

Lymphedema and nutrition: A review

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Abstract

Nutrition is considered a basic component in the management of any vascular disease. Lymphedema is characterised by an increase of interstitial fluid due to a lymphatic system morphological and/or functional alteration. Therapeutic management of lymphedema includes a multi-faceted approach based on compression and physiotherapy mainly. Weight control and anti-inflammatory and anti-edema diet are two additional necessary components of the holistic therapy in presence of primary or secondary limb lymphedema. This narrative review provides the available information derived from the scientific literature on nutrition in lymphedema, which anyway lacks robust evidence. Additional information and speculations are provided on the role of food, diet, nutraceuticals and fasting on the basic processes at the root of the chronic progressive degeneration of tissue lymph stasis, i.e. weight excess, inflammation, edema, fibroadiposis. More targeted and randomized studies are needed in order to assess and standardise the obvious, so far neglected, role of nutrition in lymphedema patients.

Introduction

Lymphedema (LYM) is a chronic vascular disease which typically involves lower and/or upper limbs, but can affect different body regions as well. Whichever edema depends upon an overload of a normal lymphatic system or upon a dysfunction of the lymphatic system for an anatomical or functional pathology of the lymphatic system.¹ In fact recent scientific studies² updated the *old* microvascular homeostasis concepts which were based on the largely prevailing role of the venous network for the reabsorption of the fluids from the interstice. These studies showed that in most body areas, namely in the extremities, the lymphatic system is responsible for over 80-90% of the interstitial fluids derived from the physiological homeostasis of the microvascular-tissue unit. By definition

edema results from an alteration of natural homeostasis with an accumulation of fluid in the interstitial matrix; consequently whichever vascular and non-vascular origin limb-edema is strictly related to lymphatic system dysfunction, hence to a fluid stasis which is linked to a lymphatic anatomic disease (LYM) or lymphatic functional impairment/overwhelming.

When lymphatic insufficiency is contemplated, it is subdivided into three categories from a pathophysiological point of view: i) dynamic insufficiency, involving high lymph flow, overwhelming the maximum load-output capacity of a physiologically normal lymphatic system; ii) mechanical insufficiency (properly known as LYM), involving low lymph flow due to anatomical alterations in the network of vessels and lymph nodes; iii) *safety valve* insufficiency, the combined effect of increased lymph flow and the reduced drainage capacity in the diseased lymphatic system. Any microvascular/tissue imbalance invariably results in an altogether of progressive different pathologic phenomena, such as: edema, hypoxia, oxidative stress, inflammation, fibrosis.

LYM is typically characterised by a chronic inflammation of the involved cellular matrix, with a progressive tendency towards a fibrotic transformation of the lymphedematous tissues.^{1,3} More generally the systemic low-grade chronic cellular inflammation (LGCCI) is definitely linked to aging and to multiple chronic degenerative diseases, such as diabetes, metabolic syndrome, atherosclerosis, neurodegeneration, cancer, autoimmunity diseases.⁴

Among the many factors that trigger edema of the lower and upper limbs (e.g. veno-lymphatic diseases protein dyscrasias, cardio-nefro-hepato-enteropathy, drugs, etc.), wrong eating habits may play a significant role through different pathophysiological mechanisms.

In particular the classic *western* nutrition, which is primarily based on carbohydrates and refined/processed foods, favours the systemic LGCCI⁵ and this pathologic process invariably generates and perpetuates any condition of edema in the human body.

Therapeutic management of limb LYM is notoriously of holistic nature, needing a multi-faceted approach^{1,3} based on the possible combination of the following treatments: i) manual lymphatic drainage; ii) compression (bandages, velcro adjustable wraps, elastic garments); iii) electro-medical devices such as intermittent pneumatic compression or bioresonance-microcurrent devices; iv) specific exercising; v) skin care and hygiene rules; vi) drugs/nutraceuticals

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and proper nutrition; vii) surgery in selective cases. Adequate nutrition and proper lifestyle represent two basic beneficial issues for the lymphedematous patients affected by a life-lasting debilitating disease. The influence of nutrition in venous and lymphatic diseases has been highlighted in literature, mainly focusing on leg venous ulcers and varicose veins of the lower limbs.⁶⁻⁸ The possible role of nutrition in limb LYM has been limitedly investigated and scarce literature evidence is available on this topic. This narrative review provides an overview on the available literature data regarding nutrition in edema and more specifically in LYM. A literature search was performed through PubMed, Embase, Google Scholar and the Cochrane Library, using the following headings and keywords: *chronic edema, lymphedema nutrition and edema, lymphedema treatment, food and edema, diet and edema, oxidative stress and edema, inflammation and lymphedema.*

Our aim is to highlight the relationship between nutrition and LYM, providing possible evidence on the beneficial/detrimental effect of proper/inadequate nutrition respectively within LYM management.

Current knowledge on nutrition and lymphedema

Nutrition studies the correct intake of macronutrients through food. Feeding provides the necessary substances for the physiologic processes of living organisms. More properly, nutrition is the act that is accomplished by taking food on the basis of physical or psychic stimuli. Food consists of three main macronutrients (carbohydrates, lipids and proteins) and micronutrients

(mineral salts, vitamins). A correct diet is essential for a healthy living and to slow down aging process, within the concept of an adequate metabolism in any pathophysiological condition, more specifically in the low-grade chronic cellular inflammation which is at the base of any chronic degenerative disease, such as LYM.

LYM is characterised in fact by a progressive increase of inflammation, fat deposition and fibrosis in the edematous tissues.^{1,3} Inflammatory processes in LYM derive from the biochemical nature of the stagnating fluids in the tissues (including the residual, larger macromolecules), which play a major role in the chronic evolution of LYM.⁹⁻¹²

The deleterious and increasing cascade of all inflammatory cytokines is recognized as the basic biochemical factor which contributes to LYM worsening and complications.^{11,12} Preliminary studies on the therapeutic possibilities of anti-inflammatory molecules in LYM have been recently reported as well.¹³

Due to the relevant pathogenicity of chronic inflammation in LYM course, the possible positive or negative role of a few pro-inflammatory/anti-inflammatory foods in this field is object of current research. Of interest, systemic lymphatic system is conversely involved in the multi-level regulation of the pathophysiological mechanisms of metabolic syndrome and inflammatory states,¹⁴ thus confirming the strict interrelationship among inflammation, nutrition, metabolic pathways and the lymphatic system of human body.

Another biochemical relevant issue in LYM patients is their higher levels of oxidative stress in the affected areas.¹⁵ The imbalance between free radical production and antioxidant systems activity has been proven in lymphatic and venous diseases as well, namely in leg venous ulcers and varicose veins.¹⁶⁻¹⁹

The role of reactive oxygen species has been elucidated in several chronic diseases, with clear repercussion on the LGCCI. Increased oxidative stress results in a growing inflammatory process, together with the well-recognised accumulation of lipoperoxidation, nucleic acid damages and protein degeneration in limb tissues cells. Several antioxidant natural substances have been tested through nutrition and supplements in vascular diseases,²⁰ but no specific beneficial effect has been clearly shown in the vast majority of the trials as to cardiovascular diseases when referring to Vitamin E, C and other similar classes of antioxidants. Conversely polyphenols exhibited a few interesting effects in vascular diseases; they represent a specific class of natural antioxi-

dant principles, which showed multiple beneficial actions on the general free radical production, as well as polyphenols elicit the Nrf2 and ARE system pathway acting as xenobiotics in a hormetic fashion.^{21,22}

The intake of polyphenols seems to provide a beneficial effect in venous²³⁻²⁵ and lymphatic diseases.^{1,3,26-29} Namely coumarin/curcumin-rich foods or, better, nutraceuticals seem to target a few of the basic pathologic processes at the root of LYM.^{26,27,29-31} In fact they showed a lymphangion/macrophage-targeted action, as well as a general anti-inflammatory and anti-edema action. Most polyphenols similarly represent a prebiotic food, which regulates the gut microbiota, one of the most innovative target in presence of a chronic degenerative disease. Lastly polyphenols are referred as to epigenetic *switches*, which are able to activate and deactivate genes with specific beneficial effects on human metabolism and aging.

The major issue, which is related to nutrition in LYM patients, is the overweight/obesity role in the onset and worsening of lymph stasis. Multiple reasons objectively link the presence of overweight or obesity to edema of upper and especially lower extremities.

Overweight or obese patients may have one or more of the following pathophysiological alterations which strictly relate to limb edema: i) impaired diaphragm function and increased intra-abdominal pressure with dysfunction of fluid cardiopetal aspiration/drainage; ii) reduced/altered ambulation/mobility with consequential musculo-vascular limb pump dysfunction and phlebolympathic stasis; iii) concomitant metabolic syndrome with multiple factors inducing edema (cardiac/renal/liver insufficiency *etc.*); iv) fluid-retentive adipose tissue in excess; v) hypertension and intake of edema-generating drugs (calcium-blockers, alpha-lytics, second-generation β -blockers *etc.*); vi) hormonal alterations such as hyperproduction of insulin and cortisol; vii) skin infections/inflammation which compromise/generate fluid retention furthermore.

The increasing incidence of obesity in western countries' population may potentially increase the rate of LYM, which seems to be strictly related to the body-mass index level.^{32,33} Similar findings have been elicited on the negative impact of obesity upon chronic venous diseases,³⁴ which may consequently lead to an increase of phlebolymphe-
dema and venolympathic incidence worldwide.

Many studies have focused on the negative impact of obesity on lymphatic system, both in terms of LYM onset and in

terms of LYM course and prognosis.^{35,36}

Lymphoscintigraphic studies have proven significant changes in lymphatic vessels/nodes in obese patients, which may explain the great influence of weight control in LYM patients. Overweight and, more relevantly, obesity proved to be a few of the most significant risk factors for the onset of LYM in patients subjected to cancer-related surgery (especially breast cancer).³⁷

Contrasting data were reported by a few authors³⁸ who highlighted that breast cancer operated women, whose BMI was ≥ 30 at the time of operation, were approximately 3.6 times more likely to develop lymphedema at 6 months after diagnosis than subjects with a BMI < 30 ($P=0.007$). Those with a BMI increase, even above 30, during their first 30 months of survivorship were not more likely to develop secondary LYM than those who did not have similar changes in BMI.

Similarly, when performing treatment of patients with primary or secondary limb LYM, the outcomes are strongly influenced by the weight variations along the time and again overweight, and especially obesity, represent important negative prognostic factors.^{39,40}

Proper nutrition, together with adequate physical activity, has represented in the history of medicine and biology the two basic pillars to achieve weight reduction. In fact caloric restriction and dietary intervention on macro-micronutrients may properly address the issue of weight loss in patients affected by upper or lower extremity LYM. Weight reduction in overweight/obese patients proved to be of significant help in reducing both limb edema and LYM-related signs and symptoms. More in detail a systematic review and metanalysis⁴¹ examined the only two available studies on nutrition and dietary interventions for LYM, indicating that positive effects were found as to LYM volume reduction in both trials. Specifically in upper limb LYM one study demonstrated that caloric reduction for weight loss resulted in a 44% decrease of volumetry. Probably even higher percentages could be expected in lower limb LYM.

In another study the authors assessed any possible difference between patients with breast-cancer related LYM undergoing a weight reduction diet, or a low-fat diet; they found a significant reduction in body weight, body mass index and skinfold thickness in both groups, compared with controls. Both groups decreased the arm volume in a non-statistically significant way, but both dietary groups showed a significant correlation between weight loss and reduction in arm volume ($P<0.02$).⁴²

The possible influence of a diet includ-

ing middle chain triglycerides added to conventional complex decongestive treatment was investigated in LYM patients;⁴³ the volumetry outcomes showed significant differences between the groups ($P \leq 0.05$), with a greater reduction in the group with the additional specific diet. No difference was reported in skin fold measurements or whole-body water content, whereas the feeling of heaviness in the arms was significantly less in the dietary group.

Similarly the limitation of long chain triglycerides in the diet of LYM patients may induce a significant improvement in volumetry and symptoms, as reported in a preliminary study.⁴⁴

Erroneous nutritional habits invariably lead to some degree of veno-lymphatic function derangement. In case of idiopathic edema of the lower limbs since 1993 a few authors demonstrated that the prevalence of this form of edema was 37.9% in subjects with eating disorders and 7.4% in subjects with normal nutrition in terms of eating attitude test outcomes ($P = 0.0001$).⁴⁵

Possibilities and limitations of nutrition in lymphedema

Generally foods have been recognized and distinguished as causal factors of body/limb edema or, conversely, anti-edema positive adjuvant factors in LYM management.

Fruits, vegetables, fermented foods, garlic, extra-virgin olive oil, nuts and fish represent anti-edemigenous foods, which work by reducing oxidative stress and regulating intestinal bacterial microflora. More specifically extra virgin olive oil is associated with a reduction in cardiovascular disease mortality, as it reduces oxidative stress and inflammation,⁴⁶⁻⁴⁸ thanks to its phenolic compounds.^{47,48}

The fibers found in fruits and vegetables (*e.g.* inulin) are rapidly fermented by bacteria that normally reside in the small and large bowel, which leads to the formation of short chain fatty acids, such as acetate, propionate, butyrate, usually metabolised to produce energy and which exhibit an anti-inflammatory activity⁴⁹ of considerable importance in chronic diseases (LYM included). Fermented products such as kefir also produce an increase in butyrate.

An adequate dietary intake of omega-3, from fish and plant foods (chia seeds, macadamia nuts, walnuts, cashews *etc.*), namely alpha-linolenic acid or ALA, and eicosapentaenoic and docosahexaenoic acids, respectively EPA and DHA, is associated with a significant reduction in inflam-

mation, by means of a reduction of pro-inflammatory eicosanoids production deriving from arachidonic acid.⁵⁰⁻⁵² Spices like turmeric, garlic, curry, prebiotics like inulin, coloured berries, vegetables as well as olive-derived foods (containing lignans) also contribute to an anti-inflammatory and anti-edema action

Among the foods, which conversely generate edema, salt, hydrogenated fats/trans omega 6 or 9, coffee, theobromine, alcohol, dairies, cereals, sauces, processed meat, junk food, sweets have been shown to increase inflammation and edema through different mechanisms.

Excess sodium tends to retain water in the blood vessels, increases arterial pressure, imbalances microcirculatory homeodynamics and lymphatic function, which subsequently worsens edema.⁵³ Consequently the limitation of sodium and foods that contain high doses of this mineral are recommended in lymphedematous patients. There are foods that promote edema through the *variation* of the endocrine system, such as soy. Soy-based food contains phytoestrogens such as genistein, which has a structure similar to natural estrogens and binds to α - and β -estrogen receptors to stimulate transcriptional activity.^{54,55} Apart from the ingredients naturally contained in foods, a special attention is to be given to the vast panorama of food additives; many of these, for example carrageenan and glutamate, have notoriously a pro-inflammatory action.^{56,57} Other pro-edema chemicals are represented by estrogen-like endocrine disrupting chemicals (EEDC), which alter endocrine system functionality and interfere with the synthesis, metabolism, binding or cellular responses of natural estrogens. EEDCs, such as ftalates, bisphenol, glyphosate, have been found in various plastic products, pesticides and many other daily used products.⁵⁸ Also negative interaction with gut microbiota/microbioma and mitochondrial death have been linked to the exposure to most substances cited above, with obvious repercussions on the microvascular/tissue homeostasis. Interestingly a diet rich in fiber may reduce the absorption of estrogens.⁵⁹

Nutrition has proven to interfere significantly with any systemic and loco-regional inflammation, edema, tissue degeneration in general and, ultimately, with metabolism and aging processes. LYM itself is characterised by a chronic inflammatory state that actively involves the extracellular matrix, which leads to the need of a proper nutritional strategy in the holistic view of LYM treatment. More than a calculation of weight and kilocalories, nutrition is intend-

ed as a correct and balanced intake of food and nutrients during the day. Any anti-inflammatory diet includes a drastically reduced intake of refined carbohydrates, redistributing portions of fats with a prevalence of essential monounsaturated and polyunsaturated fatty acids (more omega 3 and less omega 6) and raising the daily intake of antioxidants as polyphenols.

Proper redistribution of macronutrients during meals allows a better control of the hormonal response (insulin, glucagon, cortisol, estrogen), which in turn results in a significant reduction of the chronic cellular inflammatory state.⁶⁰ Additional outcomes of an anti-s balanced nutrition are weight reduction, improvement in tissue oxygenation,⁶⁰ and ultimately improved glycemic balance. Reduced amounts of refined carbohydrates (insulin stimulators, hence lipogenesis and fluid-retention stimulators) and increased supply of fibers supply, which also improves gut microbiota, have ultimately an anti-inflammatory and anti-edema action.

Dietary protein intake does not necessarily correlate with the protein excess in the interstitial matrix, hence a proper intake of protein quota is recommended to synthesize the essential amino acids in LYM patients as well.⁶¹ High quality organic protein (unprocessed lean red meat, possibly from grass-fed animals, organic white meat and especially small size fish) are usually favoured.

Fats may represent an issue in patients with LYM, who are often overweight or obese and who may get problems from a dense, fat-rich lymph from the intestine. In secondary LYM of the lower limbs, for example subsequent to abdominal-pelvic lymphadenectomy, medium-chain fatty acids (such as coconut oil and some seeds) are preferable, as the long-chain ones being absorbed in the intestinal mucosa may worsen the impaired lymph drainage at intestine level furthermore. The ultimate result of this overloading long fatty chains may be an alteration of the intestinal mucosa, which consequently deteriorates gut inflammation and permeability (leaky gut syndrome).⁶² Conversely, short/medium-chain fatty acids are preferable,^{43,44} as they do not require the secretion of bile salts for digestion and secondly they have the ability to passively pass from the gastrointestinal tract to the blood portal system, thus not overloading the intestinal mucosa.

Hydration balance in LYM disease is considered basic to maintain tissues fluid homeostasis. Coffee and alcohol have both a mild diuretic power which may lead to a protein concentration in the interstice, and may generate edema as well.

Fasting and lymphedema

Fasting is another popular form of nutrition strategy to favour weight loss, but even more to reduce chronic inflammatory diseases and LGCCI. More specifically intermittent fasting (IF) is gaining scientific evidence in metabolism literature and more generally in the therapeutic approach to chronic diseases. It has been established that regular intermittent fasting (*i.e.* 24 hour fasting once or twice a week, or preferably 16 hour fasting most days of the week) confers similar health benefits and weight loss than regular caloric restriction diets.⁶³ Moreover in controlled studies when intermittent fasting and standard low calories diet are compared, IF shows higher fat mass loss and improved insulin and leptin reduction, even if the caloric deficit is the same in both protocols.⁶⁴ The mechanisms involve a metabolic shift to fat metabolism and ketone production and stimulation of adaptive cellular stress responses that prevent and repair molecular damage.

Basically IF in lymphedematous patients may not only contribute to obesity/overweight reduction, but also it may represent a key strategy to improve inflammation and regulate altered autoimmune response. Local tissue inflammation involves hyper-activation of macrophages which produce pro-inflammatory cytokines (TNF, IL-1 β , IL-6) and reactive oxygen species. These processes have been shown as overexpressed in presence of LYM, as well as overweight and obesity clearly promote inflammation. IF was shown to suppress inflammation in human subjects and animals⁶⁵ and multiple studies have shown that fasting can lessen symptoms in patients with immunitary diseases.⁶⁶

The nutrient-responsive mTOR pathway overstimulates protein metabolism but also it negatively regulates autophagy, which may impair tissue natural clearance. Accordingly, fasting inhibits the mTOR pathway and stimulates autophagy in cells of many tissues, including liver, kidney, and skeletal muscle.⁶⁷ Autophagy mechanisms may play a role in the continuous remodelling processes of LYM tissues where necrosis, inflammation and other negative metabolic pathways are chronically activated.⁶⁸ There are several others molecular mechanisms underlying the beneficial effects of fasting on LGCCI and mitochondrial biogenesis, including NrF2 activation⁶⁹ and anti-oxidant systems, which is of interest in the oxidative stress of lymphedematous tissues. Lastly sirtuins activation in IF positively interferes with apoptosis, autophagy and inflammatory processes in

adipose tissue and more broadly in cellular life.⁷⁰

In conclusion the systemic effect of fasting on weight excess, insulin resistance, LGCCI and autoimmunity is to be re-considered in LYM management, in order to possibly include time-restricted feeding in a proper nutrition strategy.

Conclusions

Nutrition is one of the basic components in the therapeutic management of vascular diseases. LYM is characterised by an increase of interstitial fluid due to morphological and/or functional disease of the lymphatic system. Treatment of LYM is based on multiple components in a holistic and multi-faceted approach, mainly using compression and physiotherapy. The proven importance of weight control and of anti-inflammatory strategies in any chronic degenerative disease should be recognized in LYM treatment as well, in a sort of translational medicine application.

This narrative review has highlighted some literature data and information about nutrition and LYM, though the level of scientific evidence for the current knowledge is quite low, due to the lack of robust studies. The intuitive and proven role of nutrition in weight control and in combating inflammatory processes impose a reappraisal of the current therapeutic approach to LYM, so to include a series of possible nutritional measures to fight this chronic degenerative disease. Some preliminary data and our personal experience indicate that edema and chronic inflammation may be controlled through a balanced intake of macronutrients and polyphenols; additional interesting nutritional measures are represented by the introduction of time-restricted feeding (IF) periods, favouring and avoiding proper/wrong foods and additives respectively.

Future randomized studies may elicit the role of several specific foods/nutraceuticals and diets/ fasting regimes in LYM management, so to corroborate the limited literature evidence and finally to improve the necessarily holistic approach to the pathological complexity of the patient affected by this chronic and debilitating disease.

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