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Review

Optimizing Lymphedema Outcomes through Lifestyle

Leslyn Keith [1, *], Robert Erkstam [2]

1. Lymphatic Lifestyle Solutions, 6626 Gordon Rd H, Wilmington, NC 28411, USA; E-Mail: leslynkeithot@gmail.com
2. Self Care Therapy, 6626 Gordon Rd H, Wilmington, NC 28411, USA; E-Mail: robert@selfcaretherapy.com

* **Correspondence:** Leslyn Keith; E-Mail: leslynkeithot@gmail.com

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Abstract

Lymphedema, a chronic incurable condition characterized by edema, inflammation, reactive fibrosis, adipose proliferation, and compromised immune function, affects over 250 million people worldwide [1]. Further, a comorbidity of obesity increases the risk of developing lymphedema and can result in irreversible damage to lymphatic function. Access to appropriate and timely lymphedema treatment, performance of proper self-management strategies, and implementation of healthy lifestyle practices are critical for optimal outcomes for those affected. It is vitally important that a healthy lifestyle program for patients diagnosed with lymphedema include strategies for addressing both lymphedema and weight management. In this paper, we describe the essential elements of a successful program for lymphedema and weight management: ketogenic nutrition, exercise, stress resilience, and sleep.

Keywords

Lymphedema; ketogenic diet; obesity; lifestyle

1. Introduction

The lymphatic system is a unidirectional network of vessels, nodes and lymphoid organs that serves to maintain tissue fluid balance, deliver dietary fat and fat-soluble vitamins to blood circulation, and support immune functions. Revisions to Starling's Equilibrium highlights the vital importance of a functioning lymphatic system, as we now know that interstitial fluid is not absorbed by venous capillaries as originally hypothesized in 1896, but is transported to blood circulation by the lymphatic system [2].

Lymphedema is an accumulation of protein-rich fluid in the interstitium that results in edema, chronic inflammation, reactive fibrosis, and adipose proliferation in the affected body areas. Common complaints associated with lymphedema include symptoms of swelling, pain, heaviness, tightness, decreased strength and joint range of motion, impaired daily living skills, and negatively impacted quality of life [3].

Primary causes of lymphedema include various genetic disorders that result in lymphatic impairment, with symptoms presenting anytime over a lifespan [4]. Secondary causes can be rooted in an increased fluid load from an organ, or a bodily system failure that overwhelms the lymphatic system. Damage to lymphatic structures from traumatic injury such as surgery, radiation treatments, or infection can also result in lymphedema [5]. In addition, since prolonged fluid overload results in further insults to the lymphatic system, lymphedema etiology is often multi-causal [6].

1.1 Impact of Obesity on Lymphedema

One of the major risk factors for the development of lymphedema is obesity, making it critically important to adopt intervention strategies that address both conditions concurrently [7]. While the current prevalence of obesity has topped 42% in US adults [8], the occurrence of this condition is even more pervasive in the lymphedema population [9]. Unfortunately, lymphatic function may be irreversibly damaged with a BMI of above 50 kg/m^2 [10].

Although the progression of obesity to lymphedema is multi-causal, two main pathways lead to lymphedema and often occur simultaneously, magnifying the consequences. With the revised Starling's Equilibrium, the lymphatics are now recognized as the primary system responsible for absorption and transport of interstitial fluid, which is needed to maintain the proper balance of fluid in tissues [2]. Therefore, both excessive fluid load and decreased flow can lead to increased swelling and eventually to chronic lymphedema, as shown in Figure 1.

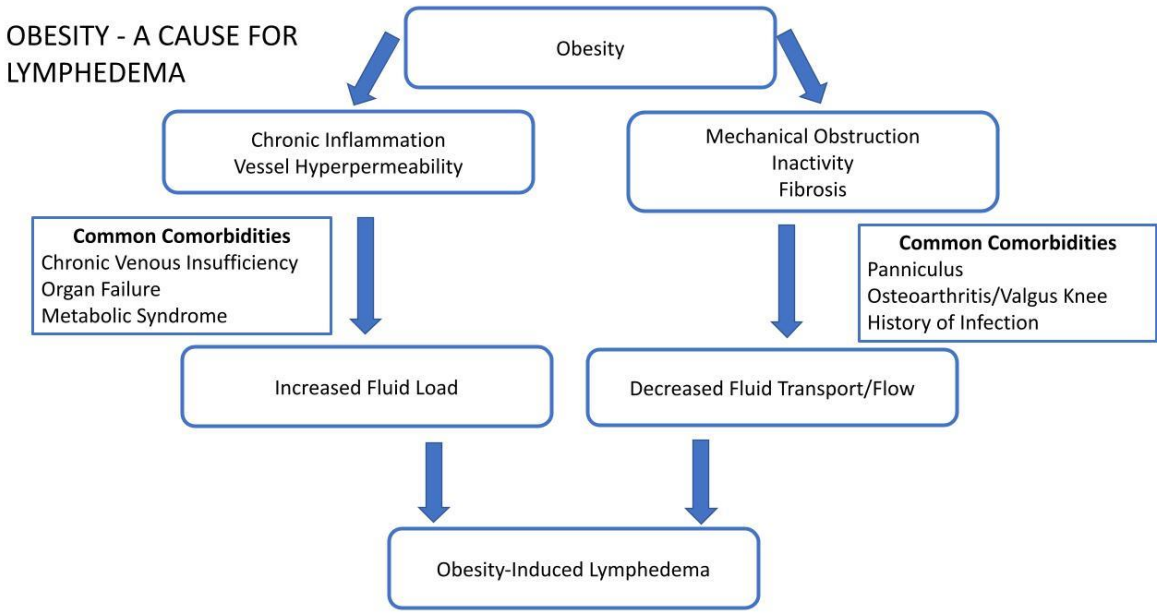

Figure 1 Two main pathways for development of lymphedema in the presence of obesity.

Chronic inflammation as well as blood and lymphatic vessel hyper-permeability experienced with obesity and its common comorbidities (chronic venous insufficiency, organ failure and metabolic syndrome) can all contribute to increased fluid load which tends to overburden the lymphatic system [7, 11]. Obesity may cause decreased flow due to a mechanical obstruction from tissue fibrosis (from a history of infection or wounds) or from the sheer weight of tissue such as a large abdominal panniculus or massive localized lobules seen in some morbidly obese patients [12]. Decreased flow might also result from pain-induced inactivity and immobility and hence a lack of an efficient muscle pump to promote lymph transport [13]. Lastly, morbid obesity alone may increase fluid load and simultaneously cause dysfunctional lymphatic vessels [10]. Weitman et al. [14] demonstrated the impairments in both lymph vessel and node function in obese mice and Yoshida et al. [15] showed marked differences in lymph vessels in obese versus non-obese adults.

A downward spiral of compromised microcirculation, inflammation, lymph stasis, and further adipose tissue deposition exists for many patients with obesity-induced lymphedema [7]. It is incumbent upon the lymphatic specialist treating patients battling this condition to facilitate the interruption of this vicious cycle. We propose that the lifestyle changes recommended here can be a potent intervention for those patients burdened with lymphedema and obesity.

1.2 Optimal Lymphedema Management

According to the 2020 Consensus Document of the International Society of Lymphology, best practice for lymphedema treatment is performed in two phases: the initial intensive treatment phase using Complete Decongestive Therapy (CDT) followed by the maintenance phase, which is an individualized program performed on a daily basis at home [5]. CDT consists of manual lymph drainage (MLD) massage, skin care, decongestive exercises, and multi-layered compression bandaging. The maintenance phase, designed to help the patient sustain the results gained in therapy, can include self-MLD, skin care practices, exercise, self-bandaging, and compression

garments. Patients may also use adjunctive practices such as a pneumatic compression pump and limb elevation. For some patients, lymphatic microsurgery and medications may be beneficial [16, 17].

Despite adherence with conservative measures in the two phases of standard lymphedema treatment, many people with lymphedema continue to struggle with their condition, suffering with greater swelling, pain, disfigurement, and repeated life-threatening infections [18]. In our clinical practices, it has not been unusual for patients to experience anxiety about an exacerbation of symptoms and their ability to manage their lymphedema appropriately.

We propose that a vital piece of lymphedema treatment has been largely ignored, namely healthy lifestyle practices. The majority of lymphedema patients may not be able to achieve ideal results from lymphedema treatment and reach their full potential unless healthy lifestyle behaviors are adopted and sustained. Figure 2 displays our philosophy that Phases I and II of lymphedema treatment must occur in the context of lifestyle practices that promote lymphatic health and function.

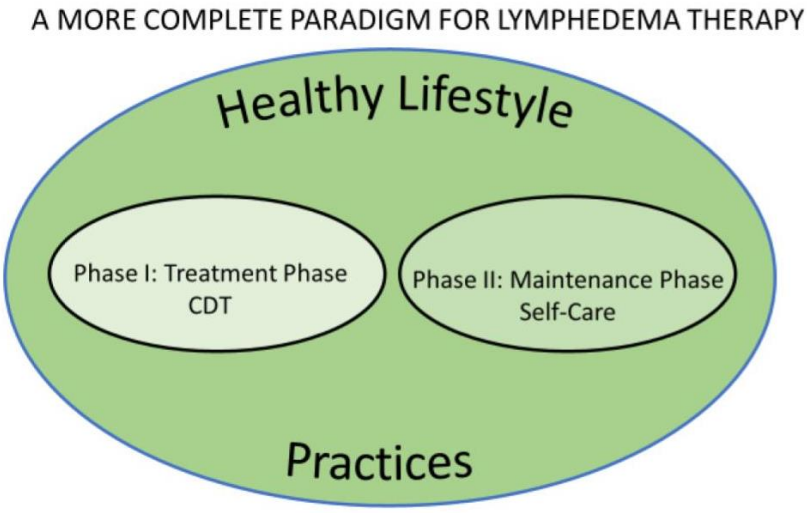

Figure 2 Phases I and II of lymphedema treatment should occur in the context of healthy lifestyle practices.

In this paper, we share our clinical experience with helping patients adopt healthy lifestyle practices that have the greatest beneficial impact on lymphedema and obesity. These practices include ketogenic nutrition, exercise, stress resilience, and sleep. Figure 3 shows that habit formation in each of the four major areas of lifestyle practice is individually essential as well as interdependent upon the others for successful lymphedema and weight management. Because positive and lasting lymphedema outcomes will always be limited unless a healthy eating plan is used, ketogenic nutrition is likely the most important of these elements. For this reason, we have represented it as a larger circle than the other lifestyle interventions.

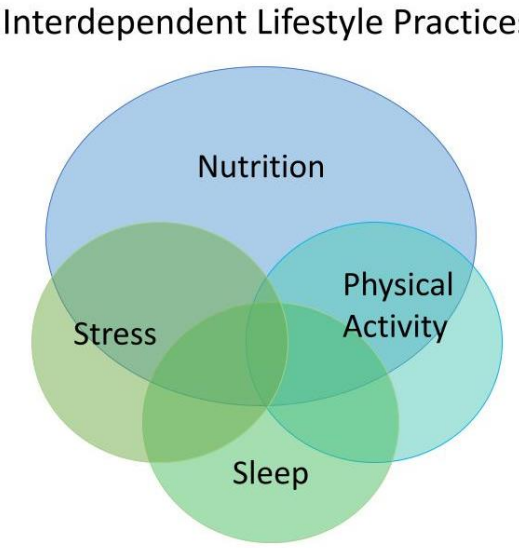

Figure 3 The interdependence of four lifestyle practices for the promotion of lymphatic health.

2. Ketogenic Nutrition

Health improvements in general, along with better lymphedema and weight management specifically, are driven by nutrition. It has been our clinical experience that without adherence to a healthy eating pattern, maximal lymphedema outcomes cannot be achieved. Here, we define ketogenic nutrition, and detail why and how this eating pattern may enhance treatment outcomes and improve quality of life for individuals with lymphedema.

A ketogenic diet is a low-carbohydrate, moderate-protein, high-fat way of eating. While it is a high-fat diet compared to most other dietary plans, the essential ingredient is keeping carbohydrates to a minimum, ideally <50 grams per day. When carbohydrates are restricted in this way, the body switches from using predominantly glucose to fuel its cells to using ketones and fatty acids instead [19]. This state is called ketosis, a healthy metabolic state that does not require the presence of insulin. Insulin halts the utilization of fat for fuel and forces excess carbohydrate intake into fat storage. By keeping glucose low, the need for insulin decreases, thereby promoting the utilization of fat for energy that the body needs [20].

The type of fat consumed in a ketogenic diet may be of importance. Long-chain fatty acids (LCFA) are absorbed by intestinal lymphatics (lacteals), while medium and short-chain fatty acids bypass the lymphatic system and are transported directly to the liver via the portal vein. For this reason, treatment for intestinal lymphangiectasia and chylous leaks may include restrictions on LCFA to reduce the burden on the lacteals [21]. However, long term use of a low LCFA diet has been shown to result in nutritional deficiencies [22]. Regardless, this dietary restriction may be unnecessary for patients without impairment to intestinal lymphatics.

2.1 Ketogenic Nutrition for Weight Management

For the best results for lymphedema and weight management, we recommend a well-formulated ketogenic diet that further restricts carbohydrate intake to below 20 grams per day. It is important to include sufficient protein for cellular health, and fat is used as the main source of energy, which

tends to improve satiety. For this reason, calorie-counting is not necessary. In our clinical experience, in the absence of an eating disorder, patients tend to respond to natural hunger signals and are able to balance energy intake and output without purposefully restricting calories. Many patients will spontaneously increase the length of time between meals, resulting in intermittent fasting. Without hunger or feelings of deprivation, consumption is reduced, which may facilitate the long term sustainability of this dietary plan [23].

Multiple studies have shown that ketogenic nutrition is safe and effective for weight loss without significant muscle loss. When compared to low-fat or calorie-restricted diets, the ketogenic diet produces better health outcomes, including weight loss, cardiovascular health, and body composition [20]. In a meta-analysis of 25 clinical trials that compared the effectiveness of a ketogenic diet to a low-fat diet, the ketogenic diet had superior results for body weight, lipid and metabolic profile, and blood pressure after at least 12 months [24].

One of the authors (LK) conducted a pilot study in her clinic with 10 participants with lymphedema and obesity enrolled in a 12-week lifestyle program that promoted a ketogenic diet [25]. Figure 4 shows the body weight change for each participant, with the 6 participants who chose to adopt a ketogenic diet (KD) in blue and the 4 participants who did not use a ketogenic diet (NKD) in red.

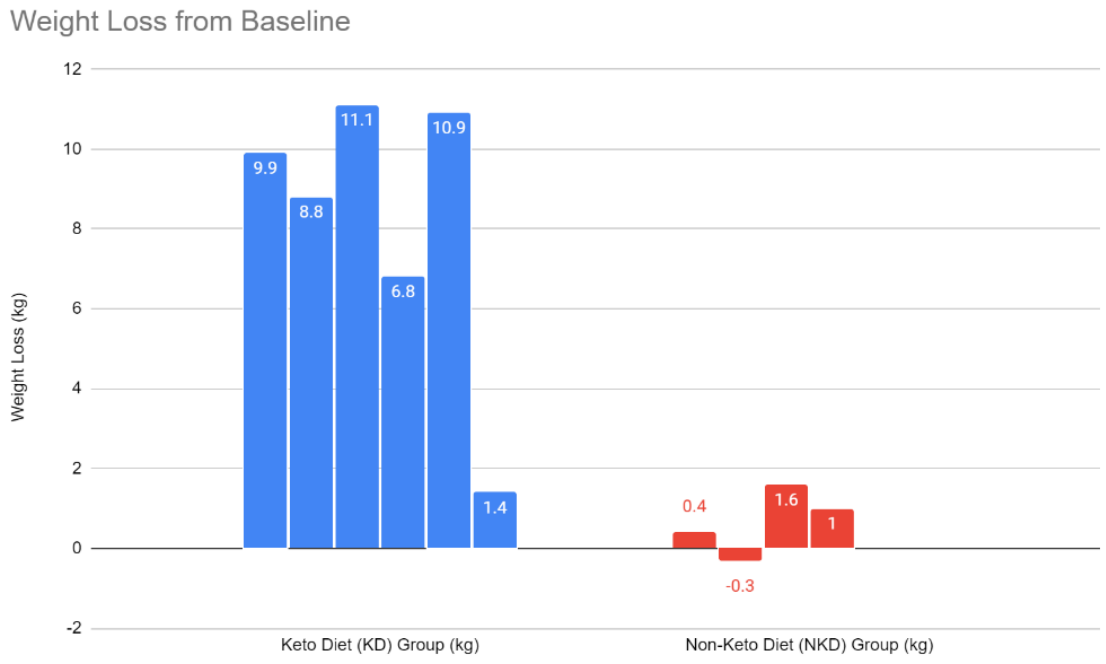

Figure 4 Individual data for weight loss from baseline in the 2 self-selected diet groups: ketogenic diet (KD) group and nonketogenic diet (NKD) group.

The KD group lost an average of 8.17 kg of total weight (SD = 3.67, $p < 0.001$) while the NKD group lost an average of 0.68 kg (SD = 0.83, $p = 0.415$). Additionally, the KD group had a mean waist circumference reduction of 7.25 cm (SD = 14.23), which is an indicator of improved metabolic health [26]. There was no reduction in waist circumference in the NKD group.

2.2 Effect of Ketogenic Nutrition on Body Composition

Another consideration when choosing a diet for weight loss should be its effect on body composition. Considering the importance of muscle activity for proper lymphatic functioning, it is important that the dietary approach does not result in the loss of muscle. Research has supported our own clinical experience that when participants lose weight on a ketogenic diet, the weight loss consists mostly of water and fat loss, especially if a plan of exercise is instituted [22, 23]. Conversely, traditional weight loss diets that are low-calorie and plant-based have been shown to contribute to higher loss of lean body mass than is favorable [27], possibly due to the lower protein and higher carbohydrate content.

Our clinical use of bioimpedance measures of body composition on patients who have adopted a ketogenic diet have confirmed that weight reduction consisted primarily of adipose tissue and water. For instance, a female patient diagnosed with obesity and lymphedema had successfully implemented a ketogenic diet and lost weight. Six months into her adoption of this eating plan, the patient became ill with a possible stomach flu, causing her to severely restrict her food intake for several days. When she recovered from this illness and returned for a follow-up visit, bioimpedance measures showed a significant loss of muscle mass. However, when she was able to resume a ketogenic diet along with exercise, she was able to regain muscle weight without regaining body fat or water.

Figure 5 shows the body fat loss experienced by lymphedema patients at the conclusion of a 12-week lifestyle course that encouraged adoption of a ketogenic diet. All 22 patients sustained a decrease in body fat, with a mean loss of 6.35 kg (SD = 4.63).

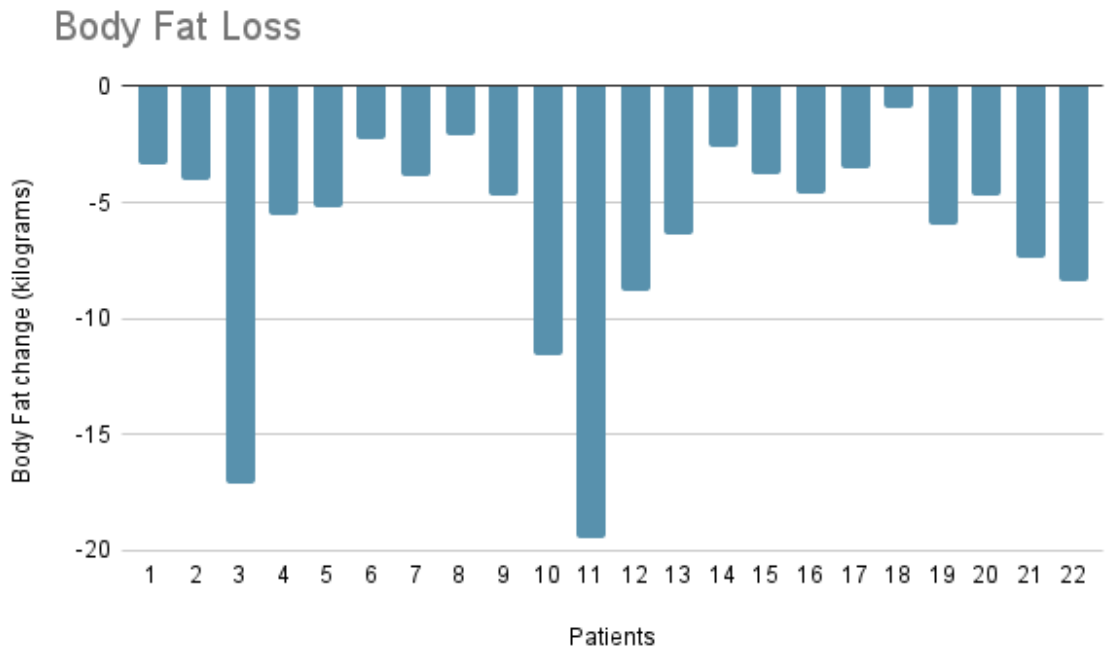

Figure 5 Individual data for reduction in body fat (kg) 12 weeks after instituting a ketogenic diet.

2.3 Ketogenic Nutrition and Lymphedema Management

Research has confirmed what we have experienced in clinical practice: a ketogenic diet has a favorable impact on the clinical symptoms of lymphedema. The success of a ketogenic diet in managing lymphedema symptoms may be rooted in the macronutrient composition of the diet, namely carbohydrate restriction and ad libitum consumption of healthy fats.

Zawieja et al. [28] showed as much as 50% reduction in transport capacity of the lymphatic system of high fructose-fed rats. This finding may have been confirmed in women with breast cancer-related lymphedema who did not experience any limb volume reduction after losing weight using a diet composed of a high fructose meal replacement [29]. These findings are consistent with research showing that a high carbohydrate diet tends to be pro-inflammatory, while a diet lower in carbohydrate has anti-inflammatory properties [30, 31]. Restricting carbohydrate intake may not only reduce inflammation in lymphedematous tissues, but it may also relieve some of the fluid burden. In this way, the anti-inflammatory properties of a ketogenic diet may both decrease fluid load and facilitate better drainage.

There is notable evidence that the lymphatic system benefits from the availability of fat. Muira et al. [32] showed an increased movement of lymphocytes by the lymphatic system in rats when consuming dietary fat. Animal studies have shown that lymphatic endothelial cells have a preference for ketones and fatty acids, even in the presence of glucose [33] and ketones can stimulate lymphangiogenesis [34]. These findings are significant in that they contradict the previously held notion that tissues are irreversibly damaged in lymphedema. We now speculate that improvement and repair of a damaged lymphatic system with a dietary approach may be possible.

2.4 Clinical Vignette

Ms. M is a 59-year-old female with primary (hereditary) lymphedema with onset in childhood. Throughout her life, her condition and symptoms gradually worsened. With a BMI of 22.4, she was not overweight and weight loss was not her goal. She enrolled in a virtual lifestyle course for individuals with lymphedema that encouraged a ketogenic eating plan. After two months on a ketogenic eating plan, for the first time in her life, she experienced a reduction of her lymphedema symptoms. She reported reduced pain and edema, as well as less reliance on wearing compression garments.

A ketogenic diet has shown significant impact on limb swelling in several studies, including the pilot study conducted by one of the authors (LK) mentioned previously [25]. Figure 6 shows a comparison of limb volume reduction between the two diet groups, with the ketogenic diet (KD) group in blue and the non-ketogenic diet group (NKD) in red. Four of the six participants in the KD group were able to reduce over 1100 ml in their affected limb(s), while two of the four participants in the NKD group showed an increase in the volume of their affected limb(s). In a number of our clinical patients who follow a ketogenic eating plan, we have noticed a reduced reliance on compression garments without increased swelling.

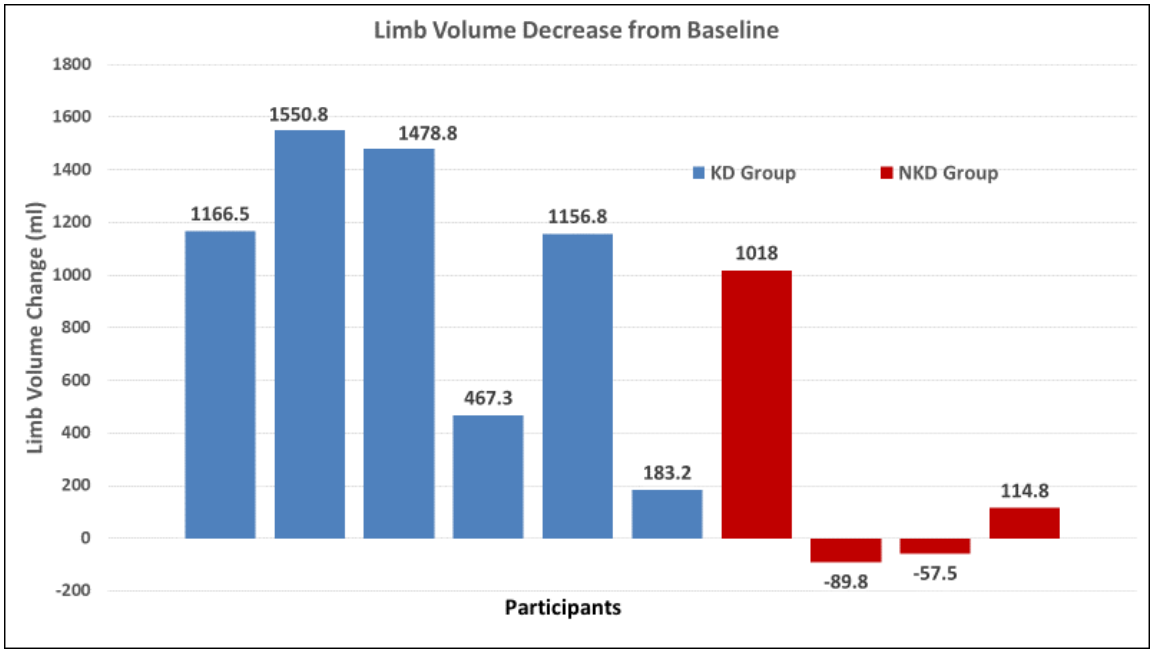

Figure 6 Individual data for limb volume decrease from baseline in the 2 self-selected diet groups: ketogenic diet (KD) group and nonketogenic diet (NKD) group.

The Rand 36-Item Short Form Health Survey (SF-36) was used to assess symptom severity in patients with lymphedema by one of the authors (RE). The SF-36 is a self-report survey that examines symptom impacts on quality of life [35]. Higher scores indicate a higher quality of life due to reduced symptoms. Patients completed the SF-36 prior to and just after completing a lifestyle course that promoted a ketogenic diet. As shown in Figure 7, patients were able to achieve significant improvements in fatigue, pain, and role limitations.

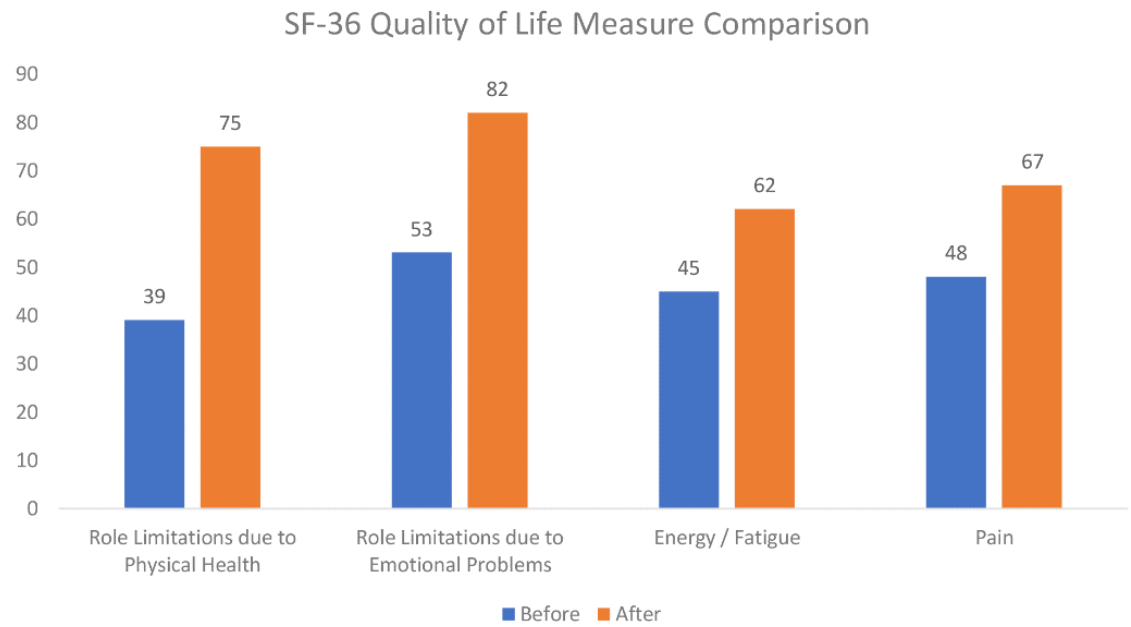

Figure 7 Comparison of Rand 36-Item Short Form Health Survey (SF-36) scores for 14 participants pre- and post-lifestyle course. Increase in score denotes increase quality of life.

The Lymphedema Life Impact Scale (LLIS), a self-report quality of life measure, was used in the pilot study described earlier [25]. A higher LLIS score denotes a greater impact of lymphedema on the respondent's life, thus a lower score indicates better quality of life [36]. Figure 8 shows the significantly greater quality of life of the KD group compared to the NKD group. The KD group demonstrated better reduction of impact of lymphedema on life in LLIS scores (M = 22.61, SD = 13.78, $p < 0.001$) compared to the NKD group (M = 2.83, SD = 5.71, $p = 0.305$).

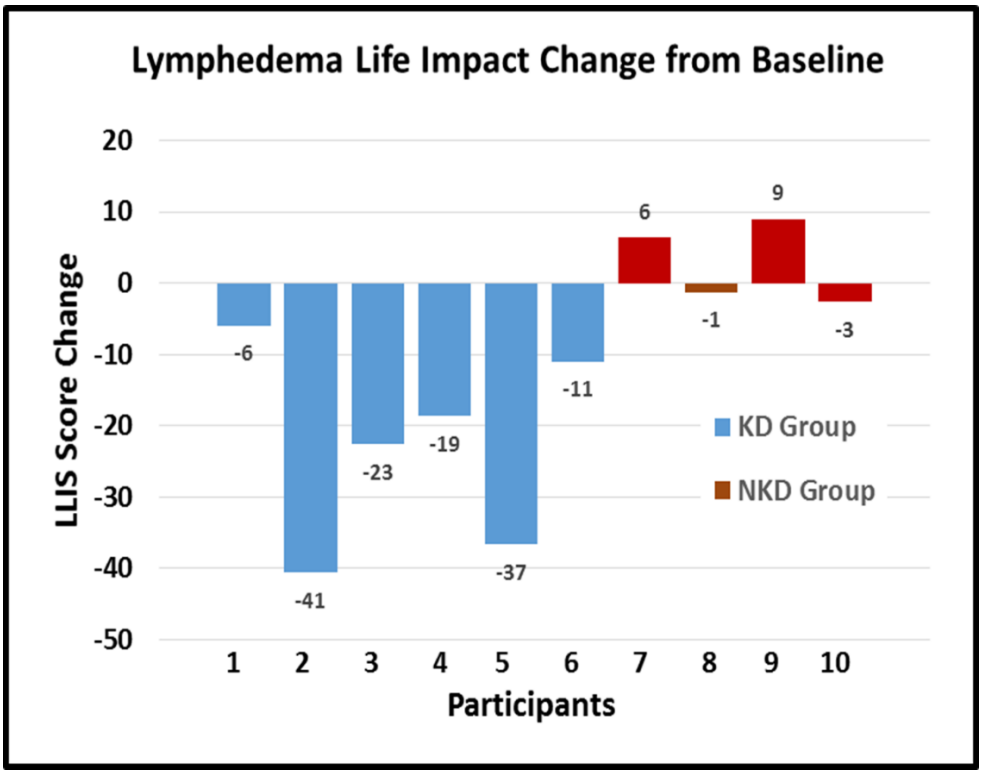

Figure 8 Individual data for impact of lymphedema on life by change in Lymphedema Life Impact Scale (LLIS) score in the 2 self-selected diet groups: ketogenic diet (KD) group and nonketogenic diet (NKD) group. Decrease in score denotes decreased impact of lymphedema on life.

A ketogenic diet has proven to be sustainable over the long term. Virta Health examined the effectiveness of a ketogenic diet for diabetes management [37]. This study showed excellent health outcomes (including better blood sugar control, weight loss, reduced need for medications, and diabetes remission) that were sustained over a period of two years. Their five-year data may prove to be just as promising. Our lymphedema patients have shown a similar adherence. One of the authors (RE) tracked body weight of patients who had adopted a ketogenic diet. The data so far shows that patients have been able to continue to maintain or lose more weight for several months, some for over a year, after completing a lifestyle program and implementing the diet (see Figure 9).

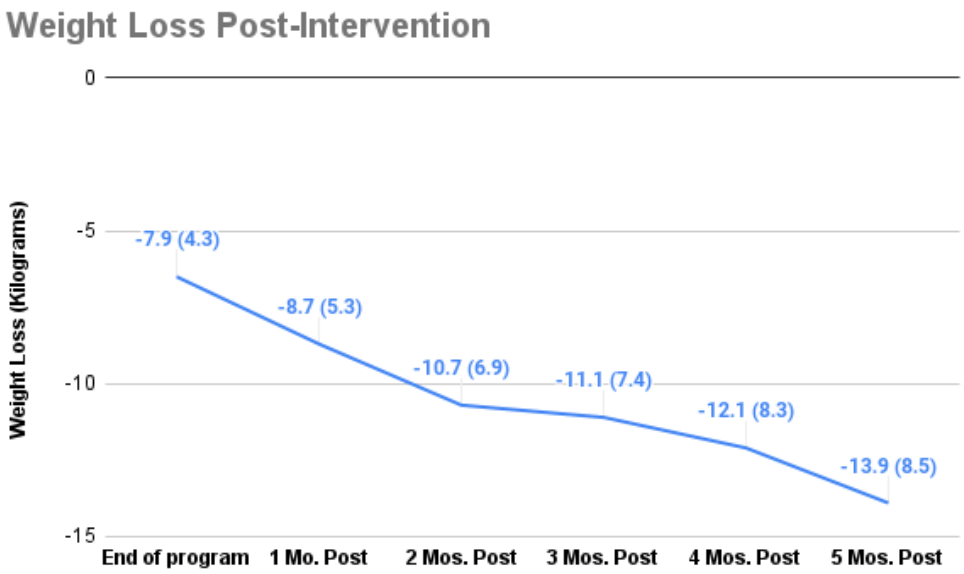

Figure 9 Weight loss expressed as mean (standard deviation) for 15 participants at monthly testing dates after completion of a 12-week lifestyle program that promoted a ketogenic diet.

As shown in Figure 9, the average weight loss was 7.9 kg (SD = 4.3) at program completion for the first 15 participants. Five months after completing the program, the average weight loss was 13.9 kg (SD = 8.5). There are some participants that have now been tracked for two years who have been able to maintain or continue to lose weight.

2.5 Clinical Vignette

Mrs. S is a 79-year-old woman (weight = 143 kg, fat mass = 76.2 kg, BMI = 46.8) who was treated for bilateral lower extremity lymphedema. She also presented with arthritis in her knees and had a history of lower extremity deep vein thrombosis and right knee replacement surgery. CDT was limited to compression bandaging and pneumatic pump as MLD was contraindicated due to her history of DVT. Mrs. S reported daily use of 3000 mg over the counter pain medication (acetaminophen) in order to tolerate her activities of daily living. After 18 months on a ketogenic diet her weight reduced to 110.2 kg (32.8 kg weight loss, BMI = 36.0). Body fat mass reduced to 52.6 kg (23.6 kg reduction). Skeletal muscle mass also reduced a negligible amount, but the percentage of skeletal muscle mass to her total weight is within range for her age. Her SF-36 Quality of Life score improved from 39% to 62%, indicating a significantly improved quality of life. She no longer needs pain medication on a daily basis. The lower extremities edema volume has reduced by an additional 4343 ml. Prior to the program, her lower extremities would present with edema after approximately 4 hours without compression. Currently, Mrs. S is able to go without compression for 4-5 days before symptoms return.

3. Exercise

The benefits of exercise for the general population are recognized to be substantial and they are no less so for those diagnosed with lymphedema. Beyond the general health benefits of exercise,

such as improved cardiovascular function, increased strength and joint range of motion, reduced fall risk, lessened fatigue, improved sleep, and improved mood and quality of life [38], exercise has also been shown to specifically reduce symptoms associated with lymphedema including edema, pain, and tissue fibrosis [39-41].

While originally it was believed that exercise, or strenuous activity of any kind, could potentially trigger the onset of lymphedema in cancer survivors, exercise is now recognized as a critical component of the intensive phase of lymphedema treatment [42]. Further, some experts hold the opinion that exercise is so crucial to lymphatic health, it may even have an impact on preventing lymphedema in an at-risk population, or at least delaying its onset for many years [43, 44].

Even as exercise has become an essential component of CDT, its use is inconsistently prescribed and implemented after a course of treatment concludes. In one study, only 58% of participants reported adherence with an exercise regime as part of their overall self-care of breast cancer-related lymphedema [45]. Almost 20% of participants in another study of breast cancer survivors reported that they did not engage in any exercise at all despite an understanding of its benefits [46].

Patients with lymphedema may experience several barriers to engaging in regular exercise, such as pain, fatigue or social embarrassment due to disfigurement associated with lymphedema [47]. The presence of other limiting comorbidities, such as obesity, osteoarthritis, or back pain can limit mobility and prevent exercise participation. Several studies suggest that a diagnosis of lymphedema itself can represent a barrier to exercise due to fears of making lymphedema symptoms worse by performing exercises incorrectly [46-48].

As discussed previously, addressing proper nutrition first may mitigate some barriers to exercise by improving energy, lessening pain, and reducing swelling [30, 49]. When these improvements are experienced by the patient, it may have the added advantage of increasing interest in exercise, which can promote adherence to an exercise regimen.

Current recommendations for individuals diagnosed with lymphedema include gradually increasing the intensity, frequency and duration of exercise, wearing compression garments during exercise to prevent exacerbation of lymphedema symptoms, and monitoring by a healthcare professional for injury, pain or increased swelling [50]. It is now recognized that with proper preparation and monitoring of symptoms, in the absence of other medical conditions which affect exercise tolerance, there is no restriction on the exercises that someone with lymphedema can engage in [45].

The physiological effects of exercise on lymphatic system function are well documented in the literature [51]. The main propulsive force that moves fluid through the lymphatic vasculature is the coordinated contraction of smooth muscle found in the larger lymphatic vessels. External forces, such as pulsation of nearby blood vessels, muscle contraction and respiration, are also integral to lymph transport [52] The muscle contraction inherent in exercise facilitates improved lymph flow by decreasing venous pressure and increasing muscle tissue pressure [53, 54]. The impact of respiration on lymphatic flow is poorly understood but is noted in the literature [48]. In one study, lymphedema symptoms reduced more when deep breathing was incorporated into self-care practices [55]. Moseley et al. [56] found that gentle arm exercises in combination with deep breathing had a significant effect on lymphedema symptoms in a group of women with breast cancer related lymphedema.

Perhaps the most efficacious form of exercise for lymphedema symptom management is water exercise. Research has shown multiple benefits for lymphedema patients, including reduced edema

volume, increased strength, and improved quality of life [51-56]. In a study of 88 female cancer survivors with lymphedema, those who participated in water-based exercise achieved better outcomes and had better adherence to exercise than those in the land-based group [57]. A systematic review and meta-analysis of aquatic intervention for lymphedema found the strongest evidence exclusively for upper extremity lymphedema related to breast cancer, but still concluded that overall, exercising in water may be superior for some patients [52].

The positive outcomes of water exercise for the lymphedema population seem to be primarily due to the particular compatibility of the physical properties of water, including hydrostatic pressure, immersion diuresis, buoyancy, and viscosity [58]. These features of water exercise mean that movements can be performed with greater pain-free range of motion than can be achieved on land. Further, risk of injury is reduced when potentially large and asymmetrical lymphedematous limbs are supported in the water [57, 59].

3.1 Clinical Vignette

Mrs. M is a 55-year-old female with a BMI of 23. She is diagnosed with primary lymphedema in bilateral lower extremities (left more severe), with onset at 7 years of age. She previously had enjoyed an active lifestyle, participating in gymnastics and other sports until she had her first child at age 26. She had also formerly enjoyed traveling with her family but had not done so for several years after suffering an exacerbation of swelling along with a cellulitis infection after a 6-hour plane flight. Her primary concern was her ability to manage her lymphedema as she ages. With encouragement, Mrs. M was able to make several lifestyle changes including incorporating water exercise into her schedule three times per week. She will now only stay in lodgings with a pool when traveling. She makes it a practice to arrive a day early to manage any increase in swelling by using the pool for several hours. By making lifestyle changes and allowing time for self-care practices, Mrs. M has been able to travel again with her family, including a trip to Europe the previous autumn.

4. Stress

Stress is an inevitable and unavoidable mainstay of human existence. We are continually called upon to respond to various physical and mental stressors as part of daily life. It is when a stressor is perceived as too intense, or its duration is too long, that our response may be maladaptive and have a negative impact on health. The effects of chronic stress on physical and mental health can be numerous and severe, impacting all body systems and functions [60]. The effect of chronic stress on patients with lymphedema may be even greater, particularly if other chronic conditions such as obesity are also present [61]. It therefore becomes imperative that for a lymphedema management program to be complete, chronic stress experienced by a patient must be assessed and strategies for improving stress resilience provided.

As discussed previously, the impact of obesity on lymphedema outcomes is tremendous.

Interesting research has also shown a strong correlation between chronic stress and obesity that is likely a reciprocal relationship [62].

Figure 10 depicts the bidirectional impacts and ultimate downward spiral of stress and obesity. Stress has been shown to lead to impaired executive function and poor self-regulation of behaviors, hormonal dysregulation, and increased appetite and cravings for comfort foods, which can all contribute to obesity. Obesity can further create greater stress by causing a further decline in

health, impairing body image, creating physical stress due to large size and body weight, increasing pain, and increasing both perceived and actual isolation [62].

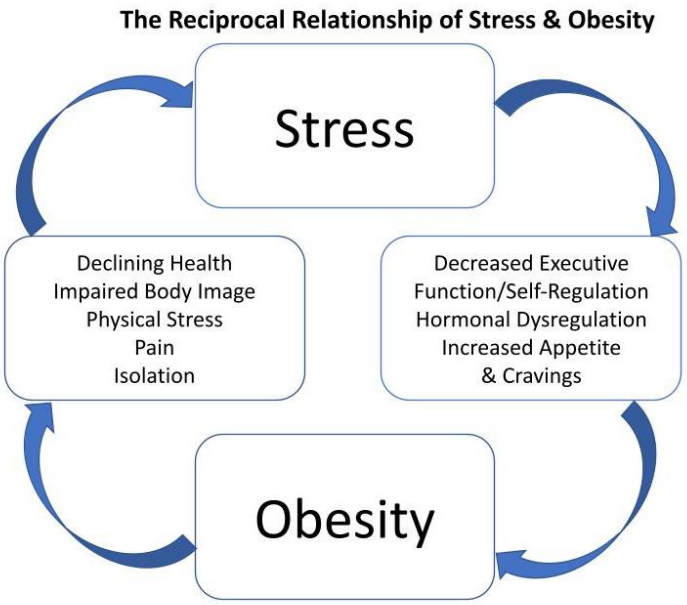

Figure 10 The reciprocal and potentially escalating relationship between chronic stress and obesity.

Chronic stress can cause physiological changes described in Figure 11, such as a chronic inflammatory response along with an increased fluid load that may be damaging to an already compromised lymphatic system in a patient with lymphedema [63] further compromising their health [62]. Additionally, psychological stress can contribute to fluid retention [64] which may present an additional burden on the lymphatic system. Dunningan et. al. [65] studied fluid retention syndrome and found that exacerbations were often preceded by emotional stress or a high carbohydrate meal. Figure 11 demonstrates the reciprocal relationship between stress and lymphedema in which emotional and physiological responses to stress can further exacerbate symptoms of lymphedema and create further stress.

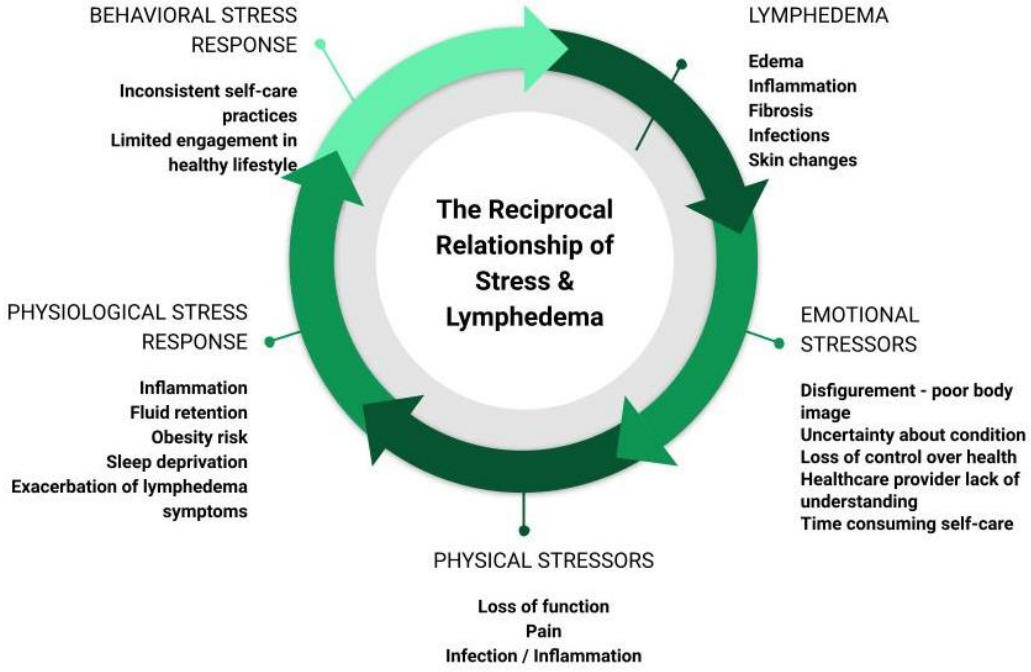

Figure 11 Repeated and chronic exposure to stress and its impact on lymphedema.

Wound healing requires an acute inflammatory phase, but chronic inflammation can actually slow wound healing [66]. Goun et. al. [67], in a meta-analysis of wound-healing models and outcomes found that the impact of psychological stress on wound healing was so significant that proper assessment and intervention strategies are required for the best wound healing outcomes.

Stress and sleep deprivation have a reciprocal relationship [68]. Chronic stress can disrupt sleep and impair the ability to achieve quality, restful sleep. Impaired sleep can in turn contribute to fatigue and increased levels of stress during waking hours. An additional correlation between sleep disturbances and obesity will be further discussed in the next section on sleep.

Having a diagnosis of lymphedema can potentially create chronic stress in a patient's life. Managing lymphedema requires multiple daily tasks such as wearing compression garments, performing self-MLD and decongestive exercises, using a pneumatic compression pump and being meticulous in skin care practices. The relentless need to adhere to self-care practices to prevent deterioration in health has the potential to become overwhelming and stressful. A qualitative study by Ridner et al. [61] examining the lived experience of breast cancer survivors with lymphedema revealed increased levels of stress due to body image issues, feeling of lack of control over their condition, and uncertainty about what their future with lymphedema will hold.

Are there interventions that can break this stress cycle? Fortunately, there is a great deal of research available for evidence-based methods to increase an individual's stress resilience [69]. Effective techniques for improving stress resilience include relaxation exercises, time management strategies, and calming music [70]. Because of its effectiveness on multiple fronts (improving sleep and increasing lymph flow), breathing exercises may prove to be a particularly useful method for reducing stress for lymphedema patients. Breathing exercises were shown to be more effective in reducing anxiety and improving mood when compared to mindfulness meditation in a recent randomized controlled trial [71]. It is our opinion that learning techniques to increase stress

resilience should be a part of a comprehensive lymphatic lifestyle program. With support, patients can learn to meet the challenges of managing a chronic condition like lymphedema in a manner that is satisfying and improves their quality of life.

4.1 Clinical Vignette

Mrs. R is a 72-year-old patient who presented at our clinic with venous insufficiency and secondary lymphedema in both lower extremities. She had a venous ulcer that had been treated at several clinics and had been present for over 2 years. The edema was successfully reduced with traditional lymphedema therapy. In most cases of chronic wounds with lymphedema, the wounds will heal when the lymphedema is properly managed. In this case, only 50% wound healing was able to be achieved and the patient was referred to a specialist for other treatment options. The client was often emotionally distressed and often cried during her treatment due to frustration over stalled healing of her wound. She was also unsuccessful with the specialist and treatment was discontinued.

Several months later, she returned to our clinic and reported that the wound had healed in the last month. We enquired about what was done differently as there was no new treatment or change to the protocol. However, she related that she woke up one morning and had this thought that she needed to accept the fact that she must deal with this wound, possibly for the rest of her life. She related that after that she was able to relax in a new way. Her stress and anxiety significantly reduced. She continued to take care of the wound as she had before and within a couple of weeks, it was completely closed.

This case stands out as a possible example of the correlation between stress and wound healing. Would her wound have healed sooner if she had been able to reduce the daily stress and anxiety with proper stress management techniques sooner? It seems likely that this patient's stress levels may have impacted her wound healing.

5. Sleep

One of the basic human physiological needs is sleep. Healthy sleep is such an essential function that it can impact every area of health and well-being including cognition, mood, energy, immune functions, hormonal balance, cardiovascular health and more [72]. Conversely, deprivation or disrupted sleep patterns can lead to or exacerbate a host of chronic health problems including cardiovascular disease, mental illness, obesity, arthritis, diabetes, respiratory diseases, and osteoporosis [73].

Optimal lymphatic functioning may depend upon healthy sleep patterns as well. For instance, the glymphatics, the lymphatic system of the brain, are much more active during sleep and largely disengaged during a wakeful state [66]. Glymphatics are required for both nutrient distribution and noxious waste removal among other functions in the brain [74]. Consequently, various neurodegenerative diseases have been associated with sleep disorders [75]. The lymphatics in the rest of the body are, conversely, less active during sleep and they may serve a similarly vital purpose as glymphatics perform in the brain. Dickstein et al. [76] have proposed that the reduced lymphatic flow in the trunk and limbs during sleep allows lymph nodes and other lymphoid organs to stockpile immune cells where they can be most effective in destroying pathogens and boosting immunity.

Sleep disorders and obesity have been shown to have a bidirectional relationship. Soylu et al. [77] found a greater incidence of sleep apnea as body mass index and waist and neck circumference increased. Likewise, in another study, as sleep quality or quantity decreased, the risk of developing obesity increased, possibly due to an elevation of inflammatory cytokines found in visceral fat that can contribute to disrupted sleep [78]. Greer et al. [79] propose a mechanism by which sleep deprivation may increase appetite, slow metabolism, decrease energy level and interest in exercise, and promote fat storage and thus contribute to the development of obesity.

Chronic sleep deprivation has been shown to affect higher executive functions including vigilance, attention, decision-making, and problem-solving [80]. Poor sleep may cause a person with lymphedema to make poor choices and be less diligent in their lymphedema self-care practices. In a study examining the nighttime management of lymphedema, 19% of participants reported that their lymphedema disrupted their sleep. Another 27% cited "exhaustion" as a reason for not donning their nighttime compression garments despite the overwhelming majority (89%) noting that swelling would invariably increase if night compression was not worn [81]. The lymphedema practitioner is a valuable resource for assessing patient comfort and ease of use with nighttime compression garments that allows for both effective lymphedema management as well as healthy sleep.

The association between sleep deprivation and lymphedema is further highlighted by a scoping review of seven clinical trials examining sleep disturbance in cancer survivors. Cancer survivors with lymphedema had an increased incidence of sleep disorders, such as insomnia, compared to those without lymphedema [82]. Lymphedema patients should be evaluated for sleep disorders, including sleep apnea, as early identification and treatment can greatly improve sleep and lead to better adherence to lymphedema self-care practices [81].

Improved nutrition may be a valuable intervention for improving sleep. While research into the impact of ketogenic nutrition on sleep is mixed, several studies have shown that sleep improved while on this eating plan for healthy individuals [83, 84], children with epilepsy [85, 86] and adults with obesity [87]. People with narcolepsy, a sleep disorder that causes overwhelming daytime drowsiness, report less sleepiness during the day while on a ketogenic diet [88].

The mechanism for improved sleep in these conditions may in part be due to the blood sugar stabilization that occurs when eating ketogenically, which has the effect of reducing fatigue and improving energy. This is often the reverse of what is experienced when eating a standard high carbohydrate diet. Additionally, several nutrients shown to enhance sleep, such as melatonin, iron, magnesium, and zinc are plentiful in a ketogenic diet and in many cases, in the most bioavailable forms. Melatonin, a hormone and neurotransmitter most plentiful in milk, is also found in fatty fish, eggs, and nuts [89]. Iron and zinc are much more bioavailable in animal-sourced foods, but are also plentiful in plant-sourced foods that fit into a ketogenic eating plan [90]. Magnesium is easily obtained in foods often consumed in a ketogenic diet. Additionally, zinc has been found to beneficially impact lymphatic absorption of fat-soluble vitamins [91].

Nocturia presents a significant disruption to sleep for many people [92]. Pelvic cancers and surgeries, medications, pelvic floor dysfunction and other common causes of frequent nighttime urination, may be present in the lymphedema patient. Nocturia should be managed to allow for adequate sleep. Management may include limiting evening fluid intake, adjustments to medications, and treatment with a pelvic floor specialist [93].

Common recommendations for improving sleep quality include sleep education, making environmental modifications, and engaging in relaxation exercises [94]. Sleep education may include information on the sleep cycle and sleep health and may provide the best results if offered in conjunction with other interventions [95]. Examples of modifications to the environment for improved sleep suggested in the literature are temperature and darkness in the bedroom, white noise, and daytime bright light therapy [96]. Relaxation exercises that have been shown to be beneficial include progressive muscle relaxation, guided imagery, and deep breathing [97]. Additionally, cognitive behavioral therapy may be beneficial for the lymphedema patient suffering from anxiety or depression which interferes with sleep [98].

5.1 Clinical Vignette

Mr. D is a 62-year-old morbidly obese male (weight = 233.1 kg, BMI = 71.7) diagnosed with bilateral lower extremity lymphedema induced by his obesity. When first referred for lymphedema therapy, he was also suffering from chronic back pain, venous insufficiency, and sciatica, and he had a history of repeated cellulitis infections and slow healing venous wounds. After two years of implementing a ketogenic diet and losing over 45 kg (weight = 185 kg, BMI = 56.9), Mr. D. still struggled with consistently adhering to his eating plan and following through with daily self-care tasks for his lymphedema such as skin care and wearing compression garments. His wife reported that he regularly fell asleep during the day even while conversing or eating a meal. He demonstrated forgetfulness with his medications and medical appointments. After participating in a home sleep study, he was diagnosed with sleep apnea. At his follow-up appointment six months after using a continuous positive airway pressure (CPAP) device, Mr. D had lost another 8 kg (BMI = 54.4), reduced volume in both lower legs, and reported improved energy levels along with reduced forgetfulness.

6. Conclusions

Although lymphedema is considered a chronic illness without a cure, our clinical experience has shown that the health and function of the lymphatic system can be improved with ketogenic nutrition and other important lifestyle changes, including exercise, stress, and sleep. The impact of lifestyle on lymphedema management has been ignored and has severely limited the ability of lymphedema patients to attain their optimal quality of life. Without lifestyle intervention, we are only addressing lymphedema symptoms in the short term. If better overall health is the goal, we must begin to treat the whole person and support healthy lifestyle habits.

Author Contributions

The authors confirm contribution to the paper as follows: initial conception and design of manuscript: LK; both authors (LK and RE) drafted the manuscript and revised it critically for important intellectual content, approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

The authors have declared that no competing interests exist.

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