans consist of a protein backbone to which glycosaminoglycans (GAGs) are bound. GAGs are negatively charged repeating disaccharide sugars that bind sodium and water (**Figure 1**). Proteoglycans upregulate when excess fat tissue, fluid or sodium is present. When the amount of fluid in the body exceeds euvolemia, LCT becomes compliant, allowing more fluid from blood vessels to enter without increasing pressure and bind to GAGs, thus protecting the intravascular space from elevated hydrostatic pressures. Stretching of LCT either by the increased size of adipocytes or increased fluid bound to GAGs in the ECM causes fibroblasts to deposit additional ECM proteins, resulting in fibrosis.[4] Fibrosis may help limit growth of fat tissue.[5] However, fibrosis also inhibits the ability of fat to be lost after diet, exercise or even bariatric surgery, which is the case for lipedema tissue.[6–10]

As with other organs, fat tissue can become sick. Sick fat or adisopathy occurs when fat increases beyond its ability to maintain its normal anatomy and function. Adisopathic fat has large adipocytes, inflammation and fibrosis, which is exactly what has been found in lipedema tissue.[11,12] Excess calories, reduced energy output (exercise) or genetic predisposition can increase adisopathic tissue. Many women with lipedema eat better and exercise more than the general population. Therefore, genetics likely plays a role in the pathophysiology of lipedema.

HOW LIPEDEMA AFFECTS THE BODY

Lipedema is a disease of increased fibrotic LCT in the gynoid area but also the arms, sparing the trunk, hands, feet, and head. The fat distribution in lipedema therefore causes a disproportion between the lower body and the arms compared to the trunk. Lipedema mostly occurs in women. Lipedema is chronically painful and increases the risk for the development of obesity, lymphedema, venous disease, thin skin, knock (valgus) knees, rotation (pronation) of the ankle and dysmobility. Lymphedema can occur at any stage of lipedema, not just in women with severe obesity and advanced disease.

In women with lipedema, hypermo-

bile joints were found in over 50%, skin elasticity was about half that of women in the control group, and the aorta was dilated in diastole and systole.[13–15] These findings are consistent with lipedema as a connective tissue disease. Anecdotal data suggest this connective tissue disease is hypermobile Ehlers Danlos syndrome (hEDS).[16] It is not clear if hEDS causes or exacerbates lipedema or both.

Women with lipedema in addition to increased fat tissue have loss of muscle strength compared to women without lipedema.[17] As LCT surrounds and connects muscle, it is not hard to imagine that the fibrotic cage in lipedema LCT also surrounds muscle inhibiting its function.

WHY IS THE LOWER BODY DISPROPORTIONATELY AFFECTED IN LIPEDEMA?

Upon standing, gravity induces a translocation of blood from the chest to dependent areas, which increases hydrostatic pressure in blood vessels in the lower aorta and legs. This increased hydrostatic pressure is managed by high-capacity veins in the legs. However, in people with lipedema, small vessels in lipedema LCT are dilated compared to controls, reflecting lower elasticity and/or other connective tissue defects of the vessels including the veins.[12] These dilated vessels may release a greater amount of fluid volume over time into the ECM, and their fragility often presents as easy bruising in many people with lipedema. Because there is no visible fluid in lipedema tissue at least by ultrasound, this excess fluid must be bound to GAGs and may drive an increase in growth of fat tissue.

A European consensus document states there is no edema in lipedema.[18] What this group failed to understand is the definition of edema—increased fluid in the interstitial space (extracellular matrix), which can be free or bound to GAGs.[19] Just because we lack the ability to "see" fluid by ultrasound in lipedema tissue does not mean that fluid is not present; in fact, it is part of the pathophysiology of LCT that has been known for decades.[20]

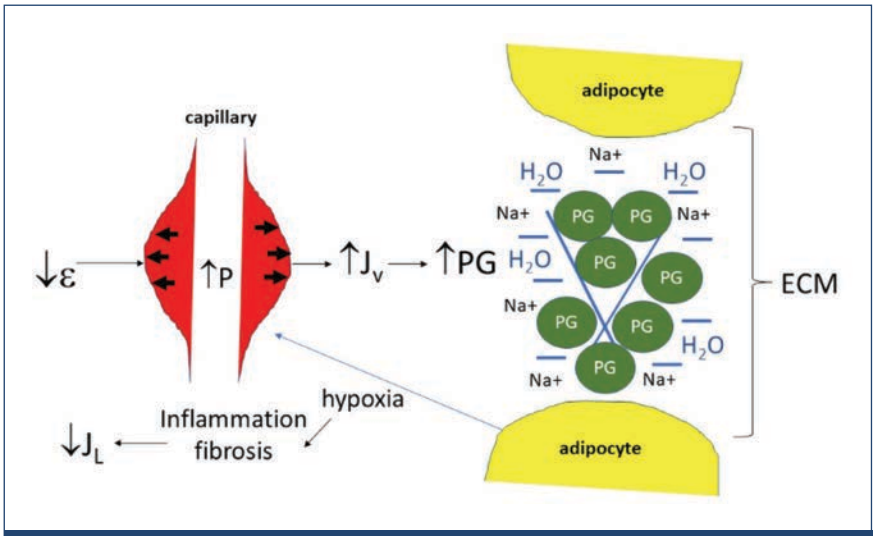

FIGURE 1. Cartoon of a capillary blood vessel (red) that has dilated due to a loss of elasticity (↓ε) causing excess plasma to leave the vessel (black arrowheads) and enter the interstitial space between adipocytes (yellow). This increase in fluid flux out of the vessel (↑J_v) induces an increase in proteoglycans (green circles; PG) that bind water (H_2O) and sodium (Na+) in the extracellular matrix (ECM). The increase in PG-bound water pushes adipocytes further from their oxygen source (capillary) causing hypoxia. The adipocytes signal to the body that hypoxia is occurring and inflammation and fibrosis result in lower lymphatic flux (↓J_L), more fluid stagnates in the ECM and adipocytes replicate. This microangiopathy due to loss of elasticity or a connective tissue disease underlies, at least in part, the development of lipedema tissue.

HOW TO DIAGNOSE LIPEDEMA

If the diagnosis of lipedema is suspected, **Table 1** shows what practitioners should ask about or look for.

Lipedema versus lymphedema. The diagnosis of lipedema is by clinical history and exam; there is no clinically available biomarker or gene. Lipedema is often confused with lymphedema. Lipedema symmetrically affects the body whereas lymphedema often presents in a single limb. Lipedema is also more painful than lymphedema with 90% of women with lipedema having daily pain.[21] People with lipedema also scored worse than people with lymphedema on all scales examined, including the Short Form-36, a standard measure of health, with pain being a major factor in the difference between the two.[22] Ultrasound imaging can also help differentiate lipedema from lymphedema by increased skin thickness and free fluid in lipedema.[23]

Lipedema versus obesity. Lipedema is often confused with obesity because of an increase in body mass index (BMI) and fat tissue. However, the dramatic disproportion of lipedema tissue on the lower body sparing the trunk is pathognomonic for lipedema. What can be confusing is that women with lipedema can also develop non-lipedema obesity. To add to that confusion, lipedema tissue can also develop on the abdomen. Fat tissue on the body of people with lipedema will go wherever the pathophysiology of lipedema occurs; i.e., higher pressure in the lower aorta affects nearby tissue; e.g., the abdomen. Fluid bound to GAGs in the ECM resides in the interstitial organ, which is filled with fluid (bound to GAGs and unbound).[24] This fluid can move within the interstitial organ to nearby tissue, thereby spreading the pathophysiology of lipedema anywhere on the body. An increase in fat tissue accompanied by inflammation that inhibits lymphatic pumping, allowing fluid to stagnate supports the spread

Table 1. Tools for Diagnosing Lipedema

History Questions	
Lipedema developed or worsened with hormone(s), shape or weight change? → i.e., puberty, pregnancy, menopause, life change → pictures are helpful	
Lipedema fat is hard to lose compared to non-lipedema fat?	
Easy bruising?	
Orthostatic edema?	
Lipedema in the mother's or father's family?	
Physical Exam Findings	
Lipedema tissue on the lower body & arms >> trunk, hands, feet, head	
Palpable fibrotic nodules → Roll the fingers on the tissue to find nodules	Upper and lower arms
	Abdomen, usually under the umbilicus
	Hips, buttocks thighs
	Lower leg
Heavy tissue—lift the upper arm fat, hips, buttocks, thighs, breasts	
Tissue pain when palpating nodules, medial knee, below knee, etc.	
Hypermobile joints by the Beighton criteria (50%)[25]	

of fibrotic tissue, which then becomes hard to lose by usual measures.

Venous disease in lipedema. Venous disease may play a role in modifying the lipedema phenotype. There are two distinct phenotypes of lipedema. There is the Allen and Hines phenotype in which women have lipedema tissue but the lower legs do not form a column, and the Moncorps type in which women with lipedema do have column-type legs (**Figure 2**).[26,27] It is likely women with Moncorps type have valvular venous disease, which increases the amount of fluid entering the ECM completely overwhelming the lymphatic system causing stagnation of fluid and fat overgrowth fueled by loss of elasticity in the tissue and gravity.

KEYS TO MANAGING LIPEDEMA

Goals of managing lipedema include reducing pain, improving mobility, reducing edema, and reducing lipedema tissue. Standard treatment recommendations for people with lipedema include:

- a healthy diet, usually low in processed carbohydrates;
- exercise, including pool therapy;
- manual lymphatic drainage as part of complete decongestive therapy to reduce pain and edema, similar to treatment for lymphedema, but also deep tissue techniques to improve the vasculature, fibrosis and connective tissue;
- compression garments to provide support against the loss of elasticity and to keep fluid moving through the tissue; and
- sequential pneumatic compression pumps, which are known to improve lymphatic flux and reduce fibrosis.[28,29]

These therapies all help reduce symptoms and may improve the quality of the tissue, but the reduction of lipedema tissue itself is limited. Even bariatric surgery has limited success in reducing lipedema tissue although non-lipedema LCT is reduced.[8–10]

Surgical reduction of lipedema tissue. Lipedema reduction surgery—including liposuction techniques, manual extraction of lipedema tissue or excision of lipedema tissue and skin—is the single best means for reducing lipedema tissue. Lipedema reduction surgery must remove not only the superficial fat tissue but also the deep tissue, all of which can become fibrotic, while at the same time avoiding damage to the skin or lymphatic vessels. While there are no studies on lipedema reduction surgery from the U.S., European data shows that tissue reduction, quality of life and pain all remain improved even 12 years after surgery.[30,31] Since there is no other way known to date to remove lipedema tissue effectively—including the ketogenic diet, exercise, standard therapy or bariatric surgery—liposuction, though considered cosmetic, is an important tool in the lipedema treatment armamentarium. Lipedema reduction surgery reduces pain, improves mobility and improves quality of life, and is therefore a medically necessary procedure for women with lipedema.

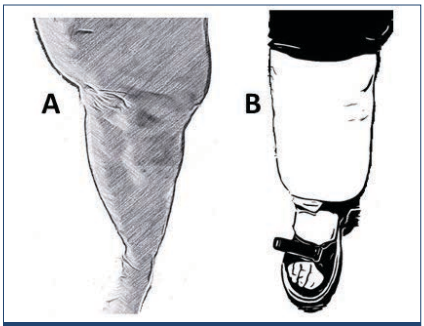

FIGURE 2. Different leg types in lipedema. A. Allen and Hines type leg. B. Column leg of Moncorps.

Medical treatment of lipedema. Medical treatment of lipedema includes a discussion on diet and exercise but also empathy for people who have been told to diet and exercise for years without good effect, supportive therapy due to the development of anxiety and depression from years of misdiagnosis and limited treatment options, and avoiding medications that cause edema or weight gain, or subcutaneous fat development including thiazolidinediones. Medications or supplements that reduce fibrosis are important to consider for lipedema tissue although there are no current medication trials for lipedema. Metformin, used to treat metabolic disease (pre-diabetes and diabetes) is known to prevent the development of fibrosis but can also reduce fibrosis that develops after tissue wounds and is a good choice for women with lipedema especially if they have also developed non-lipedema obesity.[21,32] Over-the-counter enzyme supplements such as nattokinase or serrapeptase and others act as fibrinolytics and may be useful in reducing fibrosis

in lipedema tissue so it can be then be amendable to loss after diet or exercise.[33]

LIPEDEMA IN CHILDREN

A major goal for people with lipedema is to prevent lipedema tissue from developing. This requires early identification and the development of diagnostic criteria for children with lipedema.

CONCLUSION

Lipedema is a disease of damaged LCT with a clogged ECM that allows lipedema tissue to spread in the body and prevents loss of fat by usual measures. Stagnant tissue fluid promotes the growth of new fat and fibrosis of the LCT inhibits muscle function. Lipedema reduction surgery is currently the most effective means to reduce lipedema LCT but anti-fibrotic medications that are being developed for fibrosis of other organs such as the lung and liver may one day become useful for treating people with lipedema. ■

Dr. Karen L. Herbst, MD, PhD, is a board-certified endocrinologist who has been in practice for 18 years. She has been working with people with lipedema since 2006 and won a pioneer award and career achievement award for her work. Dr. Herbst was one of the founding members of the Fat Disorders Resource Society, which supports people with lipedema as well as other diseases. Dr. Herbst is the head of the standard of care lipedema committee in the US, which has just submitted a paper for publication and she also submitted ICD-10 codes for lipedema to the CDC in October 2020. She currently is in private practice and continues research in Los Angeles and Tucson.

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