Matts' hypothesis: how simple strategies can lead to better outcomes

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Key words

Lymphatic filariasis, lymphoedema, moisturisation, oedema, podoconiosis, skin, stratum corneum barrier function

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Abstract

This article looks at the causes of oedema, lymphoedema and conditions such as lymphatic filariasis and podoconiosis – and how the treatment of leg swelling has changed over the years. It highlights Matts' hypothesis (reported for the first time herein), which suggests that lymphoedema can be caused by a breakdown of the stratum corneum's barrier function (SCBF). The author also refers to simple well-established strategies to protect the SCBF, such as washing and emollients. The article shows how Matts' hypothesis, which was formulated in response to work with people in Ethiopia who had podoconiosis caused primarily by not wearing shoes, soil irritants and bacterial foot infections, can be used across the world for people who are at risk of developing oedema. The article explores the importance of the skin and urges that attention be paid to skin failure and concludes that the simple employment of washing and emollients to ensure good moisturisation of the limbs can be highly effective in preventing or reducing the damaging effects of oedema.

All the organs begin to fail in old age – including the skin. Skin failure affects the whole body and simple therapies to restore the integrity of the skin may have profound advantages – one of which is the reduction in the incidence and severity of chronic leg swelling.

Of all the known causes of oedema, such as malnutrition and failure of the heart, liver and kidneys, it is skin failure that has been given insufficient emphasis for the longest time (Ryan, 1995). When examining the components that make up the skin, the epidermis is clearly distinguishable from the dermis and the subcutaneous adipose tissue. However, not all the components of the dermis, such as the vasculature, lymphatics, connective tissue (collagen and elastin), mast cells, macrophages and dendritic cells, can be simply identified without special stains and microscopic inspection.

It has taken a long time for people to recognise the importance of these components. Their interaction with the overlying epidermis or deeper adipose tissue is not fully explained in the literature on lymphoedema. All these components have essential roles in the maintenance of the skin's barrier function, thermoregulation, sensory function and use in communication. The skin also has a central role in non-verbal communication and signalling, and failure of this organ predisposes the owner to lower quality of life, stigmatisation and ostracism by others.

In the early stages of oedema, it will resolve completely when the person sleeps at night. In the later stages, oedema that does not resolve with elevation causes a fibrotic response in the leg and often large nodules composed of whorls of collagen will form, usually with accompanying angiogenesis and disturbances of keratinisation.

Lymphoedema (brawny and non-pitting) has traditionally been blamed on a failure of the lymphatics to remove tissue fluids laden with metabolic waste (lipid and protein), the accumulation of which stimulates hyperplasia and encourages fibroblasts to generate collagen.

The venous system

Ryan (2009) has discussed how 19th century authors believed that venous failure, even thrombosis of the leg veins, contributed to lymphatic failure. Indeed, 20th century observers found much overlap between the pathology of a failing venous system and lymphoedema. Some in the late 20th century also believed coagulation and fibrinolysis imbalances to be responsible (Burnard et al, 1980). Today, one must note that immobility and gravitational accumulation of blood in the lower leg veins contributes to capillary bed leakage and lymphatic overload in almost every case of oedema because of the tendency for affected patients to sit with their legs in a dependent position for long periods of time.

Mastectomy can affect the venous system of the upper limb, due to removal of the supporting adipose tissue in the axilla which is now thought to be a major factor of lymphatic failure in this part of the body. Bates et al (1994) and Bains et al (2015) have found

the oedema to be a transudate rather than the high protein oedema that characterises lymphoedema, and others using infrared imaging showed disturbances in upper trunk venous flow often affecting both upper limbs (Belgrado et al, 2015).

More detailed study of lymphatic anatomy isolates the initial lymphatic system and associated pre-collecting ducts (Alitalo and Carmeiet, 2002). These are not only anatomically different but also develop at a different stage to the larger collecting vessels of the deeper lymphatic system. In early embryogenesis, genes determine the first signs of lymphatic development near the developing heart and great vessels. The later, much enlarged, embryo develops peripheral lymphatics determined by a different set of genes. These then connect up with the central lymphatics, although in some genetic and congenital disorders, such as Milroy's disease (Mellor et al, 2010), they do not succeed in doing so.

A malfunction of the collectors, for example due to filariasis or cancer and its treatment, does not completely reduce the functioning of the more superficial initial lymphatics and pre-collectors. These are more likely to suffer from the inflammatory processes in the dermis due to cytokines released from the epidermis and incoming white cells as well as the penetration of bacteria and environmental irritants through the now defective epidermal barrier (Ryan, 2004; 2013).

Much of the above and more has been learned from studies of the four most common presentations of lymphoedema:

- Post mastectomy
- Immobility and frailty in older people
- Podoconiosis
- Lymphatic filariasis.

Inflammation

Besides overload from the venous system, early authors, for example Castellani (1965), at the first ever congress on tropical dermatology, reported on his longstanding belief that streptococcus was the cause of the inflammatory episodes producing exudate from the blood capillary bed and the consequent lymphatic overload that caused 'elephantiasis' (lymphatic filariasis). Three classic features of inflammation — rubor, calor and tumor — play a part in this.

Among the most common symptoms of lymphatic filariasis are pain, redness and swelling of lymphoedematous tissue, with accompanying high fever. Some patients may be affected at least monthly and 90% of patients will be affected at least once per year after the initial occurrence (Addiss and Brady, 2007). It has been blamed variously on the death of the filarial worm and secondary bacterial infection. The role of the latter became more definite when antibiotics were introduced and were able to fight the infection (Addiss and Brady, 2007).

Studies in India (Shenoy et al, 1999) showed that washing and the use of emollients on the affected areas were as effective as penicillin. Studies in Brazil (Dreyer et al, 2002; 2006) also focused on skin hygiene to reduce inflammatory episodes and so physicians everywhere began to focus on entry points on the skin where bacteria could enter and which could be remedied by skin care. The most obvious entry points are crevasses in swollen skin and between the toes, which can be examined for fungi and bacteria (McPherson et al, 2006). Maceration and poor health of the skin in these crevasses among people with lymphatic filariasis was noted, although bacteria and fungi were not always found.

Streptococcal species have long evoked the most interest and, at the turn of the 20th century, Castellani (Ito, 1984) was the greatest advocate for the contribution of these bacteria to lymphoedema. Suma et al (1997) found that 90% of patients with adenolymphangitis had raised antistreptolysin O titres. It is a cause of necrotising fasciitis, a consequence of cellulitis, notably in the non-tropical environment. Complete circulatory failure and shock is followed by death. It also activates coagulation and impairs fibrinolysis (Hammar et al, 1985) and one reason for this lies in the ability of the streptococcus to neutralise the (healthy) binding of plasminogen activator inhibitor-1 (PAI-1) with plasminogen activator; an observation made by Nishioka and Ryan (1971) when studying the role of fibrinolysis in skin diseases. PAI-1 plays an important role in mediating relationships between the epidermis and dermis (Turner et al, 1969) or in elephantiasis nostras (the chronic swelling observed in European countries).

In cases of podoconiosis in Ethiopia where the cause of the swelling was thought to be irritant volcanic soil migrating through the skin through the feet, (Sikorski et al, 2010), it was the irritant soil rather than the bacteria that was thought to cause episodes of high fever. However, as stated above, for more than 100 years, secondary infection by the *streptococcus* was believed by investigators such as Castellani to explain recurrent fever in elephantiasis nostras.

Moisturisation

Other conditions in which the failure of the barrier function of the skin has been explored, have included atopic eczema. A wide body of literature has developed around the roles of emollients and skin moisturisation for this condition. Ryan (2004) has written about eczema: 'the first commandment: oil it!' He pointed out that a healthy epidermis could be at rest unstimulated by the stretch of body movements, external trauma or infections, with no mitotic figures, low rates of turnover and an intact epidermal barrier function. Many have pointed out that, with barrier disruption, the epidermis went into repair mode becoming a factory for eiconosides, cytokines and growth factors, transferring these molecules into the dermis to activate the blood capillary bed (Ryan, 2004). This repair mode encourages the action of neutrophils and other white cells, as well as inflammatory material needed for restoration of epidermal function. Applying emollients puts a stop to this inflammatory process (Ryan, 2004).

An outspoken proponent for emollients was Paul Matts (a research fellow at Procter and Gamble and visiting professor to the University College London School of Pharmacy and University of the Arts, London). He was introduced to the problem of podoconiosis in Ethiopia and put forward the hypothesis that, besides reducing the contact with soil by wearing shoes, the other elements of care including washing and the use of emollients should be interpreted through a single defining lens, namely maintaining the stratum corneum barrier function (SCBF). He also introduced workers to simple surrogates of SBCF, including hand-held electronic moniters of transepidermal water loss (TEWL; the rate of water lost through the SC by diffusion and evaporation, expressed in $gH_2O/m^2/hr$).

The amplitude of measured TEWL provides an indication of SCBF integrity and gives a metric indication of the extent of intervention required by sustained rehydration (moisturisation) of the skin surface. The delicate water gradient across the SC exists primarily to:

- Reduce the elastic modulus of this layer, to maintain a plastic, flexible unit resistant to cracking and splitting
- To enable efficient desquamation by providing the necessary micro-

environment for optimal functioning of the battery of protease enzymes in the upper SC.

With even modest dehydration, desquamation fails, the SC thickens, loses plasticity and becomes mechanically brittle (Rawlings and Matts, 2005) with resulting entry points for bacteria and irritants. With this author, Matts focused on the cleansing and conservation of water for the washing of skin and then put forward the hypothesis that the observed lymphoedema was due to loss of SCBF which could be restored and augmented by low-cost, readily-available emollients and humectants, such as petrolatum and glycerine.

Matts' hypothesis was tested in a randomised controlled trial (n=200), conducted in the field in Ethiopia in people with podoconiosis carried out by Jill Brooks which has yet to be published and is part of her Phd thesis at Hull university. She employed wireless, portable probes to assay SC hydration and TEWL after the use of:

- A simple washing/emollient regimen
- The additional significant incremental effect of 2% v/v glycerine, a known moisturiser.

The regimen restored the SCBF and has an accompanying positive clinical outcome within a 12-week time frame. The only possible explanation for the striking effects of these simple, low-cost interventions is a significant improvement in SCBF that helps restore dermal-epidermal homeostasis and reduces to a minimum the flux of exogenous inflammatory material and bacteria to the inner, viable compartment.

Matts' hypothesis may be expanded by stating that all oedematous leg swelling may have increased vascular permeability due to the contributing factors of heart failure or venous hypertension. Inflammation, whether due to irritants or immune factors, induced by trauma, bacteria or soil, is a common cause. The critical importance of SCBF integrity has not always been sufficiently emphasised.

Control of SC hydration and TEWL is such a necessary determinant of epidermal and dermal health that the use of washing, emollients and humectants are essential. The fact is that the oedematous leg causes loss of the primary function of the skin: the stratum corneum barrier function. Furthermore, loss of this prime function leads to an epidermal repair mode which does more harm than good (Ryan, 2013) and which can induce oedema.

Matts and Brooks have done a great service to people who experience oedema, particularly in developing nations, by testing their ideas on people with podoconiosis. The benefits of employing this hypothesis now need to be spread to all those at risk of oedema and who are experiencing a breakdown in SCBF.

Conclusion

The rules of care for people with chronic oedema of the leg should be to:

- Reduce the risk of SCBF breakdown by providing protective footwear
- Strengthen and defend the SCBF by washing and using emollients and humectants.
- Recognise and treat heart failure which is frequently present in older people who have heavy, swollen legs
- Recognise that in any adult with heavy and swollen legs that the leg needs to be elevated and ankle exercises should be employed and support bandaging or hosiery used
- Inflammatory episodes may be due to microbes whose ingress is allowed through vulnerable entry points (typically through the failure of the SCBF), but they act in part through the release of inflammatory cytokines which can equally be released from epidermal macrophages and mast cells as part of the repair mode triggered by injury.

The Matts hypothesis emphasises failure of control of transepidermal water loss, triggering a repair response that inflames the dermis, increasing vascular permeability and overloading the lymphatics. Skin care with moisturisers, such as glycerine, reverses the process.

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