

Chronic peripheral oedema: the critical role of the lymphatic system

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Oedema is an excess of interstitial fluid and is an important sign of ill health in clinical medicine. It may occur in the lungs (pulmonary oedema), the abdominal cavity (ascites) and other body cavities (synovial, pericardial and pleural effusions) but in this article only peripheral (subcutaneous) oedema is discussed.

In medical practice peripheral oedema tends to get pigeonholed according to possible systemic or peripheral causes eg heart failure, nephrotic syndrome, venous obstruction or lymphoedema. This viewpoint fails to appreciate the many dynamic physiological forces contributing to oedema development and in particular the central role of the lymphatic drainage system in tissue fluid balance. Consequently, the clinician's approach to chronic oedema is often misguided and the necessary medical intervention inappropriate, for example, empirical use of diuretics. In this article we propose a system for managing peripheral oedema, which is based on physiological principles, that can then guide treatment.

Why is chronic oedema important?

Besides being a physical sign of a potentially fatal systemic condition such as heart failure, chronic oedema impairs local cell nutrition due to increased interstitial diffusion distances of oxygen and nutrients so tissue viability can become compromised. Swollen limbs can be painful, giving rise to impaired mobility as well as a predisposition to infection and blistering progressing to ulceration.

Chronic oedema is a common problem in the community particularly for district nurses. A recent epidemiological study in South West London estimated a crude prevalence of 1.33/1000 population rising to one in 200 people over the age of 65. 29% of the oedema cases had experienced cellulitis in the preceding year with one quarter of these cases requiring admission. Oedema caused time off work in more than 80% of sufferers and employment status was affected in 9%. Quality of life suffered, with clear deficits in many domains of the well-validated SF-36 questionnaire.¹

Key Points

Lymph transport, not venous capillary reabsorption, is the main process responsible for interstitial fluid drainage

All oedema is due to an imbalance between capillary filtration and lymph drainage

Elevation and diuretics reduce venous pressure and consequently capillary filtration but do not improve lymph drainage

Lymph flow is stimulated by tissue movement and in particular exercise

In theory an increase in lymph transport, if achievable, should benefit all forms of oedema

Calcium channel blocking agents should be contraindicated in the presence of any peripheral oedema unless there is no alternative treatment

Diuretics should only be prescribed long-term in circumstances of salt and water overload, eg heart failure, venous disease, and not on an empirical basis for any oedema

Movement through active or passive exercise should always be the preferred option for reducing leg oedema due to decompensated lymph drainage, with elevation practised during the periods of rest

Understanding oedema

Oedema develops when the microvascular (capillary and venules) filtration rate exceeds lymph drainage for a sufficient period, either because the filtration rate is high or because lymph flow is low or a combination of the two. Filtration rate is governed by the Starling principle of fluid exchange, which is described succinctly and quantitatively by the Starling equation for flow across a semipermeable membrane:

$$J_v = L_p S [(P_c) - P_i - \sigma (\pi_p - \pi_i)]$$

where J_v = capillary filtration rate
 L_p = hydraulic conductance of capillary wall
 S = surface area
 P = pressure within capillary (c) or interstitium (i)
 σ = osmotic reflection coefficient of capillary wall
 π = osmotic pressure of plasma (p) or interstitial fluid (i)

In simple terms filtration of fluid from capillary into interstitium is driven by the hydraulic (water) pressure gradient across the wall ($P_c - P_i$) and is opposed by the osmotic pressure gradient ($\pi_p - \pi_i$), which is the suction force keeping fluid in the circulation. Strictly speaking, π_i and P_i are the forces immediately downstream of the semi permeable membrane rather than the global interstitial values.²

Other factors important in determining filtration

- a) L_p , which refers to the ease with which water can cross the capillary wall
- b) S , which is the surface area for filtration, and
- c) σ , which refers to the ability of the capillary wall to prevent leakage of plasma protein from the circulation.

The Starling equation provides a logical approach for classifying oedema that is due to increased filtration:

- a) Raised capillary pressure; because capillary pressure is more susceptible to changes in venous pressure rather than systemic (arterial) blood pressure as post-capillary resistance is much lower than pre-capillary resistance. Peripheral venous pressure is raised in:
 - Right ventricular failure
 - Salt and water overload (overtransfusion)
 - Venous obstruction
 - Venous reflux (chronic venous disease) eg following deep vein thrombosis, primary varicose veins
 - Dependency (the effect of gravity)
 - Certain drugs, especially calcium-channel blocking agents.
- b) Reduced plasma osmotic pressure (COP) essentially means hypoalbuminaemia, which can arise from:
 - Malnutrition
 - Intestinal disease (malabsorption or protein loss)
 - Nephrotic syndrome
 - Hepatic failure – failure to synthesise albumin due to liver disease or chronic inflammatory states.
- c) Increased capillary permeability, when inflammation causes a breakdown in the endothelial barrier facilitating the passage of both plasma proteins and water across the capillary wall.³ In addition, vasodilatation causes a rise in capillary pressure (and blood flow).

The importance of lymph transport rather than venous capillary reabsorption for interstitial fluid drainage

Accumulation of capillary filtrate in the tissue spaces is avoided mainly through lymph drainage and not, as was previously thought, through reabsorption by the venous capillaries. Traditionally it was taught that the arterial end of capillaries filtered fluid while the venous end reabsorbed the bulk of fluid

filtered. This view is not supported by modern evidence, which demonstrates that in most vascular beds there is a net but dwindling filtration along the entire length of well-perfused capillaries. It is true that pressure in venous capillaries does fall below plasma COP. However, when direct measurements of P_i and π_i in muscle, mesentery or warm skin at heart level are made directly these are far from negligible, contrary to popular belief. The sum of all Starling forces is not an absorptive force in venous capillaries. It is a slight filtration force. Data from 12 tissues confirm that venular blood pressure exceeds the sum of pressures opposing filtration.⁴

Exchange vessels (mainly capillaries and post-capillary venules) can reabsorb fluid for a short period if the Starling pressures are disturbed. For example, following haemorrhage precapillary vasoconstriction, coupled with a drop in both arterial and venous pressures, will reduce capillary pressure sufficiently for absorption to develop transiently. Very soon, however, the reabsorption of interstitial water raises the protein concentration in the pericapillary space, so raising the local osmotic pressure there (π_i). Consequently reabsorption stops and slight filtration is restored. For reasons explained in Levick and Mortimer's 1999 paper,⁴ sustained absorption of fluid into the microcirculation is a normal feature of intestinal mucosal capillaries, renal peritubular capillaries and lymph node capillaries but not peripheral tissues.

Since the old concept of sustained fluid absorption by venous capillaries is no longer tenable, this places the major responsibility for drainage of interstitial fluid in the hands of the lymphatic system. The latter is now perceived to be of even greater importance to tissue volume homeostasis than was formerly realised.⁵

Restraining factors against oedema

Several factors 'buffer' the capillary filtration rate, and thus tend to prevent oedema formation.

Elevation of interstitial fluid pressure

Stiffness of tissues resists swelling. A small increase in interstitial fluid volume in a stiff tissue (low compliance) will cause a relatively large increase in interstitial pressure (P_i) which then opposes filtration eg subfascial muscle compartments. Conversely a tissue such as eyelid skin is loose and compliant and P_i will not increase so much for a given volume increase. Therefore, oedema continues to form and accumulate to large volumes. Conversely, placing a bandage or rigid stocking around a leg will reduce compliance (increase stiffness) and resist stretch. Consequently, P_i will increase more steeply for a given amount of interstitial volume increase, and the increased P_i will oppose filtration.

Fall in interstitial COP (π_i)

An increase in filtration rate will dilute the interstitial protein concentration and consequently reduce the osmotic pressure immediately outside the semipermeable membrane (π_i). The

resulting increase in the osmotic pressure gradient ($\pi_p - \pi_t$) will raise the suction force, keeping fluid with the blood compartment. This is probably of major importance in the protection against pulmonary, as well as peripheral oedema.

Increased lymph flow

Increases in interstitial fluid pressure and volume stimulate lymph flow.⁵ Transport of interstitial fluid into and along initial lymphatics is a complex, poorly understood process dependent on intermittent changes in tissue (interstitial) pressure from movement (active and passive exercise), massage, local arterial pulsation and, in more central tissues, breathing. Lymph flow in the larger more proximal-collecting lymphatics is generated by active lymphatic pumping. Collecting lymphatics contract and are mainly responsible for pumping lymph up the leg against gravity to the inguinal lymph nodes. Successive segments of collecting lymphatic vessel behave like mini hearts in series and the contractile cycle bears striking similarities to the cardiac cycle. Sympathetic input influences the pumping rate while the diastolic filling (lymph supply from upstream initial lymphatics) largely controls the force of contraction. Flow in collecting lymphatics is only as good as the supply from initial lymphatics. Influx of calcium ions is important for smooth muscle contraction in the walls of the collecting lymphatics.⁶ Therefore calcium channel blocking agents are likely to work at least in part on the lymphatic in causing peripheral oedema.

The important point is that it is the lymph vessels that return the capillary filtrate back to the blood stream via the lymph nodes and eventually the thoracic duct. This completes the extravascular circulation of fluid and protein and maintains tissue volume homeostasis. If lymphatic drainage is impaired in the face of normal filtration, oedema will occur (lymphoedema). Lymph flow should respond to increases in capillary filtration and so prevent oedema. By failing to compensate fully for increased capillary filtration and so permitting swelling, the lymphatic is to some extent failing in its duty in all types of oedema. This could help explain differences in the degree of leg oedema seen in patients with venous disease and also in right-sided heart failure. It is possible that 'true' lymphatic failure, namely reduced lymph transport, does eventually occur in circumstances of high capillary filtration when high lymph flow cannot be sustained.

The leg has additional buffering mechanisms to resist oedema. These include:

- a) postural vasoconstriction in a dependent leg resulting from activation of the veno-arteriolar response
- b) a rise in plasma colloid osmotic pressure in the venules of a dependent leg in response to increased concentration of plasma proteins following increased microvascular filtration
- c) activation of the calf muscle pump, which not only reduces venous pressure by increasing venous return, but also increases lymph transport.⁷

Diagnosis

Chronic oedema can occur in any subcutaneous tissue – face, trunk, breast, genitalia, but more often than not it develops in a limb, usually the lower limb. For the purpose of simplicity the following scheme deals with lower limb oedema but the principles stand for any site. Oedema that is symmetrical eg equal between right and left legs, is more likely to be of systemic origin, for example, right-sided heart failure or hypoproteinaemia. Oedema that is asymmetrical, eg worse in the left than the right, may still have a systemic contribution but is likely to be due predominantly to peripheral pathology ie impaired local venous or lymph drainage. Oedema that is unilateral eg one leg only is likely to result from pathology arising within the limb or adjoining quadrant of the trunk.

The first consideration in assessing peripheral oedema must be to exclude serious systemic causes such as heart failure. This is not always straightforward. Careful examination of the jugular venous pressure is crucial, but the reliability of a clinical diagnosis is poor and investigations including a 12-lead ECG and measurement of B-type natriuretic peptide may be necessary.⁸ Other explanations for raised venous pressure eg venous obstruction, chronic venous disease and prolonged periods of dependency should be sought and plasma proteins measured. Cancer uncommonly presents with peripheral oedema unless advanced at diagnosis but relapsed cancer may frequently be a cause of limb swelling. Therefore cancer should always be considered and investigated appropriately. In advanced cancer numerous factors may contribute to oedema, including both venous and lymphatic obstruction, hypoalbuminaemia and immobility.

Distinguishing lymphoedema from oedema due to increased filtration (filtration oedema)

It is important to distinguish lymphoedema from filtration oedema because the treatment is different. Currently there are no drug or surgical interventions effective in treating lymphoedema. Diuretics do little and may be harmful if used long term.

When taking a history there are certain features of the oedema that can help distinguish an oedema due to impaired lymph drainage from an oedema arising from overwhelming filtration. Here we refer to oedema arising from an increased capillary rate as a filtration oedema and oedema arising from a fundamental failure in lymph transport as lymphoedema. Oedema where both mechanisms contribute will be referred to as oedema of mixed origin.

Pitting

It is often said that lymphoedema does not pit but this is not true. Pitting is invariably present but sustained pressure for some 20 seconds may be necessary owing to the firmer (and thicker) nature of the skin and subcutaneous tissues. In established lymphoedema the skin may double in thickness particularly at

the base of the second toe, a sign first noted by Kaposi. An inability to pinch up a fold of skin indicates lymphoedema (Fig 1).

Elevation

Elevation is always recommended for reducing oedema but its effect is much less marked in lymphoedema because elevation almost certainly does not improve lymph flow. In addition, lymphoedema swelling consists of an increase in fibro-fatty tissue and not just fluid. Most filtration oedemas results from higher venous pressures and therefore elevation by reducing venous (and consequently) capillary pressure will reduce filtration and, as a result, oedema. Filtration oedemas will tend to improve by 90% or more with overnight elevation but lymphoedema will improve by only 10–20% at best and often not at all.

Diuretic therapy

The clinical response to diuretic therapy can be a useful guide in diagnosis. By excreting salt and water, diuretics reduce circulating plasma volume and therefore venous and capillary pressure. This will have much greater benefit where oedema results from increased filtration and much less effect on lymphoedema because diuretics do not, to our knowledge, improve lymph drainage. Patients with lymphoedema may notice their swelling to be softer but with little volume change. Any initial benefit is usually lost with continued use.

Management

Most cases of ankle oedema observed in clinical practice, particularly in the community, will not be caused by systemic disease alone. The elderly and particularly those with controlled heart failure, respiratory disease or infirmity from arthritis or neurological conditions will spend increasing amounts of time sitting in a chair. Indeed, some may spend most of the night as well as the day in a chair. This results in prolonged periods of raised venous pressure with sustained filtration into the most dependent parts, namely feet and ankles. The lack of movement and, in particular, walking, means that there is little stimulus to lymph drainage. Unlike blood flow, which is predominantly driven by the heart, lymph flow falls to low levels unless stimulated by movement and in particular exercise. Walking would also have the beneficial effect of reducing venous pressure through activation of the calf muscle pumps, an important factor in venous return. Chronic congestion within the legs



Fig 1. Kaposi-Stemmer sign – An inability to pinch and pick up a fold of skin at the base of the second toe predicts lymphoedema. The skin is thickened as a result of the impaired local lymphatic transport.

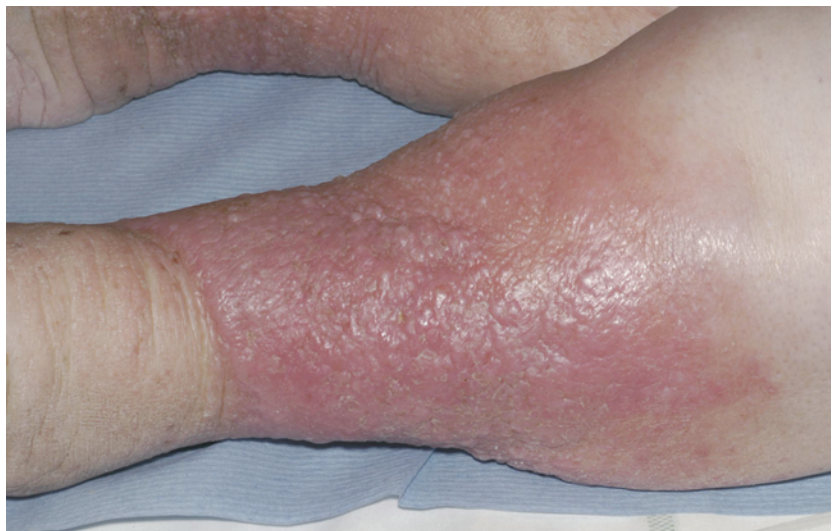


Fig 2. Lipodermatosclerosis refers to the inflammatory change that occurs in the skin and subcutaneous tissues as a result of chronic congestion. It occurs with venous and lymphatic hypertension and is always associated with peripheral oedema. It can resemble streptococcal cellulitis, but does not respond to antibiotics, only to decongestive therapy, ie elevation and/or compression.

with no overnight respite from elevation in a bed has profound effects on the skin and subcutaneous tissues leading to weeping of fluid, 'varicose' eczema, plum red erythema and fibrosis (lipodermatosclerosis) and eventually ulceration. The red skin of lipodermatosclerosis often leads to a misdiagnosis of cellulitis and the inappropriate use of antibiotics (Fig 2). With time and lymphatic failure, skin changes of lymphoedema are also frequently observed in chronic high-filtration oedema, namely a warty surface change (hyperkeratosis) with surface bulges resembling cobblestones (papillomatosis).

Improving lymph flow by physical means

One approach that is theoretically of value in all forms of peripheral oedema is an improvement in lymph drainage. As explained previously, all oedema arises either because of a primary failure in lymph drainage (lymphoedema) or because increased capillary filtration overwhelms increased lymph drainage (which under-compensates). Therefore, means that improve lymph transport are desirable when lymph drainage is failing. Unfortunately no drug therapy is effective at increasing lymph flow. Lymph drainage can be improved by using simple physiological principles to stimulate lymph flow.

As already mentioned movement and exercise, by inducing alternating changes in interstitial fluid pressure, increase initial lymphatic filling, and hence lymph flow. This may also promote flow in conducting lymphatics whose contractility has failed. Patients with lymphoedema often notice that walking reduces swelling. The addition of a bandage or equivalent form of outer pressure on the leg will enhance the effect of movement. The idea is not to squeeze fluid out of the limb with force like squeezing toothpaste out of a tube, but to create an outer collar to the leg against which the calf and foot muscles can press to improve pumping. A short stretch bandage will generate higher interstitial pressure during muscle contractions to stimulate lymph flow but result in low tissue pressure during muscle relaxation which then permits lymph vessel refilling. Such treatment has the added benefit of lowering venous pressure in the leg and so reducing filtration. Care is needed during the first application of any bandage in case rapid fluid shifts back into the circulation cause pulmonary oedema in anyone with heart failure. Care also has to be taken in circumstances where arterial supply and cutaneous sensation are compromised.

'Decongestion' of the legs may reverse more or less all the co-morbidity from the swelling, particularly the skin changes. Once swelling has been reduced, control needs to be maintained through encouragement of movement and exercise while wearing appropriately fitted support hosiery. In the elderly and those patients with hand arthritis or disability, the application and removal of hosiery can be problematic but technique can help and aids to application do exist.

Elevation

Elevation of the legs is often chosen over exercise for infirm patients who spend long periods in a chair. Unfortunately, leg elevation is only of partial benefit unless the trunk is reclined because there remains a considerable venous pressure increase from heart to legs when sitting upright. Only by lying completely flat (or, better still, with ankles above heart level) will venous pressure be reduced sufficiently to reduce oedema. Elevation acts by reducing local capillary pressure and thus filtration, allowing lymph drainage to outpace the reduced capillary filtration rate. Some degree of leg movement through active or passive muscle exercise would always be the preferred option for reducing leg oedema, with elevation practised during the periods of rest.

Pneumatic compression pumps

In theory, pneumatic compression pumps would offer additional benefit for patients spending considerable time in a chair. Unfortunately there is no evidence that such pumps improve lymph flow and they may simply displace fluid.⁹ Once again, care has to be taken in case of rapid fluid shifts. The equipment is not prescribable so patients may have to purchase it themselves. It is often the patients in most need who can ill afford the cost.

Diuretics

Too often, diuretics are prescribed for oedema on an empirical basis without due thought to underlying pathophysiology. Diuretics should only be prescribed in circumstances of salt and water retention, such as happens in heart failure and nephrotic syndrome. Arguably, they should not be prescribed in any other circumstances particularly in the long term where adverse effects including electrolyte imbalance can be harmful. Indeed, the development of 'idiopathic oedema of women' has been largely attributed to diuretic abuse.¹⁰ Rebound oedema on diuretic withdrawal can be an exacerbating factor in many forms of chronic peripheral oedema.

Lymphoedema clinics

Until recently it has been a long held view that nothing can be done for lymphoedema and patients have been told to put up with it despite the morbidity and risk of life-threatening septicæmia through cellulitis. In Europe in the early 1980's treatment was introduced which did not use drugs or surgery but used physical methods designed to stimulate lymph transport. This decongestive lymphatic therapy for limb lymphoedema employed isotonic muscle exercise (not strength building but exercise that involved lengthening and shortening of muscles) as the cornerstone, with compression (bandages or hosiery) to enhance the effect of exercise.¹¹ A specific form of massage (manual lymphatic drainage therapy) was used concurrently to stimulate lymph drainage from the root of the limb and adjoining quadrant of the trunk to normally draining lymphatic basins. The massage was therefore intended to 'clear the way ahead' for limb lymph drainage and avoid congestion above the level of compression. In moderate to severe lymphoedema an intensive period of treatment using multi-layer bandaging, exercises and manual lymphatic drainage is used to reduce swollen limbs so that subsequent maintenance treatment with hosiery and exercise is more effective at controlling the condition.¹²

These combination treatments have a sound physiological basis but the quality of evidence proving efficacy is limited. A randomised, controlled parallel group clinical trial comparing multi-layer bandaging followed by hosiery versus hosiery alone demonstrated significantly greater limb volume reduction with bandaging and hosiery at 24 weeks.¹³

Since the mid-1980s an increasing number of lymphoedema clinics have been established throughout the UK.¹⁴ Most are

cited in palliative care or oncology units in response to Calman directives for provision of cancer services. These clinics are staffed by a range of healthcare professionals, mainly led by nurses and physiotherapists, who have specifically trained in lymphoedema therapy. They have proved a very useful resource for management of chronic peripheral oedema of mixed aetiology not just cancer-related lymphoedema. Unfortunately, as non-cancer cases are probably in the majority, demand is now exceeding available resources. The patients' association, the Lymphoedema Support Network, perceiving great benefit from these clinics has been lobbying Parliament with success. It has so far achieved an Adjournment Debate¹⁵ and well supported Early Day Motions.

One weakness in the provision of care for chronic oedema is the availability of suitably trained vascular, and more specifically, lymphatic, physicians. Lymphoedema has been traditionally seen by vascular surgeons yet in the UK very little, if any, lymphatic surgery is performed. As explained in this article, most cases of chronic peripheral oedema are more appropriately managed medically.

Conclusion

Chronic peripheral oedema is seen commonly in medical practice but the controlling role of the lymphatic in its development is not appreciated and consequently management is often inappropriate. It is important to consider and treat serious underlying systemic conditions such as heart failure, nephrotic syndrome and cancer but once these are excluded a lymphoedema-directed treatment programme should be introduced.

Contact details

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