

Lipedema and Lymphedema: the “Leaky Lymph,” Weight Loss Resistance and the Intestinal Permeability Connection

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Introduction

In the practice of clinical nutrition we might be missing the elephant in the room, especially when it comes to the morbidly obese. The ill-informed assume that the morbidly obese just continuously abuse their food intake and gorge uncontrollably. There are two conditions that have a potential genetic, epigenetic and inflammatory component that could drastically affect these people’s weight gain and weight loss resistance. These conditions are very seldom spoken about and hardly ever addressed in the mainstream media. The dietetic world is still too tangled up in the archaic outdated calories in and calories out theory, thus it might be the appropriate time to address this extremely overlooked issue. These conditions became interesting to the authors when an active, fit and dedicated client got diagnosed with Lipedema. She eats a whole food diet, rides a bicycle competitively for hundreds of miles at a clip and works out religiously with enough recovery. Her legs and upper thighs have clear Lipedema and dietary intervention has helped temporarily but with no permanent effect. This paper will discuss the differences between Lipedema and Lymphedema and the potential tie into the compromised digestive health, inflammation and fat emulsification systems. There also seems to be a correlation between intestinal permeability and these conditions. It might just be that the majority of morbidly obese people actually suffer from lipedema as much as they are insulin and leptin resistant. The epidemiology of this condition claims it is present in 11% females and vary rare in males less than 1% [1]. It is a grossly misdiagnosed condition and one that did not even make it to medical journals until recently. What is even more revealing is that Lipedema has not been included in the International Classification of Diseases (ICD), thus no insurance coverage for this condition. Self-reported familial lipedema according to [2] is between 16% - 64%. A review article by Forner-Cordero in 2012 indicated that by 2011 there were less than 100 articles on this topic and after exclusion less than 12 provided valid data [3].

Lymphedema and Lipedema

Lymphedema is a condition of edema (swelling) from excess fluid or lymph tissue accumulating, this condition unlike Lipedema is not bilateral. Primary Lymphedema is generally diagnosed at birth or puberty and is a condition of a defective or severely compromised lymphatic system due to genetics. Secondary Lymphedema could be caused by the overloading or damaging of the lymphatic system. Most of these causes are not totally known, but certain tumors, cancers, injury, trauma to the venous system, obesity and heart failure have been indicated [4]. There are many lymphatic vessels in the skin, and even more surrounding the intestines. They have a series of ducts that pump the lymph into the bloodstream to help remove wastes, toxins, debris. The major functions of the lymphatic system are fighting cancer, infections, controlling fluid balance and digesting fats. In the USA the biggest cause of lymphedema are woman that have had breast cancer or underwent radiation therapy. Worldwide lymphedema is caused by a parasite called Filariasis. It affects well over a 170 million people living in the tropics, it is transmitted through mosquito bites.

Lipedema is also known as “painful fat syndrome”. It is an interesting syndrome as it starts below the waste, going down the legs but stopping at the ankles. In some cases the arms can also be involved, but it is mostly below the waste and is bilateral. The fat seems to be

symmetric, bruises and is frequently painful. Lipedema is a progressive disease and almost resembles the growth of a rather slow but progressive spreading cancer. It seems not to affect men as much and has “growth” spurts during puberty, pregnancy or menopause. It is the opinion of the author of this paper that men are more affected than we think, especially when men are experiencing elevated estrogen and low testosterone, thus showing female characteristics and even hypogonadism. Lipedema is interesting in the weight loss aspect, people seem to lose the weight elsewhere as the body seems to hold onto the lipedema fat areas. Lipedema seems to be causative in Lymphedema and the combination of both is called Lipolymphedema.

Lipedema is broken down into the progression of these five phases [4]:

- Phase 1: Adipose tissue increases on thighs and buttocks
- Phase 2: Fat pads are developed on the inner side of the knees
- Phase 3: Total lipedema from hips to ankles, bilateral
- Phase 4: Arms and legs get affected, bilateral
- Phase 5: Lipolymphedema aka “elephantiasis” a disfigurement

Therapy

Current therapy for lipedema and lymphedema is decongestive lymphatic therapy (DLT), by the use of a massage technique called manual lymph drainage (MLD). In some cases a technique called intermittent pneumatic compression (IPC) is used to improve venous flow and slow down lymph production. There is also surgery, liposuction however it seems contraindicated because of iatrogenic damage to lymphatics [5]. Tumescant liposuction is more effective in removing excess adipose tissue and less likely to damages lymphatic vessels and a much safer alternative to lipoaspiration [6]. Currently hardly any nutritional therapies other than severe caloric restriction has been addressed in the literature for these conditions.

Visuals of Lymphedema and Lipedema

There seems to be some associations or resemblances between figure 1-6. The common denominator in all of these picture is the destruction or inhibition of a normally functioning lymphatic system. We cannot deny the strong correlation between exogenous fat digestion, emulsification and absorption and the lymphatic system. The lymphatic system has a very strong association with our immune system through elimination and detoxification pathways. We need to properly investigate the correlations between all these systems and our new processed western diet of inflammation. Figure 4 portrays what would be perceived as obesity however it is truly a severely compromised lymphatic system. This Lipedema condition has the modern face of obesity and something we should term “Leaky Lymph Syndrome”.



Figure 1: Courtesy of: www.globalnetwork.org – Lymphatic Filariasis.



Figure 2: Courtesy of: www.medscape.com – Breast Cancer Lymphedema.



Figure 3: Courtesy of: www.lymphedemblog.com – Secondary Lymphedema.



Figure 4: Courtesy of: www.thedoctorstv.com – Lipedema.



Figure 5: Courtesy of: www.Medicaldictionary.thefreedictionary.com – Hypertrophic/Hyperplastic Obesity.



Figure 6: Courtesy of: www.healthwealth.com – Elephantiasis.

Physiology and Biology of Lymphedema and Lipidema

In order to understand the complexity of these conditions we need to familiarize ourselves with the terms and “players” involved in the lymphatic system and inflammatory processes. First and foremost we need to look at the organs and systems in the lymphatic system and understand its direct correlation to the GI system. We often state that the GI tract hosts 70% of the immune system, the lymphatic system is actually the main reason for this profound statement. Therefore we cannot really discuss the GI – tract without giving complete clarity to the lymphatic system and its essential involvement.

Thymus: Immature lymphocytes are made mature T - cells through the thymus located in the thoracic cavity.

Spleen: Measures the quality of our RBC by filtering our blood. Old RBC are removed by phagocytosis through macrophages. It can also release lymphocytes if it picks up viruses or bacteria.

Tonsils: They are part of immune system and help fight infections, modern medicine fails to acknowledge the importance of them.

Appendix: It was thought to be of very little importance but recently has come under further investigation as it relation to microbiota and regulation of certain pathogenic species. Some refer to it as the hypothalamus of the enteric nervous system.

Gut Associated Lymphoid Tissue (GALT) is broken into three categories:

1. **Peyer’s patches:** Located in the mucosa and submucosa of small intestines, very concentrated around the ileum. They contain mostly B-cells.
2. **Lamina Propria Lymphocytes:** Located in the mucosa of the small intestine, contains mostly B-cells.
3. **Intraepithelial Lymphocytes:** Located between the cells of the epithelial layer of the small intestines, and located between the tight junctions. We might postulate that tight junction dysregulation through intestinal permeability might have a profound effect on lipedema and lymphedema.

According to Ryan [7] “lymph stasis” and fluid leakage from lymphatic vessels may promote the accumulation of fat. The consistent leaking of these vessels will result in edema in the interstitial spaces of the skin, this will lead to the eventual fibrosis. Early stage lipedema/lymphedema results in “pitting edema”, the depression of the skin upon touch. As the lymph fluid lies dormant for a while (lymph stasis), this will cause fibrous like growths called fibrosis and the eventual result will be “non-pitting” edema. If not treated this will tend to accumulate in the area and could become infected with a condition called “cellulitis”. It is interesting to note that nearly all lymph nodes are located in adipose tissue, lymph is mostly emulsified fat and it appears that fat deposition occurs first around the lymphatic structures [8]. This information clearly demonstrates the interrelated association between lymph and fat. Essential Fatty Acids form the main fuel for our lymphocytes, actually most of the triacylglycerols found in lymphocytes come from areas adjacent to the perinodal adipose tissue [9]. This area also seems to house more PUFA’s than areas of adipose tissue situated further away.

Hypertrophic obesity

Increase in the size of the fat cells, where the number of fat cells stay approx. the same. The importance of the lymphatic system in fat deposition and inflammation has been reported by [10] who postulates that inactivation of a single allele of the gene Prox1 in mice led to adult-onset obesity due to abnormal lymph leakage from mispatterned lymphatic vessels. It seems to increase the storage of leaking lipids in existing adipocytes and might be causing adipocyte hypertrophy. In lipedema the fat cells are bigger in size and seem to have a shorter cell lifespan. The macrophage involvement causes the tissue to have more of a crown shape due to its scavenging properties. In the same breath as the evolutionary healing process takes place adipose derived stem/progenitor/stromal cells are produced to heal and repair the fat cells, which are being scavenged [11].

Hyperplastic obesity

Increase in the number of fat cells, where the size of the fat cells stay approx. the same. According to the same [10] study the second lymphatic leakage issue is that once adipocyte reaches maximum storage capacity hyperplasia is stimulated.

Hypertrophic/Hyperplastic obesity

Where both occur at the same time, thus according to the above information lymphatic leakage is a prime example of potentiating both hypertrophic and hyperplastic fat cell development. Fat cells living primarily in stagnant fluid like in lipedema and lymphedema can only grow by taking in glucose as an energy source. Thus elevated glucose in the blood and elevated insulin levels could be adding fuel to the fire. Many researchers still hypothesize that lipedema is a combined “effort” of hyper/hypo fat cell development. These fat cells stimulate the recruitment of carbohydrates in specific hyaluronic acid. This long sugar structure is found in abundance in most living organisms and it likes to bind water. The hyaluronic acids gives the lipedema fat a quality similar to gelatin, making the body feel heavy. Hyaluronic acid is also one of the reasons the WBC are attracted to the area, as it causes an inflammatory response due to all the trapped water inside of the cell.

Vascular Endothelial Growth Factor (VEGF)

We frequently mention leaky gut, leaky brain and even leaky mouth. Let’s add to this equation “leaky lymph”. Macrophages in adipose tissue secrete signaling factors including VEGF which trigger the formation of leaky lymphatic vessels leading to further swelling, inflam-

mation and obesity [12]. It appears that the literature supports that people with lymphedema and lipedema have various sources of VEGF signaling. Missing lymphatic vessels, smaller than normal lymphatic vessels, incompetent lymphatic vessels and overgrowth of lymphatic vessels seems to be the result of genetic polymorphisms in primary lymphedema [13]. In a study people with a diagnosis of lymphedema had higher VEGF levels than controls [14]. Another study showed that elevated VEGF levels in patients with lymphedema resulted in tissue edema due to abnormal leaky blood vessels [15]. Lipedema patients had a fourfold increase in VEGF over controls [16]. There might be an evolutionary principle attached to all of this, the lymphatic system was designed to produce VEGF in response to inflammation to promote vessel growth to clear the inflammation. However it was never intended to take care of consistent inflammation of unknown artificial and processed origin. Thus it appears lipedema and lymphedema might be nothing more than just an inflammatory response with no shut down period. VEGF is also stimulated by various stress triggers like hypoxia (low oxygen due to hypertension, diabetes, and smoking), mechanical stress (very tight clothing, or just extreme body weight), metabolic stress (hypo/hyperglycemia or functional metabolic acidosis), and psychological stressors (work, relationships, and finances). Anyone with lymphedema should avoid smoking at all costs due to the extreme VEGF signaling.

Fibroblast Growth Factor 2 (FGF2)

Fibrosis seems to be caused by the excess signaling of FGF2. It appears that many anti-angiogenic foods also trigger the FGF2 response [17].

Mononuclear Phagocyte System Cells (MPS)

We all know the importance of salt in the human diet, especially the “impure” forms such as Himalayan and Sea Salt. However in lipedema and lymphedema there might be a negative correlation with salt. It is unclear at this time whether refined processed table salt might be at the heart of the problem or if unrefined salts also promote the same issues. The literature is clear that excess salt will be stored in the skin as NaCl ions. The lymphatic system, immune cells and blood pressure seems to somehow regulate this storage with mechanisms not fully understood. These MPS cells seems to be the monitoring agent and complete regulator of the electrolyte balance in the fatty tissue fluid. With extended abuse of high salt diets it seems that abnormal capillary growth in the skin results in another form of cellular hyperplasia (Wiig, *et al.* 2013). High salt diets seem to stimulate the production in Th-17, a highly pro-inflammatory agent (IL-17 produce CD4 helper T-cells). Certain autoimmune conditions have been associated to Th-17 like psoriasis, RA and asthma [18].

Chyle

The absorption of exogenous fats: Short chain and medium chain fatty acids can be readily absorbed from the small intestines to the bloodstream, however fatty acids in excess of 12 carbon chains including essential fatty acids needs to first make their way through the lymphatic system. Almost half of the lymph in the body has its origin in the abdominal viscera [19]. In the GI tract exogenous fats (from fats we consume) are broken down into cholesterol and triglycerides. They are packaged into something called a “Chylomicron” and then sent through the lymphatic system (aided by the lymph nodes). This chylomicron attaches to a lipoprotein called B-48 that bypasses the liver into the bloodstream, it is believed that the B-48 regulates the direction of the chylomicron in the lymphatic system towards the bloodstream. In the bloodstream two more lipoproteins are attached, “C2” and “E”. C2 steers the chylomicron towards the adipose tissue, at the site of the adipose tissue an enzyme LPL (Lipoprotein Lipase) causes the chylomicron to deposit the triglycerides as free fatty acids. In this process the C2 is cleaved off and the process is done. The remaining structure is now called a chylomicron remnant and the E- lipoprotein steers the remnant and remaining cholesterol to liver, there it attaches to the LPL-r (Lipoprotein Receptor) and deposits the remaining cholesterol. The human diet mostly takes in fats in the form of long chain fatty acids, these are processed in the GI tract as explained above. The intestinal villi assists in the absorption of these fats and contain vessels inside called “lacteals” where they are converted into a liquid called “Chyle”, it has the appearance of milk. Thus the more long chain fatty acids we eat the more chyle we will produce. Eating a very high fat diet can add two liters of fluid to the lymphatic system daily due to excess chyle [20]. Failure in the process above to properly transport and emulsify exogenous fats and chyle could trigger subcutaneous edema, chylous ascites or chylothorax [12].

Leptin

Fatty acids are the largest secretory product provided by the adipose tissue. However the adipocytes also secrete peptides, complement factors, hormones, cytokines, and enzymes. These cytokines are better known as adipocytokines. Leptin is an adipocytokine and has been associated to many pro-inflammatory conditions. Leptin is expressed in inflamed colonic epithelial cells however research shows that adipose tissue might be a significant source of leptin in IBD [21]. Leptin can also stimulate the production of TNF – alpha [22].

Adiponectin

Adiponectin another adipocytokine can actually reduce the TNF-alpha expression from macrophages [23]. This proves again the continuous interaction between hormones and the bodily organs and tissues. This complex system of counter intelligence was put there by evolution to deal with intermittent inflammation as a healing agent not chronic inflammation as we are exposed to today. Adipose tissue also hosts a significant amount of macrophages and it is indicated that as fat increases so do the macrophages [24]. These macrophages like adipocytes can store fat and glycogen and clearly rely on this nutrient supply to keep this going.

Dendritic Cells

Only fully matured dendritic cells are located in the lymphoid tissue, they are generally present in non-lymphoid tissues such as respiratory system, GI tract and skin but are found there in the immature state. They have to reach the lymphoid organs to undergo a full maturation, they also seem to add on fatty acid stores in their travels to reach maturation. Maroof, *et al.* [25] states that dendritic cells may actually transport fatty acids and carry them into the lymph node like a Trojan Horse, fueling and altering immune activities and lending support through diet and immunity.

Macrophages

They also circulate the lymph but not in the same amount as dendritic cells. All organs drained by lymphatic vessels contain macrophages, they are heavily implicated in obesity induced inflammation [26]. Macrophages secrete growth factors VEGF and they are implicated in the potential trigger for lymphangiogenesis [27].

Arachidonic Acid Cascade

The Cyclooxygenase (Cox) enzyme activates thromboxane, prostacyclin and leukotrienes (Eicosanoids) by virtue of the prostaglandin H2. If Cox is inhibited we have no ability to produce prostaglandin H2. There are three steps that come out of the cox pathways via prostaglandin H2:

1. Prostaglandin H2 in the endothelium (blood vessels) produces prostacyclin this is actually helpful for the heart. This is why aspirin is recognized as being heart “friendly”.
2. Prostaglandin H2 through platelets converts to thromboxane A2 this is not good for the heart and has been correlated to CVD.
3. Prostaglandin H2 converts to more stable prostaglandins (PGD2, PGDE2, PGF2), these are helpful especially in the stomach creating protective effects. They could also cause pain, fever and inflammation. This is actually a positive thing for us. As they say “show me a fever and I’ll show you a cure” in the western world we have decided that all inflammation is bad and sometimes confuse “healing inflammation” as bad. Remember inflammation is not an infection!

Some studies have shown that certain lymphatic vessels show spontaneous contractile activation in the presence of arachidonic acid inhibitors [28]. This once again should bring the excessive use of NSAIDs into question. In another study by Johnston [29] on prostaglandins he found that cyclooxygenase and lipoxygenase are excitatory and inhibitory in nature and produce very powerful responses on isolated mesenteric lymphatic vessels, indicating the intrinsic network that should not be excessively manipulated by Pharmacia.

Diet, Intestinal Permeability and Lipedema/Lymphedema

Non Celiac Gluten Sensitivity (NCGS) has various symptoms in common with people suffering from Lymphedema and Lipedema. The adaptive immune system is activated in people with gluten sensitivity especially those that have the genetic factors for gluten sensitivity

(HLA – DQ2 and HLA – DQ8). The process starts with shortened villi due to atrophy, this causes the rather large alpha-gliadin protein to activate the CXCR-3 receptor on the epithelial cells and they send a signal to zonulin (the protein that regulates tight junction release), this process allows alpha-gliadin to escape into bloodstream. In the bloodstream the dendritic cell becomes an antigen presenting cell looking for gliadin, at this time alpha-gliadin has made its way to the tissue transglutaminase enzyme sitting on various tissue, like pancreas, thyroid, liver and others. The immune cells engulf the alpha-gliadin but in the same process the tissue it is attached to, due to the “guilty by association” verdict. As we already discussed some of the Gut Associated Lymphoid Tissue (GALT), is also strongly associated with tight junction function. It can be postulated that if zonulin is dysregulated it can affect the GALT in the same way. This leakage in the gut will lead to edema not very different from what we see in Lipedema. Damage to the intestinal lymphatics due to NCGS can lead to edema of the trunk and legs, chyle leakage (chylous ascites) or excess fluid in the lungs (pleural effusion) might occur in severely intestinal permeable cases.

Li [17] promotes the following VEGF and FGF2 inhibiting foods, which could play a huge role in the reduction of inflammation and the stagnation of lymphedema and lipedema.

1. Green tea catechins
2. Genistein in soy beans
3. Lycopene in tomatoes, watermelon and other bright red fruits
4. Omega 3 fatty acids
5. Glucosinolates, Isothiocyanates, Indole-Carbinol 3, DIM, basically cruciferous vegetables
6. Flavonoids in spinach, onions, parsley, beets and thyme
7. Polyphenolic flavonoids in lettuce, chicory, arugula and red lettuce
8. Proanthocyanidins in cacao, cinnamon, cranberry, apples, grapes, black current, persimmon and choke berry
9. Anthocyanidins in berries, grapes and red wine
10. Curcumin, turmeric
11. Vitamin K2 and fermented foods, pre-biotics
12. Beta-cryptoxanthin in bright orange, red or yellow foods
13. Pomegranate, berries of all kinds, walnuts, pecans, red grapes
14. These patients cannot use diuretics

As previously mentioned a low salt diet needs to be followed with lymphedema and lipedema due to MPS cells as previously discussed. Keeping your salt intake at less than 1500 mg/day and increasing your potassium containing vegetables will improve the lymph and blood circulation. Himalayan salt has a natural balanced sodium and potassium and might be a good choice when using salt. Drinking 8 - 12 ounces of potassium broth per day might be helpful in sustaining a more acceptable Na/K balance. A very strict attention needs to be paid to processed foods and their sodium content.

A ketogenic diet is contraindicated for people with lipedema and lymphedema. As referenced earlier patients suffering from these conditions have compromised lymphatic systems and struggle with exogenous fats, especially long chain fatty acids. The Trans fats are especially inflammatory in specific Palmitelaidic Acid (16: 1n 7t), others include c 18 Trans Isomers: Elaidic Acid, Petroselaidic Acid, Transvaccenic Acid. These fats actually interfere with eicosanoid synthesis.

It appears that a plant based whole food diet, with additional omega 3 fatty acids at this time might hold the biggest promise in research. A diet that can be formulated around as little as possible long chain fatty acids with a large emphasis on medium chain triglycerides. It appears very seldom or ever that vegans and fruitarians are disabled by these conditions, however there has been some mention of anorexics eventually developing lipedema. According to the University of Maryland Medical Center eliminating suspected food allergens, such as dairy (milk, cheese, and ice cream), wheat (gluten), soy, corn, preservatives, and chemical food additives will help reduce edema [30].

Conclusion

It appears that we need to re-evaluate our general definition and diagnosis of obesity. We need to start looking at categorizing this “disease” into far more descriptive causes and defining criteria. Lipedema was not put into the IDC coding as a disease or disorder until after 2011, but yet 11% of the population have the condition according to epidemiological studies prior. It is a grossly underestimated and undiagnosed disease or disorder. Anytime you walk around in a mall or supermarket and see a person morbidly obese on a mobile scooter, because they are physically incapable of walking, think of lipedema and elephantiasis. Both of which are lymphatic diseases and disorders. Our research in the future needs to go deeper into understand the connection between the 16 - 18 carbon trans-fats and how they might be dysregulating the lymphatic process, as well as LPS, GMO, gluten and other prolamines that dysregulate zonulin. Further investigating needs to be focused on carnitine deficiency and how it relates to lipedema, might we perhaps find these people also have severe beta oxidation issues? It is time to finally shift away from calories in and calories out, many people with lipedema have been on less than 500 calories per day and gained weight. Might it be as simple as measuring FGF2, VEGF, TH-17, IL-6, TH-2, Carnitine, Leptin, Zonulin and IGF-1 in serum to build up enough diagnostic criteria to actually diagnose this condition before it shows physical symptoms? The connection of bile and the gut biome was not discussed in this paper but needs to be seriously investigated in the future research, the connection of bile to the gut biome and/or fat emulsification is irrefutable. Could there be a connection between all the cholecystectomies and lipedema? From clinical experience there seems to be an indirect correlation between gallbladder removal weight loss resistance and edema. At this point the only dietary data we have associated to this condition is attempts to reduce VEGF in serum measurement. This is a great starting point as the diet containing these VEGF reducers seems to be a whole plant based diet low in saturated fats. However maybe the trans-fats are more the problem due to their isomer form and mostly long carbon design. Controlling blood glucose levels through glycemic control seems once again vital in this condition as glucose seems to feed the fat cell and even the dendritic cell. In my final conclusion I want to finish with the following profound statement made in 1983 by Dr. Mandell – clearly ahead of his time [31]:

“Allergic edema or water retention, is one of the most misunderstood problems of overweight. It is a reversible disorder of the capillaries... During an allergic reaction, some of the fluid that is part of the blood plasma leaks through the allergically enlarged pores of the temporarily malfunctioning capillaries into the surrounding tissue, causing it to puff up with fluid...When the food of chemical that caused the allergic reaction is no longer present in the body...the ‘allergic’ fluid that has leaked into the tissues returns to the general circulation...taking with it important pounds of your unnecessary water weight...”

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