

REVIEW

Dietary supplements in lymphedema

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Keywords

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Summary

Lymphedema is a chronic inflammatory disorder resulting from ineffective fluid uptake by the lymphatic system, and the effects are principally felt in the lower limbs. The condition is said to be primary when caused by genetic mutations and secondary when caused by injuries, infections, or surgery. Lymphedema, a worldwide pathology, does not have an effective therapy so far. Leukotriene B4 has recently been identified as a key molecule in lymphedema pathogenesis. Surgical, nonsurgical, and pharmacological treatments have been proposed; however, they do not cure the disease and only ameliorate the symptoms. Nutrition and nutritional status are extremely important in lymphedema physiopathology. Obesity is a comorbidity that exacerbates the risk for secondary lymphedema and constitutes a negative prognostic

factor. Indeed, anti-inflammatory foods and their effects on the inflammatory state and on oxidative stress are now being investigated for their possible therapeutic role in lymphedema. Although no special diet has so far been proven to be very effective, specific dietary tips could help in alleviating the edematous state of patients with lymphedema. A few supplements have been tested for lymphedema treatment. Among them, GARLIVE® containing hydroxytyrosol, hesperidin, spermidine and vitamin A, exhibited promising effects in the animal model. Hydroxytyrosol, a polyphenol from olives, showed anti-inflammatory effects and reduced leukotriene B4 synthesis, thus holding promise as a potential natural candidate for lymphedema treatment.

The lymphatic system

Our body maintains health and prevents diseases thanks to the coordinated action of different organs and organ systems, among which the lymphatic system is of utmost importance. The lymphatic system is composed of three main components: lymph, i.e. the interstitial fluid, originated by extravasation of fluid and proteins from blood capillaries; lymphatic vessels, which drain back lymph from the entire body into the bloodstream; and lymphocytes, cells of the immune system that concentrate in lymph nodes and check lymph content, including for the presence of microbes and viruses. The lymphatic vessels originate in the peripheral tissues and convey the lymph to the venous circulation [1, 2]. These vessels also transport antigens and immune cells to the draining lymph nodes, which foster immune response or tolerance [3]. Apart from participating in immunity, the lymphatic system is involved in many other physiological processes, among which circulation and metabolism are the most important [2]. The lymphatic system collects the lymph that is filtered from the arterial side of the capillary bed and also transports dietary fats, hormones, and waste substances [4, 5].

Always considered of secondary importance compared with the blood vascular system, growing evidence sup-

ports the primary role of the lymphatic vascular system. Blood vessels and heart develop earlier than the lymphatic vessels in embryos, and this first vascular system also has lymphatic functions crucial for defense mechanisms. Indeed, macrophages develop before erythrocytes, and in vertebrates, the early blood vessels express the lymphendothelial receptor VEGFR-3 [6]. Lymphatic vessels transport the lymph from the periphery to the venous circulation. Similar to blood vessels, they can have different dimensions, from the small lymphatic capillaries (or initial lymphatics) to the large collecting vessels (lymph ducts or collecting lymphatic vessels) [1]. The lymphatic vessels possess unidirectional valves and are composed mainly of lymphatic endothelial cells (LECs) and lymphatic muscular cells (LMCs) [1]. Dysfunction in any of these components can lead to different pathologies, among which the most prevalent is lymphedema [5].

Lymphedema

A chronic inflammatory disorder resulting from fluid accumulation, lymphedema affects 3 million people in the United States and 140-250 million people globally. Lymphedema is considered primary when it is caused

by genetic variants and secondary when it develops after surgery, infections, or injuries. Primary lymphedema has a prevalence of 1/100,000, whereas secondary lymphedema has a prevalence of 1/1000. The disorder mainly affects the lower limbs, but it can also affect the upper limbs, genitalia, and face [7-10]. Lymphedema is more frequently diagnosed in women than in men, because of: 1) hormonal differences, that lead to more severe manifestations in females, and possibly 2) the fact that women consult clinicians more readily than men [11]. The pathophysiology of lymphedema and the molecular pathways underlying the disease remain unclear although several studies have advanced our knowledge in this field. It is known that inflammation is an essential component of lymphedema and that it results in lymphatic damage, pain, fibrosis, and adipose tissue deposition [12-14]. Several genes, such as *FOXC2* [15, 16], have been found to be involved in primary lymphedema development or in secondary lymphedema predisposition; nevertheless, more research is needed to define new diagnostic and therapeutic targets [9]. Moreover, lymphedema treatments are currently unsatisfactory. Lymphedema, despite the etiology, is still virtually incurable, and the current therapeutics merely provide symptomatic relief by reducing swelling and preventing inflammation without offering a definitive cure for the disease [17].

Primary lymphedema

Lymphedema is classified as primary when it results from genetic mutations. Primary lymphedema is rare, and it is usually caused by malformations of lymphatic vessels and/or malfunction of lymphatic drainage [18]. More than 20 genes have been associated with various forms of primary lymphedema, but their mutations can explain only a portion of all primary lymphedema cases and a high degree of genetic heterogeneity is found among patients with lymphedema [19]. Apart from Milroy disease, many forms of primary lymphedema are usually sporadic. The disease can present at birth (congenital) or evolve during childhood, puberty, or even adult life, and may be diagnosed through genetic screening methods [18, 20].

Secondary lymphedema

Secondary lymphedema evolves after birth and results from lymphatic damage by different agents, such as infections, surgery, or traumas [18]. Particularly, lymphatic filariasis results from infections caused by nematodes belonging to the *Filarioididea* family, and it is the most common form of secondary lymphedema worldwide. The infection is mainly found in sub-Saharan Africa and India and affects more than 120 million people globally [18]. Moreover, herpesvirus infection can rarely cause lymphedema [21]. Secondary lymphedema typically results from malignancy-related therapeutic interventions.

Surgical procedures usually lead to dissection or excision of lymph nodes. Furthermore, radiation therapy can damage dermal lymphatic vessels and cause nodal fibrosis [18, 22]. Finally, obstruction of lymphatic vessels by adipose tissue and reduced physical activity, which is typical of morbid obesity, can also cause secondary lymphedema [18, 23].

Pathophysiology of lymphedema

Lymphedema is a chronic inflammatory disorder. Fluid accumulation stimulates the activation of inflammatory cells, which in turn modify the extracellular matrix, decreasing lymphatic function [24]. Several inflammatory cells participate in its etiopathogenesis, mainly T cells and macrophages. CD4⁺ cells, specifically Th2 differentiation, are essential in controlling fibrosis and inflammation and in the development of lymphatic dysfunction [24, 25]. M1 inflammatory macrophages can be activated by Th1 and Th17 cells and release nitric oxide and VEGF-C, which reduce the contraction of lymphatic vessels and increase lymphangiogenesis, respectively. On the other hand, M2 anti-inflammatory differentiation of macrophages seems to be beneficial in the initial stages of lymphedema and regulates lymphangiogenesis and tissue remodeling [24-26].

Following inflammation, lymphedema results in fibrosis and adipose tissue deposition. Fibrosis impedes the functioning of lymphatic vessels and exacerbates the symptoms of lymphedema and reduces lymph drainage. Fibrosis is positively regulated by Th1 and Th2 cells, which release TGF- β , IL-4 and IL-13, whereas macrophages negatively regulate the process. Adipose tissue is influenced by IL-6 dysregulation and Th2 cells, a negative regulator of adipose tissue deposition, whereas lymph stasis and leakage typical of lymphedema sustain adipose tissue proliferation [24, 25].

LEUKOTRIENE B₄

Several studies have reported that leukotriene B₄ (LTB₄) is involved in the pathogenesis of lymphedema [21]. Leukotrienes are synthesized in leukocytes from arachidonic acid by the action of different enzymes, among which 5-lipoxygenase is prominent. Leukotrienes bind cognate G protein coupled receptors and elicit an inflammatory response. LTB₄ signal is transduced by the receptors LTB₄R and LTB₄R2 [27]. LTB₄ controls CD8⁺ and CD4⁺ cells as well as the recruitment of neutrophils and macrophages in the lymphedematous tissues. These inflammatory cells, especially neutrophils, produce more LTB₄ upon activation, thus recruiting even more leukocytes to the inflammatory site [27, 28]. LTB₄ stimulates Th17 differentiation and acts as a molecular link between adaptive and innate immunity in lymphedema [29]. LTB₄ modulates VEGFR-3 and Notch signaling, both of which are important in lymphangiogenesis, and mediate pruritus caused by localized lymphedema. LTB₄ has been proven to diminish the function of lymphatic vessels.

phatic endothelial cells, worsening the progression of lymphedema [25, 30].

Treatments

No absolute cure is available for lymphedema. The therapeutic approaches are divided mainly into nonsurgical (lymphatic drainage, compression therapy, electromedical devices, and specific exercising) and surgical (lymphatico-lymphatic bypass, used only in selective cases) methods. Other than specific treatments, skin hygiene and mild-to-moderate physical activity are of utmost importance [31, 32]. Some pharmacological treatments have been proposed for chronic edema pathologies, all with unsatisfactory results. Particularly, diuretics, analgesics, antibiotics, antifungals, and benzopyrones are being or have been used.

- Diuretics, used only in the initial stages of lymphedema, are usually ineffective, and their long-term use can result in fluid and electrolyte imbalance.
- Analgesics are used in cases of severe edema when the size and weight of the limb causes unbearable pain.
- Antibiotics are used in the presence of cellulitis, a common complication that results from lymphatic dysfunction and local immunodeficiency.
- Antifungals are used for treating athlete's foot and fungal nail infections, typical complications of lymphedema in the lower limbs.
- Benzopyrones are considered the most effective pharmacological treatment because they stimulate proteolysis by macrophages, thus reducing excess proteins, swelling, fibrosis, and chronic inflammation and controlling microbial infections [31, 33, 34].

The lack of effective lymphedema treatments calls for research on new active molecules.

Proposed supplements and hydroxytyrosol

Apart from pharmacological therapies, a few studies have proposed the use of dietary supplements for the treatment of lymphedema. A combination of caloric restriction and synbiotic supplementation reduced the edema in survivors of breast cancer-related lymphedema, mainly via the antioxidant properties [35, 36]. Moreover, selenium supplementation proved to be effective in the treatment of secondary lymphedema and reduced the production of reactive oxygen species [37]. Finally, a new promising molecule has been recently proposed for the treatment of lymphedema in the form of supplements, namely hydroxytyrosol (HT). HT is a biophenol extracted from olive oil and leaves, exhibiting anti-inflammatory, antioxidant, and antimicrobial properties. HT has no side effects at any concentration; thus, it was proposed for prolonged consumption in the form of a nutraceutical. HT has been established to be an efficient inhibitor of LTB₄ synthesis [8, 25, 38]. LTB₄ inhibitors

have already been tested for lymphedema treatment. Ketoprofen, a nonsteroidal anti-inflammatory drug, inhibits 5-lipoxygenase activity and regulates LTB₄ synthesis. Ketoprofen alleviates inflammation and induces prolymphangiogenic factors, thereby reversing edema and re-establishing the lymphatic function [39, 40]. HT consumption has recently been correlated with an improvement in the quality of life in patients with lymphedema, supporting its therapeutic value [41].

Supplementation of HT in an animal model of lymphedema

A dietary supplement containing HT, GARLIVE[®], was tested in a mouse tail model of lymphedema [7]. Other than HT, GARLIVE[®] contains the anti-inflammatory molecules spermidine, hesperidin, and vitamin A. Spermidine is derived from rice seeds, and it inhibits the production of proinflammatory mediators, such as TNF- α , IL-1 β , NO, and PGE₂ [42]. Hesperidin is extracted from citrus fruits and has been tested for lymphedema treatment, with promising results [43]. Vitamin A is usually correlated with low levels of inflammation. Moreover, retinoic acid, a metabolite of vitamin A, can interact with the receptor encoded by the *RORC* gene. Deleterious mutations in this gene have recently been reported in patients with lymphedema [44]. GARLIVE[®] supplementation resulted in reduced tail swelling after surgical intervention. The treated group presented a decreased tail volume, the peak of the swelling was reached faster, and the swelling remained for less time [7]. Considering the molecular effects of the used molecules, their possible synergistic effects, and the promising results in the animal model, further clinical studies should be conducted to establish the use of GARLIVE[®] in patients with lymphedema.

Lymphedema and nutrition

Diet plays an essential role in lymphedema progression. Particularly, the classical Western eating habits, based on carbohydrates and refined foods, favor systemic low-grade chronic cellular inflammation, which in turn stimulates edema. Proinflammatory and anti-inflammatory foods are now being actively investigated for their possible roles in lymphedema. Oxidative stress, another important aspect of lymphedema pathophysiology, could be reduced via nutrition and using supplements containing several natural antioxidant substances. Polyphenols seem to target the molecular pathways that form the basis of lymphedema. Polyphenols exert anti-inflammatory and antiedematous actions, and they elicit an effect directly on the lymphangion [32]. High body mass index has been correlated with lymphedema onset, and weight loss achieved via caloric restricted and healthy dietary patterns has been proven to reduce breast-cancer related secondary lymphedema [45]. Moreover, weight loss has been shown to improve lymphedema-related

symptoms and also offers other benefits such as improved body image and insulin control [32]. In the scope of dietary control, the intake of medium-chain fatty acids has been established to be correlated with a reduction in the volume of the limbs. Medium-chain fatty acids are hydrolyzed by pancreatic lipase and then absorbed in the duodenum. These fatty acids are not esterified or absorbed by the lymphatics but directly enter the portal system, thereby reducing accumulation and pressure in the lymphatic ducts [46]. However, extremely low-fat diets could require specific vitamin supplements; thus, the specific diet should be controlled by the clinician. Restricted fluid intake has also been proposed as a possible lymphedema intervention, but it has not been demonstrated to be beneficial in peripheral lymphedema. Thus, no special diet has so far been proven to be of high therapeutic value for patients with lymphedema [31]. Nevertheless, specific dietary tips could help in reducing the edematous state. Fibers present in fruits and vegetables lead to the formation of short-chain fatty acids in the bowel, which exhibit an anti-inflammatory activity [32, 47]. Other anti-inflammatory dietary molecules, such as omega-3, and several spices (turmeric, garlic, and curry leaves) may reduce inflammation and edema [32, 48]. On the contrary, foods such as salt, caffeine, omega 6 or 9, alcohol, and sweets exert the opposite effect [32, 49]. Thus, they should be avoided by patients with lymphedema. Finally, foods can control the physiologic hormonal response, which in turn influences inflammation and edema [32]. Apart from nutrition, specific physical exercises have been shown to be extremely important for improving the quality of life and ameliorating the symptoms of patients with lymphedema. In patients with secondary lymphedema, yoga practice, for instance, has been shown to be highly effective [50].

Lymphedema and obesity

Lymphedema may be a comorbidity of obesity. Several studies have correlated obesity with lymphedema onset, course, and prognosis [32, 51]. Patients with obesity also exhibit other conditions leading to limb edema, such as reduced mobility, concomitant metabolic syndrome, excess of fluid-retentive adipose tissue, hypertension, and hormonal alterations [32]. Obesity exacerbates the risk for secondary lymphedema by up to three times. Moreover, even without other conditions, people with a body mass index of > 30 have an insufficient lymphatic flow. Adipose tissue physically compresses lymphatic vessels and triggers local inflammation. Obesity has been proven to strongly influence the treatments for both primary and secondary lymphedema, thus representing a negative prognostic factor [32, 52]. Several studies also suggested that a high-fat diet can deregulate gene expression in lymphatic endothelial cells, which implies a genetic link between obesity and lymphedema. In a recent study on 71 patients with lymphedema, 20% were obese, and several mutations in genes related to lymphedema pathogenesis were also detected in patients with obesity.

These findings suggest the presence of a genetic association between lymphedema and obesity [41, 53, 54].

Conclusion

Lymphedema is a worldwide-diffused disease, still without an effective therapy. Surgical, non-surgical, and pharmacological treatments have been proposed, but they only ameliorate the symptoms. Several supplements have been proposed for lymphedema treatment, with GARLIVE® having promising effects in the animal model. New research and clinical studies will be needed to find the best treatment for lymphedema patients.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; GB, KD, Serena M, Silvia M, Sandro M, MR, MC: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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