

# Lymphatics are an Active Player in Major Healthcare Challenges

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*“The lymphatic system is fundamentally important to cardiovascular disease, infection and immunity, cancer, and probably obesity — the four major challenges in healthcare in the 21st century. This Review will consider the manner in which new knowledge of lymphatic genes and molecular mechanisms has demonstrated that lymphatic dysfunction should no longer be considered a passive bystander in disease but rather an active player in many pathological processes and, therefore, a genuine target for future therapeutic developments.”*

– Drs. Mortimer & Rockson

## **LYMPHATIC PRESERVATION OF TISSUE FLUID BALANCE**

The lymphatic system is primarily responsible for returning capillary ultrafiltrate and plasma proteins back into blood circulation (not reabsorption into veins as previously thought). While peripheral edema is generally classified by cause (e.g., heart failure, nephrotic syndrome, venous insufficiency, etc., and in any combination), it is lymphatic function that plays a central role managing this edema and maintaining fluid equilibrium between tissues and plasma volume, regardless of systemic cause. When a chronic condition such as venous insufficiency taxes lymphatics for an extended period of time, lymph drainage is exhausted, fluid buildup causes tissue changes that permanently damage the lymphatic vessels and lymphedema occurs. Therefore, with the development of any peripheral edema, attention should be given to lymphatic support, in addition to the root condition, as all peripheral edema represents a failure or insufficiency of lymphatic drainage. Failure to appreciate that the central role of lymphatic drainage is to maintain tissue fluid balance may lead to inappropriate clinical response such as when diuretics are empirically prescribed.

Identification in recent years of multiple causal genes for primary lymphedema has brought clarity to the nature of the malfunctions—with mutations often having additional cardiovascular consequences. Lymphedema was previously classified as congenital, praecox, or tarda, based on time of symptom onset. It is now known that the same causal gene, a FOXC2 mutation, can produce onset as soon as adolescence or as late as a person’s fifties. In addition, both the VEGFR3 and FOXC2 mutations have high correlation with venous valve failure, with 100% of FOXC2 mutations showing superficial vein incompetence making it difficult to distinguish via clinical evaluation which patients suffer from lymphedema secondary to venous insufficiency and which have venous insufficiency because of a primary lymphedema gene mutation. Since genetic evaluation of every patient is not practical, this reiterates the importance of giving consideration to treatment of the lymphatics whenever peripheral edema is present.

## **LYMPHATICS AS HOST DEFENSE**

A primary function of the lymphatic system is host defense as lymph nodes filter and process antigens in the lymph fluid and produce lymphocytes, dendritic cells, and

macrophages as appropriate. Compromised lymphatic function (and therefore immunologically active cell tracking) likely disrupts immune surveillance and leads to increased risk of various infections. Patients with lymphedema are 71 times more likely to develop cellulitis infections, sometimes the first sign of subclinical lymphedema.

Several causal genes for primary lymphedema including CCBE1, GATA2, and NEMO gene mutations also cause systemic immunodeficiency. VEGFR3 mutations are associated with increased infection rates of the feet and legs and many immune diseases are likely to have lymphatic involvement, such as Crohns' disease, which has lymphatic abnormalities noted even in the original descriptions of the disease. There is growing evidence pointing to immunodeficiency possibly caused by lymphatic system breakdown instead of autoimmunity as the culprit of these disease states.

### **LYMPHATIC RELATIONSHIP TO FAT**

It is well understood that fat is transported by the lymphatics after absorption by the intestinal lacteals, but evidence connecting lymphatics and peripheral fat is just now coming to light. Lymphatic function has possible connections to peripheral tissue lipid transport and homeostasis, explaining why those with lymphedema often have increased fat deposits (as is often observed by surgeons operating on lymphedema patients describing

“wet fat” or mixture of both lymph and fat). As removal of interstitial proteins is a duty of the lymphatics, the inclusion of lipoprotein removal by the lymphatics is reasonable. The influence of impaired lymphatics on fat distribution is likely to work both ways as weight gain is also a strong risk factor for developing breast cancer related lymphedema. Mechanisms linking lipid pathologies to lymphatics are fascinating, but require extensive further study.

### **KEY POINTS**

- Lymphatics are responsible for managing peripheral edema and should be given equal consideration to the root cause as all peripheral edema indicates lymphatic failure
- Impaired lymphatic function also compromises immune function not only on a localized level as is seen with increased risk of cellulitis infections, but even with some causal gene mutations linked with systemic immune deficiency
- The link between lymphatics and fat is well established, but the specific mechanism, impacts, and implications are not well understood
- The extensive reach of the lymphatic system in the human body and the significant evidence linking it to many of today's pressing healthcare needs warrant both a significant increase in attention to this system, better treatment understanding, and extensive further study

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