

In this article...

- How the lymphatic system is structured and how it drains tissue
- Causes, symptoms and treatment of different types of oedema, including lymphoedema
- How the lymphatic system transports fat and contributes to immunity

The lymphatic system 1: structure, function and oedema

Key points

The lymphatic system works in parallel with the cardiovascular system and has a network of vessels and key lymphoid organs

The system circulates lymph around the body, draining tissue, transporting fat and activating immune responses

An over-accumulation of lymph leads to swelling of the soft tissues called oedema; this includes lymphoedema, which is caused by poor lymphatic drainage

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Abstract This article is the first in a six-part series about the lymphatic system. It discusses how the system is structured and how it functions, focusing on tissue drainage, fat transportation and activation of immune responses. It also examines the causes, symptoms and treatment of oedema. Part 2 will focus on the lymphatic organs, part 3 will examine immunity in more detail, part 4 will discuss allergies, anaphylaxis and anaphylactic shock, part 5 will focus on vaccinations and immunological memory, and part 6 will discuss immunotherapies.

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This is the first article in a six-part series examining the lymphatic system and immunity. It provides an overview of the structure and function of the lymphatic system, focusing primarily on its role in tissue drainage. It also examines factors that can compromise lymphatic flow, briefly explores the role of the lymphatic system in fat transportation, and introduces the overlap and synergy between the lymphatic and immune systems.

The lymphatic system

The lymphatic system can be thought of as a second circulatory system that runs in parallel, and in conjunction, with the cardiovascular system; it extends into every major region of the body, with the notable exceptions of the brain and spinal cord (Moore and Bertram, 2018). The major anatomical components of the lymphatic system are highlighted in Fig 1.

The lymphatic vessels form the conduits of the lymphatic system, and a watery fluid called lymph runs through them; the term 'lymph' comes from the

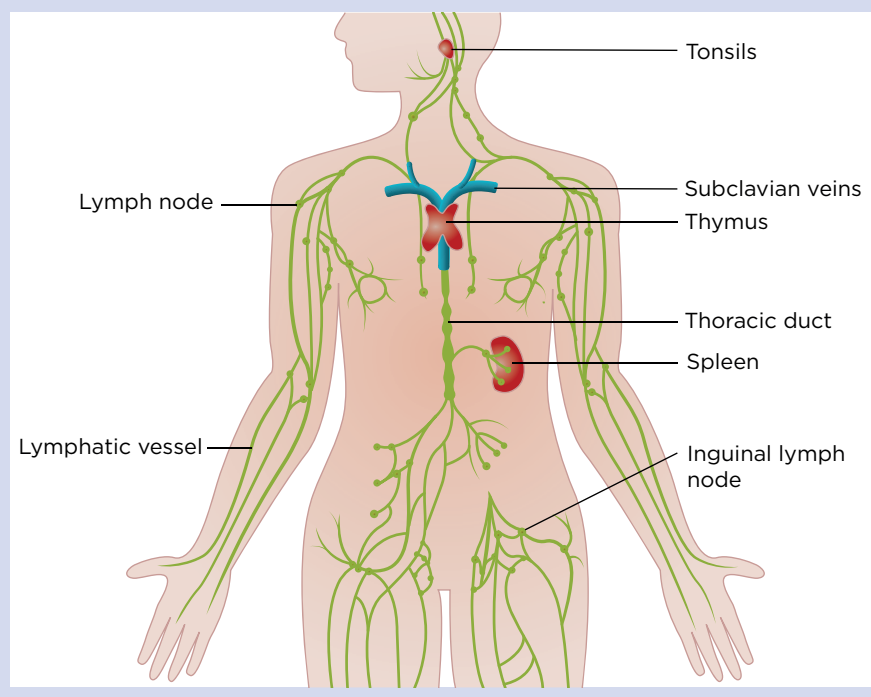
Latin word *lymphā*, meaning water (Bit.ly/CollinsLymphDefinition). Unlike the cardiovascular system, the lymphatic system is not a closed system and does not have a discrete pump analogous to the heart. However, in many respects, the lymphatic vessels are structurally similar to veins: they have relatively thin walls and carry lymph under low pressure. For this reason, like veins, most of the larger lymphatic vessels are equipped with valves to prevent the backflow of lymph under the influence of gravity.

Lymph flows through several key lymphoid organs, where its composition is monitored and modified. The lymphoid organs are divided into:

- Primary lymphoid organs (red bone marrow and the thymus gland), where lymphocytes are generated from immature progenitor cells;
- Secondary lymphoid organs (the spleen and lymph nodes), where lymphocytes reside and are positioned to mount immune responses.

The location and roles of the lymphoid organs are summarised in Table 1 and will

Fig 1. The major components of the lymphatic system



Cellular signals such as hormones. The flow of blood into capillary beds is regulated by small rings of smooth muscle called pre-capillary sphincters; when these are dilated (open), blood from the arterioles flows in under high pressure. In most tissues, the capillary walls are porous, which allows fluid to be driven out through the capillary walls by a process called filtration. As this fluid collects in the small interstitial spaces that surround cells, it is referred to as interstitial fluid or tissue fluid.

Interstitial fluid bathes most human cells and has a composition similar to that of blood plasma, minus the larger plasma proteins that are too big to physically pass through the pores in the capillary walls. The average adult human body has around 11-12L of interstitial fluid filling interstitial spaces, where it functions as the primary exchange medium in most human tissues. Freshly produced interstitial fluid is a complex mixture that is rich in oxygen and several other components, such as:

- Sugars (primarily glucose) – for metabolism;
- Amino acids – for building proteins;
- Lipids – for metabolism and synthesis of cell membranes and chemical signals such as hormones;
- Electrolytes, including sodium, potassium, calcium and chloride – essential for osmotic/electrochemical balance and as co-factors for enzymes and structural cellular proteins;
- Hormones – to regulate internal physiology and ensure homeostasis;
- Waste products from cellular metabolism, including CO₂ and

be explored in more detail in subsequent articles in this series.

The lymphatic system has three major functions, which are discussed here:

- Tissue drainage;
- Fat transport;
- Immune responses.

Tissue drainage

Interstitial fluid formation

The left ventricle of the heart ejects oxygen-rich blood under high pressure into the aorta, which is the major systemic artery. Large arteries branch off the aorta

to supply the upper and lower regions of the body with blood. Within the organs, arteries subdivide into progressively smaller vessels and eventually into the smallest arteries of the body, which are termed arterioles. Most arterioles connect to capillary beds, which permeate into the tissues (Fig 2).

The major role of capillaries is to distribute blood, ensuring adequate oxygen and nutrients are delivered to all cells, while simultaneously acting as conduits for:

- The collection of metabolic waste products, such as carbon dioxide (CO₂);

Table 1. Primary and secondary lymphoid organs and their functions

Lymphoid organ	Lymphoid organ type	Description	Function
Red bone marrow	Primary	In adults, this is diffusely located in the central portions of flat bones such as the ribs, sternum, pelvis and vertebrae, with smaller amounts found in the epiphyses of some of the larger, long bones, such as the femur	To act as the major haemopoietic tissue, producing all the formed elements of blood including erythrocytes (red blood cells), leukocytes (white blood cells) and platelets (thrombocytes)
Thymus gland	Primary	A small, butterfly-shaped gland located on the superior surface of the heart (Fig 1)	Plays a key role in programming the immune system to recognise 'self', and provides a site for the maturation of T-lymphocytes
Spleen	Secondary	The largest lymphoid organ, the spleen has a lobular structure and is located on the left-hand side of the abdomen, between the ninth and 11th ribs	Helps trap foreign material and remove damaged and aged erythrocytes, while also acting as a reservoir for erythrocytes, leukocytes and platelets
Lymph nodes	Secondary	Small, bean-shaped lymphoid organs found in major clusters, including the cervical nodes (neck), axillary nodes (armpits) and inguinal nodes (groin regions)	Primarily filter lymph, trapping foreign material such as bacterial and viral particles

nitrogenous waste products such as urea and uric acid.

As interstitial fluid is forced out at the arterial end of the capillary bed, the blood remaining in the capillaries is thicker and more viscous, and so moves more slowly. It also has a higher concentration of soluble materials, such as plasma proteins albumin and fibrinogen, which exert an osmotic pull. As a result, interstitial fluid rich in waste metabolites returns to the blood towards the venous end of the capillary bed, eventually draining into the venules to be carried away in the venous system.

Interstitial fluid drainage and lymph formation

Approximately 85% of the fluid lost at the arterial end of the capillary bed is reclaimed into the blood at the venous end (Herlihy, 2018). The remaining 15% is added to the interstitial fluid bathing the cells. As this process is perpetual, the interstitial fluid surrounding the cells is continually being renewed and replaced.

Without adequate drainage, excess interstitial fluid can accumulate in the tissues, leading to swelling (oedema) and, potentially, compression of local blood vessels and subsequent tissue damage. The major role of the lymphatic system is to continually collect excess interstitial fluid and drain it away from the tissues.

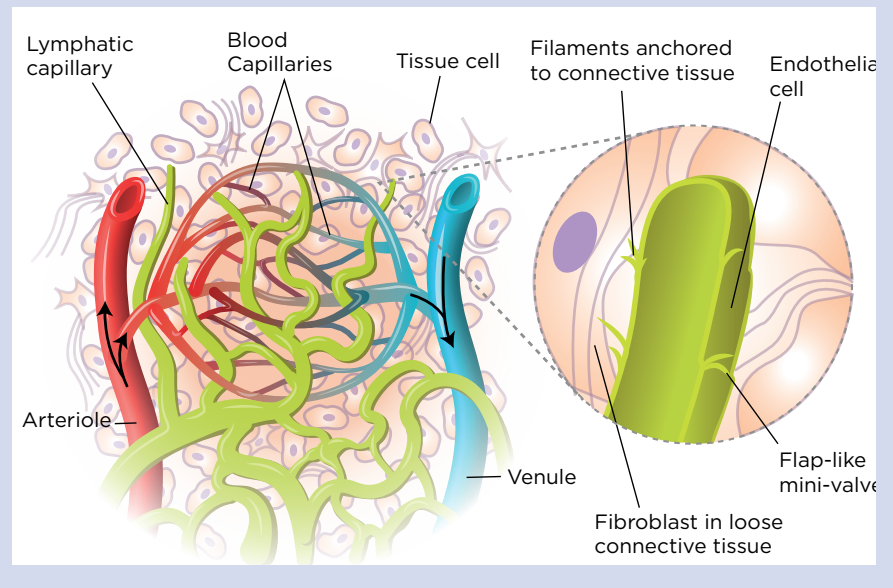
Interwoven among the capillary beds are blind-ended lymphatic capillaries (Fig 2); the walls of these vessels are composed of cells that form overlapping flaps, which function as unidirectional mini-valves. Highly porous, they act like sponges, soaking up excess fluid from the interstitial spaces. Unlike the larger lymphatic vessels, these lymphatic capillaries lack a muscular wall or internal valves; as such, they rely on capillary action to draw excess fluid away from the tissues and carry it to the progressively larger lymphatic vessels.

As soon as interstitial fluid enters the lymphatic capillaries it is referred to as lymph; at this stage, newly formed lymph is usually a clear, transparent fluid that resembles water.

Movement of lymph

It was previously thought that the movement of lymph through the lymphatic system was a passive process, reliant on the physical movements of the body. As with veins, contraction of skeletal muscles compresses lymphatic vessels, raising the pressure inside with internal valves in the

Fig 2. Capillary beds and the structure of lymphatic capillaries



600
Number of lymph nodes adults usually have

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medium and larger lymphatic vessels ensuring a progressive upward movement of the lymph.

Although bodily movement does play an essential role, it has subsequently been discovered that the walls of larger lymphatic vessels are equipped with a specialised type of muscle, which is structurally intermediate between the smooth muscle that lines arteries and veins and the cardiac muscle located in the myocardium of the heart (Scallan et al, 2016). This unique muscle type actively pumps by contracting in rhythmic waves (similar to the peristaltic movements of the gastrointestinal tract), ensuring progressive, steady movement of lymph. These rhythmic contractions of the lymphatic vessel walls complement the movement of lymph generated through bodily movement; they also ensure adequate movement of lymph while the body is stationary or at rest.

Composition of lymph

Initially, in the smaller lymphatic vessels originating in the tissue capillary beds, lymph is usually transparent or straw-coloured, similar to plasma. This reflects its origins, and it is chemically virtually identical to interstitial fluid. However, by the time it reaches larger lymphatic vessels, it has mixed with the products of fat digestion and takes on a cloudy or milky appearance; at this stage it is referred to as chyle.

Return of lymph to the cardiovascular system

Lymph eventually enters the larger-diameter lymphatic vessels known as lymphatic trunks, which are equipped with robust valves to ensure lymph is progressively transported upwards against the pull of gravity. The largest of the lymphatic vessels is the thoracic duct, which is typically 50-70mm in diameter and carries around 75% of the body's lymph (Johnson et al, 2016). As the name implies, the thoracic duct carries lymph upwards through the thoracic cavity (Fig 1); lymphatic flow is aided by normal breathing movements, which rhythmically compress the walls of the thoracic duct, effectively creating a 'milking' effect. The thoracic duct terminates at and discharges its contents into the left subclavian vein, ensuring blood volume is maintained by recycling fluid that originated from the blood during capillary filtration. At the point where the duct empties into the subclavian vein, a small bicuspid valve prevents backflow of venous blood into the lymphatic system (Ilahi et al, 2020).

Thoracic injuries, for example following a road traffic accident, can result in tearing of the thoracic duct and leakage of chyle into the pleural cavity. This type of pleural effusion is known as a chylothorax and can lead to lung compression, making breathing difficult. Chylothorax may also follow accidental injury to the thoracic duct during surgery or blockage of the thoracic duct, for example through malignancies such as lymphoma. This increases the hydrostatic lymph pressure and causes chyle leakage (Rudrappa and Paul, 2019).

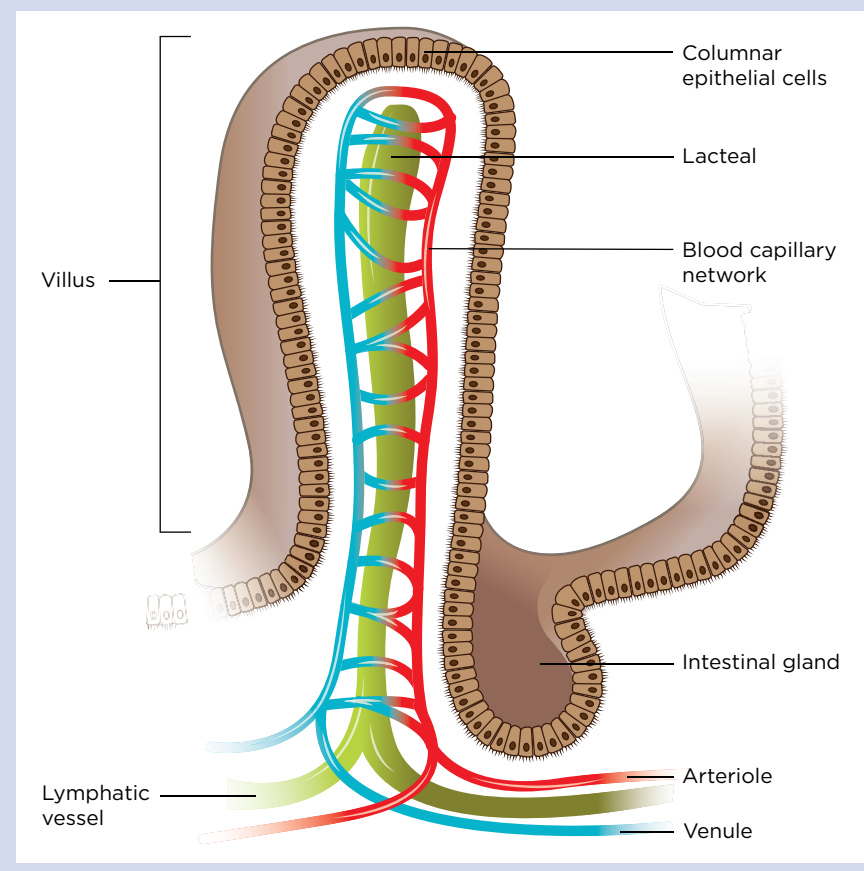
Oedema and lymphoedema

Oedema can be defined as an over-accumulation of fluid in the interstitial spaces, which leads to visible swelling of the soft tissues. Because oedema is subject to gravity, it becomes more apparent in the distal regions of the lower limbs and is often particularly noticeable in the ankles and feet. Most oedema is referred to as pitted oedema, because pressing the area causes a pit to form as the fluid is pushed away; the pit slowly disappears after several seconds as fluid returns.

Oedema can have a variety of underlying causes; the three discussed below are poor venous return, increased vascular permeability, and poor drainage by the lymphatic system.

Poor venous return is commonly seen in right-handed heart failure, where the right side of the heart becomes less efficient at collecting venous blood from the inferior and superior vena cava and pumping it through the pulmonary circulation of the lungs. This leads to a back-up of venous pressure, reducing the reabsorption and clearance of interstitial fluid from the capillary beds. This type of peripheral oedema is particularly noticeable in the lower limbs, with ankle and foot swelling frequently observed. In later stages of heart failure, the oedema may become so severe that fluid leaks through the skin of the legs (weeping oedema) or collects in fluid-filled blisters (Aviles, 2019). Long periods of immobility, such as prolonged hospital bedrest, also reduce blood flow in the veins of the legs and can lead to venous stasis and reduced venous return (Knight et al, 2018). Many women

Fig 4. Internal structure of a villus



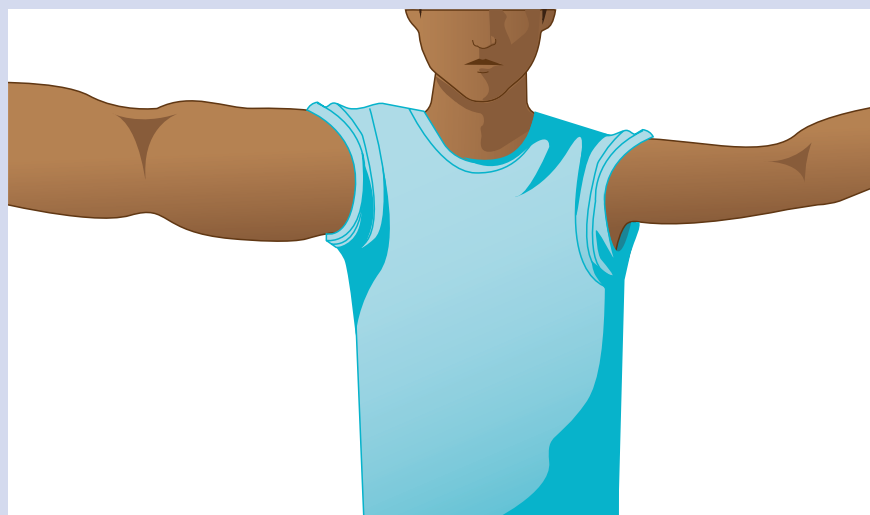
“Oedema that occurs as a result of poor drainage of the lymphatic system is usually referred to as lymphoedema”

experience a mild oedema in the later stages of pregnancy when the large veins such as the inferior vena cava in the abdomen become compressed as the baby grows; this often leads to fluid accumulation and swelling in the legs.

Increased vascular permeability is frequently seen in areas of infection, irritation or injury where inflammatory mediators, such as histamine and prostaglandins, induce loosening of the junctions between adjacent cells in the capillary walls. This results in the leakage of inflammatory exudate, which accumulates in the interstitial spaces. Increased vascular permeability can also be associated with fluctuations in the female sex hormone oestrogen that occur during the menstrual cycle and pregnancy.

Oedema that occurs as a result of poor drainage of the lymphatic system is usually referred to as lymphoedema. In the UK this is most frequently associated with cancer, either caused by blockages that occur due to metastatic spread or following surgery to remove local lymph nodes. For example, removal of the axillary lymph nodes (axillary dissection) is recommended in many cases of breast cancer. Lymphatic drainage

Fig 3. Lymphoedema of the right arm resulting from axillary dissection



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of the arm normally passes through the axilla, therefore, axillary dissection can lead to pronounced lymphoedema of the arm (Fig 3).

Symptoms include a heavy, aching limb and weakness. Left untreated, it may progress to chronic lymphoedema and, in severe cases, the formation of hard fibrotic tissue, which inhibits oxygen supply to the affected areas. Patients may become prone to repeated skin infections and develop skin ulcers that are difficult to heal. Severely obese patients with a body mass index (BMI) over 50 are also prone to lymphoedema which, in many cases, can be severe and disfiguring. The link between extreme obesity and lymphoedema is unclear. However it has been hypothesised that increased adipose tissue accumulation may collapse lymphatic vessels, reducing tissue drainage, while increased inflammation may damage lymphatic vessels, reducing their tissue density and ability to collect and pump lymph (Nitti et al, 2016; Greene et al, 2015). The complete blockage of lymphatic vessels can lead to an extreme lymphoedema called elephantiasis.

Filarial elephantiasis

In tropical regions, the bites of infected mosquitoes transmit microscopic, threadlike, filarial worms. The parasites enter the lymphatic vessels and are carried to regional lymph nodes, where they cause significant blockages in a disease called lymphatic filariasis, which can result in lymphoedema (Mohammad, 2018). Because lymphatic filariasis predominantly occurs within poor urban and rural populations, the lymphoedema often remains untreated and develops into irreversible elephantiasis. In 2018, 893 million people in 49 countries were living in areas that required preventive chemotherapy to stop the spread of infection ([Bit.ly/WHO-LymphFil](http://bit.ly/WHO-LymphFil)).

Treatment of lymphoedema

There are several treatments available for relieving chronic lymphoedema, including:

- Manual lymphatic drainage (MLD), which involves gentle, rhythmic massage to encourage the flow of lymph;
- Complete decongestive therapy, which incorporates therapeutic exercise, application of short-stretch compression bandages, skincare and MLD;
- Sequential gradient pump therapy, which helps break up fibrotic tissue to re-enable movement of lymph.

“Many women experience mild oedema in pregnancy; this often leads to fluid accumulation and swelling in the legs”

Fat transport

Within the gastrointestinal tract most nutrient absorption takes place in the ileum, which is equipped with tiny, finger-like projections called villi that massively increase its total surface area. Each villus contains a complex, highly convoluted blood capillary network and a central blind-ended lymphatic vessel called a lacteal (Fig 4).

Following the processes of mechanical and chemical digestion, the products of carbohydrate digestion (monosaccharide sugars such as glucose) and protein digestion (amino acids) are absorbed directly through the walls of the villi into the blood capillary network and transported to the liver via the hepatic portal vein.

Larger-chain fatty acids do not enter the blood directly; instead they enter the columnar epithelial cells lining the villi, and are coated and packaged with a mixture of cholesterol and protein to form small spherical aggregates called chylomicrons which are then absorbed directly into the lymphatic system's central lacteals (Nigam et al, 2019). The lymphatic system is a major route for the transportation of the products of fat digestion and, although it carries large amounts of modified lipids, it does not appear to be susceptible to the build-up of fatty plaque that can affect arteries.

Immune responses

Virtually all tissues in the human body are drained by the lymphatic system, therefore, any infections within organs or tissues usually result in the pathogenic particles – bacteria, viruses or fungal cells – circulating in the lymph. Throughout the lymphatic system, strategically located collections of lymphoid tissue called lymph nodes trap and process pathogens and activate specific immune responses that ultimately lead to pathogen destruction. Adults usually have around 600 of these bean-shaped nodes, which vary in size and typically enlarge and become tender and inflamed in the presence of infection (Mohseni et al, 2014). Enlargement of the lymph nodes is called lymphadenopathy; swollen, tender nodes are usually readily palpable by experienced

clinicians. Lymph node assessment can provide valuable diagnostic information about potential sites of infection – for example, the cervical lymph nodes of the neck commonly show lymphadenopathy in upper-respiratory-tract or middle-ear infections. The role of lymph nodes in sequestering foreign material and participating in immune responses will be examined in detail in the third part of this series, which examines antibody-mediated immune responses. **NT**

- Part 2 of this series will focus on the major lymphatic organs, including the red bone marrow, thymus and spleen.

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