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Perspectives

Lymphoedema: Pathophysiology and management in resource-poor settings - relevance for lymphatic filariasis control programmes

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Abstract

Low cost reduction of morbidity in lymphoedema is an essential goal in the management of lymphatic filariasis. This review emphasises the role of movement and elevation, and refers to the literature on the effects of these on the venous and lymphatic system. The patient with lymphoedema becomes increasingly immobile and the affected limb is often in a permanently dependent position causing venous hypertension and resultant overloading of the failing lymphatics. The evidence that breathing exercises are important for reducing venous hypertension and inducing lymphatic flow is discussed.

The contribution of a damaged epidermis to lymphatic failure is emphasised. Loss of barrier function encourages penetration of bacteria and stimulates repair mechanisms that generate cytokines, which, in turn lead to inflammation. Management programmes that improve the health of the epidermis play a part in reducing lymphatic load.

In taking morbidity management of lymphoedema into the general health services there are benefits in promoting skin hygiene and self-help regimes that can ameliorate many diseases along with lymphoedema.

Background

To alleviate and prevent both the suffering and disability of lymphoedema is a principal goal of the Global Alliance for the Elimination of Lymphatic Filariasis http://www.filariasis.org/. Although filariasis is believed to be responsible for some 40 million cases of lymphoedema, in countries where filariasis is not seen, cancer and its management by surgery or radiotherapy is one dominant cause and the failure of the venous system, especially in the lower leg, is another.

The field of lymphatic filariasis has drawn special attention to recurrent inflammatory episodes as a leading cause of morbidity in this tropical disease. It is however worthwhile looking at some of the statistics recently published from the City of London [1], which may shed new light on lymphatic filariasis in the context of lymphoedema in general. Eight hundred and twenty three patients were identified from a population of 619,000 (1.33 per 1,000) with the prevalence rising to 0.5% in those more than 65 years old. 37% had experienced acute inflammatory episodes and 10% had experienced a medical admission for their swelling, with a mean in-patient stay of 11.7 days. In this population neither lymphatic filariasis nor cancer were to blame.

This review of lymphoedema management is written for the reader familiar with filariasis but unfamiliar with the literature and the management of lymphoedema in general. It focuses on self-help and will not describe the treatments such as bandaging and hosiery, which are expensive skills largely unavailable in the tropics.

Although there are no Cochrane reviews in the field of lymphoedema management, this article discusses some of the evidence base for focussing on the venous system and on the health of the epidermis.

A theme that increasingly pervades the lymphoedema literature is that one cannot separate lymphatic failure from venous failure whatsoever its cause. Furthermore, there are elements of management, such as elevation and ankle movement, that are especially valuable for venous disease which are self-help measures for lymphoedema that are potentially sustainable at low cost.

Venous failure and its role in lymphatic failure

The normal lymphatic system is a network of lymphatics in the upper dermis, which preferentially drains into and along low resistance preferential lymphatic trunks leading directly to the lymph nodes. In lymphatic filariasis the main lymphatic channels become dilated and flow is impaired. The network of peripheral lymphatics in the skin becomes a 'safety valve' and acts as a conduit through the skin until healthy lymphatic trunks are found proximally to the damaged vessels. This 'safety valve' is a secondary system which fails if overloaded by a failing venous system or by the demands of a damaged epidermis.

The human upright posture encourages blood to collect in the veins of the leg, and humans alone commonly suffer from varicose veins and venous ulceration. The veins of the leg are emptied by elevation and by movement of the ankle, which results in compression of veins by leg muscles. Blood flow away from the legs into the chest is encouraged by the lowering of venous pressure in the thorax consequent on breathing effectively. The venous system of the legs when overloaded leaks blood contents into the tissues, and, in all who are immobile for a prolonged period, such as when sitting on a long distance flight, the veins are overfilled and oedema results. This is usually compensated by a healthy lymphatic system. It is a feature of chronic lymphatic failure that the limb becomes heavy and stiff and this immobilises the limb in a dependent position and encourages such venous failure. A further consequence of venous failure is the growth of new and leaky capillaries in the dermis, which in the immobile limb further aggravate the oedema. Persons affected by lymphoedema need instructions on how to maintain venous flow and thus to prevent overloading of the venous system.

Venous hypertension in lymphoedema

Venous hypertension is a coexisting feature of lymphoedema. Kim et al., [2] showed venous insufficiency in all 41 patients in their series with lymphoedema. All patients had increased venous pressure and volume with a decreased ejection fraction, all of which were proportional to the size of the swollen leg.

Increased blood flow has been recorded in post mastectomy lymphoedema [3,4]. This was thought to worsen the oedema present. Jacobsson [5] using radioactive isotope clearance showed a 42% increase in blood flow in 25 such arms. An increase in arterial flow that increases venous filling and causes venous hypertension was postulated. Svensson [6] noted that 70% of post mastectomy lymphoedema patients had abnormal arm venous outflow. Solti [7] suggested that the increased blood flow through the arm together with arteriovenous shunting caused by angiogenesis in lymphoedematous arms may lead to increased venous pressure. Mayall of Brazil and his co-workers have termed the condition the Hyperostomy Syndrome following an initial description by Pratesi in 1952 [8].

Evidence exists therefore, to associate the presence of venous hypertension with lymphoedema. That venous hypertension can cause changes in lymph flow has been shown in a number of studies.

Chen et al., [9] looked at the effect of increasing venous pressure on immediate changes in lymph flow in the dog paw. They noted an increase in lymph flow on average 5.3 minutes after pressure elevation. Impaired lymph transport secondary to venous thrombosis has been shown in at least two studies [10,11].

A recent study of warming the skin, which is one treatment of lymphoedema, has found a significantly improved venous flow in healthy patients and to have no effect on lymph flow itself. The authors concluded that if thermal therapy has a salutary benefit on lymphoedema, then it must be operating through some other physiologic mechanism, perhaps involving greater venous return [12].

The accumulation and reduced clearance of inflammatory mediators in venous failure is well known [13] and it is the basis of the Matrix Trapping Theory [14] put forward as a cause of skin pathology induced by venous hypertension. Hence it can be concluded that chronic venous hypertension is a feature of lymphoedema and can cause overload of lymphatics through a direct effect of increased capillary filtration and inflammation.

Evidence of Angiogenesis and Leakage in Lymphoedema

Casley-Smith [15] described increased blood vessel volume (0.009 ml/cm^3 to 0.2 ml/cm^3) in the deep fascia of experimental and congenital canine lymphoedema models. Snowden and Hanmerberg [16] demonstrated this using angiography in a filarial canine model.

Angiogenesis has also been widely observed in human lymphoedema. Histologically it is seen in the upper dermis, where in normal skin a mobile fluid compartment of tissue fluid has been shown to exist [17,18]. The venules seen are thick walled, extended and tortuous. Roberts et al., [19] noticed an increase in the number of sub papillary capillaries in a series of 15 post mastectomy patients – this resulted in a constant capillary density despite a 14% increase in cutaneous area, strongly suggesting that neovascularization had occurred. This was confirmed by Mellors et al. [20].

It is well known that the new vessels of the capillary bed have an increase in permeability. The explanations for this include the leaky structure of new vessels and release of inflammatory mediators, which range from histamine to Vascular Endothelial Growth Factor (VEGF, initially called Vascular Permeability Factor or VPF) which is, as an inducer of permeability, up to 5000 times as potent as histamine [21]. Plasma levels of VEGF [22] and VEGF production are higher in patients with venous hypertension [13]. VEGF plays a fundamental role in the growth and differentiation of vascular and lymphatic endothelial cells. The VEGF family consists of VEGF-A, B, C and D [23]. VEGF-C and D both act on VEGFR-3 (vascular endothelial growth factor receptor 3), which is a receptor for tyrosine kinase selectively expressed on lymphatic endothelium. Familial Milroy's lymphoedema has recently been attributed to mutations of the VEGFR-3 gene, which leads to disturbed transduction of the receptor. The epidermis has been found to be the likely source of VEGF [24]. It is produced in response to any damage leading to hyper-proliferation, including one of dermatology's favourite tools, (and the cause of sunburn), ultraviolet B irradiation [25].

Angiogenesis could result from the failure of clearance of angiogenic factors such as normal metabolites, inflammatory agents and growth factors (including VEGF). The key point is that angiogenesis, however it is initiated, does exist in lymphoedema and may lead to increased venous hypertension and lymphatic overload in lymphatic disease through a number of mechanisms.

Breathing and Lymphatic Failure

Breathing exercises have been used as a standard component of lymphoedema management known as complex decongestive physiotherapy (CDP). The rationale for this is that the main lymphatic trunks lead to the thoracic duct through which their contents empty into the large veins above the level of the heart. Unless the main lymphatic trunks become emptied, they act as a static reservoir into which the peripheral lymphatics drain with difficulty.

The clearance of central lymphatics is essential before peripheral manoeuvres are taken to increase lymphatic drainage. The dangers of trying to clear peripheral fluid before clearing central drainage routes was illustrated by Boris [26] who showed a significant increase of genital oedema (43% versus 3%) following the use of compression pumps for the lower limb. Emptying of the lymphatic system into the venous system requires that the pressure in the latter is lowered, increased venous pressure causes an increase in thoracic duct pressure as shown in sheep by Gabel and Drake [27].

Severe oedema in the newborn has been attributed to lymphatic failure consequent on elevation of venous pressure impeding lymph flow in a thoracic duct [28,29]. A rise in central venous pressure of 4 mm of mercury was sufficient to cause oedema in one study [30].

Breathing acts by increasing flow from the lymphatic system into the venous system through the thoracic duct. Schad et al., [31] found increased thoracic duct flow during hyperventilation in anaesthetized dogs, while opening the thoracic cavity decreased intrathoracic pressure, and as a result, decreased flow through the thoracic duct. These authors suggested that during inspiration there is a drop in intrathoracic pressure and an increase in intra-abdominal pressure as the diaphragm pushes down, with consequent movement of lymph from the abdominal to the thoracic cavity. During expiration they suggested that the increase in intrathoracic pressure causes lymph to be expelled through the thoracic duct into the upper thorax. Further evidence comes from Dery et al., [32] who noted that closed thorax compression on mice can result in lymph uptake from distant parts of the body. That breathing (hyperventilation) has an effect on the lymphatics of the skin has been demonstrated by Allegra et al., [33] in both primary lymphoedema and in patients with chronic venous insufficiency. Using a Servo Nulling system, a counter pressure pump and a pressure transducer, hyperventilation was found to lower lymphatic pressure in the skin by approximately 50%.

It was Walker and Pickard [34] who demonstrated that deep inspiration dropped the pressure in the inferior vena cava immediately above the diaphragm. It is interesting to note that an effective form of breathing used for lymphoedema patients involves taking a deep breath through the nose, holding the breath and then a long slow phase of breathing out through the mouth. It is a system of

breathing used by many traditional systems of medicine especially in Asia [35].

Movement in Lymphatic Failure

Movement increases both blood flow and lymph flow through the limbs. Small amplitude movements can produce these effects, and, in lymphoedema, are better than vigorous exercise, as exercise can increase blood flow and tissue fluid formation in the limb.

Movement can improve lymph flow through 3 possible mechanisms:

1. Increased uptake by initial lymphatics due to increased tissue hydrostatic pressure variations.

2. Increased pumping of lymphatics due to smooth muscle contraction in collecting lymphatics.

3. Emptying the venous system and reducing overload of the failing lymphatics and allowing them to recover their function.

Movement at the ankle joint in particular has been investigated. Mortimer et al., [36] noted increased radioisotope clearance from the lymphatics of the lower limb with even small amplitude ankle movements. Godoy and Godoy [38] in six patients showed a change in the fluid volume of the leg of only 160 ml on elevation but a volume change of 830 ml after passive extension and flexion of a foot, suggesting that even passive movement of the foot can cause significant volume change in the lower limb. However, patients with lymphoedematous limbs typically have poor mobility of the affected limb. Andrade et al., [37] reviewed the literature and compared ankle mobility in patients (120 limbs) with lymphoedema with that in 22 normal volunteers and found the range of movement between ankle flexion and extension was about halved (normal 61.1%, lymphoedema patients 34%).

The literature on the role of movement and exercise on the management of post-mastectomy lymphoedema has been reviewed by Bingham [39].

Movement is known to affect the venous system. Much of the evidence that movement reduces venous hypertension comes from studies of patients with leg ulcers. Reduced ankle mobility has been shown to be a risk factor for poor ulcer healing. Barwell et al., [40] showed that chronic venous ulcers were slower to heal in patients with reduced ankle mobility – 13% of ulcers healed in patients with less than 35° ankle mobility, whereas 60% of ulcers healed in patients with greater than 35° of mobility. Similar findings were observed by Doherty et al., [41] and Brooks [42] who found decreased recurrence of venous ulceration in legs of patients with full ankle movement.

More direct studies looking at the venous system have been done as early as 1965. Daly et al., [43] noted that a passive pumping motion of the legs decreases the venous pressure. Furthermore, Gardner [44] observed in dog and sheep models that simple dorsiflexion of the ankle joint leads to the emptying of foot veins, and suggests that the venous system is most efficient in pumping venous blood back to the heart during normal walking. In lymphoedema there is a restriction of ankle movement. Kigler et al., [45] studied the effect of joint restriction as a result of wearing a limb cast. They measured peripheral venous pressure and found that an actual reduction of venous pressure in the dependent limb was reduced in limbs with restricted joint mobility.

Hence it can be concluded that movement is essential in order to drive blood through the veins out of the swollen limb, and, in order to promote both the normal function of healthy lymphatics and to relieve the overload on a failing lymphatic system. Continuous low amplitude ankle movements are extremely effective in doing this.

Limb Elevation and Lymphatic Failure

To the encouragement of movement for swollen limbs should be added exhortation to elevate. It is common sense that fluid flow through any tissue plane will be influenced by gravitational effects. However, the key point made here is that the main influence of gravity is on venous flow rather than lymphatic flow.

The significant effect of elevation on the venous system has long been known in the field of venous ulcer care. Patients have long been told to elevate their limbs as much as is reasonably possible, with healing being facilitated by the degree of elevation of the limb [46]. Indeed Abu-Own et al., [47] found that elevation of the leg 30 cm above heart level for 30 minutes, 2 or 4 times a day, reduced oedema and improved cutaneous microcirculation in many patients with chronic venous disease.

Pippard and Roddie [48] found that gravitational changes influence venous pressure but not the pressure within adjacent lymphatics of the hind limb of the sheep when tilted on a tilt table. This suggests that limb elevation serves mainly to increase venous return to the heart and reduce venous pooling of the lower limb, thus reducing venous pressure in the lower limb rather than directly increasing afferent lymphatic flow. This has clear implications in the reduction of venous pressure of the lymphoedematous limb.

Swedborg et al., [49] found that elevation effectively reduced the volume of control and lymphoedematous arms of patients suffering from post-mastectomy lymphoedema. They state that elevation is thought to act mainly by decreasing the hydrostatic pressure gradient from the venous system to the tissues. This reduced the leakage of proteins and fluids from the vascular system. They also concluded that there was a limited effect of gravity on the lymphatics themselves.

The Skin Barrier Function and Lymphoedema

Another important low-cost intervention that should be considered for the management of lymphoedema is that of maintaining the integrity of the epidermis by washing and emollients. One of the most important qualities of the skin is its ability to form a barrier within the epidermis preventing access of potentially harmful agents into the skin while at the same time preventing excess loss of fluid from the skin. Managing this barrier function takes precedence in all dermatological therapies and especially those which prevent penetration of bacteria through the skin.

Most episodes of inflammation in lymphoedema were blamed by early investigators on recurrent streptococcal infections [50]. This is still the most important causative organism but it is not the only cause of inflammation, since we now know that mediators of inflammation such as cytokines can be released by many triggers. Patients develop a high fever, and increased redness, swelling and pain in the tissues. This has been termed dermatolymphangioadenitis (DLA). Doubts have been raised as to whether bacterial infection is the whole story. The episodes can regress within two days spontaneously and the 'devastating flesh eating responses' of contemporary streptococcal infections are very rarely seen in these lymphoedematous limbs. Control trials comparing the effects of long term antibiotics to simple washing [51] have shown that washing alone may decrease the number of inflammatory episodes per annum. Shenoy et al., [52] also found that neither DEC nor antibiotics altered DLA attack frequency in their study of 65 patients with filarial lymphoedema. They found that 'simple hygienic measures combined with good foot care and local antibiotics/fungal cream when required were effective at reducing the number of DLA attacks'. Similarly the experience of Dreyer et al., [53] in Brazil suggests that simple hygiene can protect against infections.

Pani and Srividya [54] found that the frequency of inflammatory episodes correlated positively with the progression through the grades of lymphoedema. Since recurrent inflammatory episodes are a common complication of lymphoedema and seem to exacerbate the condition further, it seems reasonable to suppose that they cause overload of the lymphatic system.

In the developed world most practitioners managing post-mastectomy lymphoedema, or lymphoedema of the leg due to venous disease, recognise that inflammation need not be due to bacteria, and indeed we suggest that not all cases of DLA are caused by infection and that simple care of the skin may reduce the inflammatory mediators produced as a result of any kind of damage to the epidermis.

It is only during the last decade that the skin has been discovered to be a rich factory of cytokines and growth factors. It produces very little of these at rest and in good health with an intact barrier function, but they are massively produced when the skin is injured and during the process of repair. Much of the effect of the release of such agents is to increase vascular permeability and adhesion of white cells to the vascular endothelium in the dermis.

The epidermis is a reservoir of large quantities of IL-1 and other cytokines like TNF made in response to irritation and secreted into the dermis. Olszewski et al., [55] showed the accumulation of several immune proteins and cytokines in filarial lymphoedema, suggesting ongoing inflammatory responses, despite the lack of overt dermatitis. These proteins, of which interleukin-1 is probably the most important, accumulate in the interstitium due to poor lymph clearance in the limb, and may cause DLA episodes in absence of infection. Importantly, Foldi [56] found recurrent DLA attacks were nearly eliminated in post mastectomy lymphoedema patients treated with Complex Decongestive Physiotherapy (CDP) which included skin care with washing and emollients, but did not include antibiotics. This suggests that reduction of oedema through improved lymphatic drainage can clear inflammatory mediators. Interestingly, systemic symptoms of DLA have been observed in some patients following initiation of CDP with no preceding signs of infection and may be caused by the release of accumulated inflammatory proteins from the lymphoedematous limb into tissue both locally and directly above the swollen portion of the limb or systemically throughout the body. Foldi et al., [57] also found a decrease in expression of pro-inflammatory genes after CDP, suggesting that CDP affects the inflammatory process in a fundamental way

Studies of skin integrity include a number of interventions that adversely affect the barrier function of the skin that can be remedied by the use of emollients:

1. Removal of surface fats by acetone/alcohol or excessive washing with alkaline soaps

2. High turnover states of the epidermis as may be seen in psoriasis, nutritional deficiency diseases and electrolyte disturbances

3. Sellotape stripping of surface layers of the skin

In addition to the above, skin barrier function correlates with a low pH, the acid mantle of the skin. Pre-antibiotic studies by Sulzberger and Baer [58] showed that heavy contamination by a wide variety of organisms only produced inflammation responses if the barrier function of the skin was first impaired. Studies in IL-1 and TNF receptor deficient mice have recently shown a clear relationship between the induction of cytokines within the epidermis and loss of barrier function [59]. The IL-1 receptor deficient mice had accelerated barrier function recovery following barrier disruption, suggesting that the increase in IL-1 following barrier disruption normally delays components of the repair response. The relationship between the recovery of barrier function and decreased production of inflammatory cytokines, prostaglandins and other inflammatory mediators by the epidermis, including VEGF, in response to skin care products deserves further study. The high mast cell content of lymphoedematous tissue, first shown more than a century ago by Ehrlich, merits re-examination in view of the fact that mast cells are the richest source of histamine which acts through H1 and H2 receptors on cells. Contemporary studies on Keratinocytes have shown that blocking such H1 and H2 receptors accelerates skin barrier repair and prevents epidermal hyperplasia [60].

Thus there is currently a view of skin care procedures which recognises the existence of sub-clinical vulnerability of the skin due to the above and the possibility of restoring the barrier function and other aspects of skin health by simple procedures such as washing and emollients. They are already the focus of study by industries manufacturing cosmetics, soaps and laundry products. Against the background of the eczematous changes that occur in venous disease and the gross warty changes that are seen in lymphoedema, not withstanding the deep crevices and the effects of fungal infections, there is clearly potential for barrier breakdown and enhanced production of inflammatory mediators.

Consequently, there are procedures widely used to reduce such eczematous/dermatitic changes, including the washing away of debris and crusts, the replacement of skin surface natural emollients by emollient substitutes and the use of anti-fungals.

A number of emollients have been suggested for recovery of skin barrier function – lanolin, mineral oil, vegetable oil and petrolatum.

The main functions of an emollient are [61]:

1. Water absorption by the epidermis. This smoothes the skin surface, allowing minor fissures and cracks to close and thus improving barrier function. Some emollients, for example, hold up to twice their own weight in water and hold moisture in the skin.

2. Reduced loss of water from the epidermis. Thus some emollients protect the skin and reduce trans-epidermal water loss by up to 30%.

A strong case can be made for the study of traditional soaps and emollients, such as the coconut oil habitually used in Tanzania, to seek whether they have similar properties to the above. Some are known to have useful properties such as antisepsis. At least 300 traditional plant based soaps have been identified and they have the advantage of being locally available at low cost as well as a sustainable source of supply (Burford and Ryan, in preparation).

The second important component of skin care is bathing. Emollients can be used as a soap or after a bath when the skin is still wet and water will be trapped. There is no consensus on the frequency of bathing or on the mode of bathing (shower versus bath tub) in the treatment of dry, damaged skin – but a common view is that super hydration of the skin is important and compliments emollient use [62]. Dermatologists and the nursing profession emphasise the damage done by over washing such as pre-surgical 'scrubbing'. The minimum length of bathing has been suggested to be 10 minutes by Brown et al., [63] who found that this significantly improved dry feet over a period of 2 weeks, and Hardy [64] who found a 10 minute soak daily significantly improved the skin condition of 15 institutionalised elders.

Warm Water versus Cold Water

There are no clear pointers as to the advantages of using hot or cold water. The optimum temperature for most biological systems in the human is 37°C. The skin of peripheries is adapted for a cooler metabolism. Mortimer and Ryan (unpublished studies) have shown that warmth increases the clearance of technesium colloid from the skin by the lymphatic system. Shimotoyodone et al., [65] used topical warming 40–45°C, for 2 minutes only, to supplement massage of the gingiva and clearance of C^{14} methylated albumin. Cool water has no such effect. Ohkuma [66] has also found that the effects of vibration on lymphatic flow are enhanced by warming. There have been fashions in the use of heating or cooling for inflammation and there has been recent re-emphasis of the fact that keeping patients warm during surgery helps them to heal [67]. It has been shown that epidermal repair is delayed by the use of cold water and it is relevant that the removal of fibrosis by collagenases requires an optimum

temperature in the region of 37°C [68]. Chen et al., [69] have shown that warming attenuates protein micro-vascular leakage through a mechanism involving heat shock proteins.

It is the view of the authors that the use of cold water for washing/bathing in those with lymphoedema should be discouraged and water that is fit for drinking, and that has been cooled after boiling (at just above body temperature) should be used.

The Epidermis and Skin Infection

In arguing that washing with emollients restores the skin to health and is a necessary resource for the management of lymphoedema, one notes that in the field of wound healing simple tap water for washing a wound has, in some centres, replaced antibiotics and antiseptics. This also draws attention to the barrier function of the skin and the importance of its breakdown in determining clinical infection, as already explained above, when describing the pre-antibiotic studies by Sulzberger and Baer [58] and others. Also in the days before effective anti-fungals there were studies of skin vulnerability predisposing to infection.

Baer and Rosenthal [70] attempted to infect 150 young adults by bathing for 30 minutes in footbaths containing *Trichophyton rubrum* or *T mentagrophytes* but none became infected. By producing inflammatory changes in the skin using croton oil and cantharidin, 10 out of 33 persons developed transient asymptomatic infection. Persons who developed blisters were more likely to develop active disease. Thus 20 of 71 persons had clinical infection at one to four weeks after developing blisters. Five persons took three months to develop active disease.

The part played by trauma and the degree of preceding damage to the skin has long been shown to be an important factor in the development of fungus infection. Kogoj (quoted by Aravijskij, [71]) showed that trauma to the skin of guinea pigs encouraged active disease following the intracardiac injection of fungi. Aravijskij describes a surgeon in whom control of fungus of the hands, by usually effective therapy, only occurred after scrubbing up regimes had been less traumatic.

Conditions such as venous disease or lymphoedema predispose to infections of the skin. Andriasian, via a personal communication reported in [72], found that 76% of 117 patients suffering from venous disorders of the legs were suffering from epidermophytosis of the soles. Out of 143 patients with varicose veins, 73.4% were suffering from epidermophytosis of the soles and 90% of patients with arterial disease were suffering from epidermophytosis. Healing of the epidermophytosis led to considerable improvement of the main disease. These themes of the interaction between the epidermis and potentially infective organisms with the functions of the underlying vasculature and lymphatic drainage in the dermis continues to draw attention to the well-being of the epidermis and the fact that this can be induced by washing and emollients. In the exploration of the inflammatory responses of the epidermis in lymphoedema, one can now recognise that bacteria have several roles to play in the generation of inflammatory responses of which superantigens and shock proteins are only part of the story. The damaged epidermis of mice is known to produce antimicrobial peptides such as LL-37-enhanced by interferon gamma (IFN-γ), which have been shown to influence the survival and multiplication of streptococcus A in wounds [73], which remains the commonest cause of dermal and hypodermal infection in lymphoedema.

While Dermatologists have recognised a streptococcal pretibial cellulitis as a marker of fungal infection between the toes, the profession of lymphologists have long recognised it as a marker of lymphoedema. The focus of today's management is restoring barrier function of the epidermis by washing and emollients.

When examining the microcirculation of the skin or nail bed in persons infected with *Candida* or ringworm fungi, one notes considerable hypertrophy of the blood vessels supplying the epidermis. Frequently there are microhaemorrhages and there are completely irreversible thromboses of the papillary vasculature. Since there is a correlation between the structure of keratin and its invasion by dermatophytes and yeasts [74], and since keratin formation normally depends on healthy epidermal capillary relationships, there is a tendency for fungal infection to encourage the kind of disturbances in both keratin and blood vessels which provide an ideal environment for their growth.

The Use of Antibiotics

The organisms that invade the skin and cause dermal and hypodermal infection exist on the skin or in the throat in 10–20% of persons and in most of these they are not causing any pathology. They have the potential to do great harm, especially if they cross barriers, penetrate deeply and are not destroyed by the host. Most recurrent inflammatory episodes (DLA) produce local inflammation of the tissues but rarely cause their destruction nor shock or death of the patient. The streptococcus that is most commonly blamed remains sensitive to penicillins, tetracycline and several other antibiotics.

For most cases of DLA one can afford to await resolution as a result of simple hygiene and use of emollients, but antibiotics should be prescribed if improvement is not

quickly apparent. Aggressive pathology such as blisters and extreme pain with high fever out of proportion to the local appearance may require intravenous antibiotics, and rarely when cellulitis progresses to necrotizing fasciitis, surgical debridement may be required. Prophylactic long-term antibiotics (penicillin, 1–2 million units twice daily) are often prescribed in the developed world where they are fully affordable. Fortunately, the risks of antibiotic resistance seem exceedingly low in the case of the organisms responsible for bacterial inflammatory events of the DLA kind.

Bandaging and Hosiery with Manual Lymphatic Drainage

Bandaging and hosiery with manual lymphatic drainage are components of the gold standard management of lymphoedema. They are largely unavailable in the developing world due to the lack of trained personnel and the cost of materials. The pioneering efforts of Godoy in Brazil [75], providing a simplified self-help massage system in a well-illustrated booklet, should be more widely disseminated. In the long term, all countries need this expertise, and for the difficult case, there needs to be investment in the training of specialists. However, we are promoting in this paper low cost, self-help.

Models of Lymphoedema Management

Patients and caregivers may find the concepts underlying the management of lymphoedema somewhat complex. To illustrate breathing and movement one may describe the lion after a good meal and a prolonged sleep, who will first yawn and take a deep breath, this will be followed by stretching of shoulders and hips and back muscles, before extending and moving the legs and paws. This sequence of events ensures central emptying of the lymphatics and venous system before emptying the periphery.

To explain this sequence of events using another model one may describe the process of emptying an auditorium filled with people. First there must be an opening of the doorways to the outside of the building and then the corridors should be emptied and the seats nearest the gangway similarly emptied before it is possible to exit rapidly from the centre of a row of seats.

A model illustrating overload is the drain of a house that is affected by a partial blockage and cracked pipes. Sewage will seep away satisfactorily through low resistance pathways until there is a flash flood or the household entertains an excess of guests. The system then becomes overloaded and the failure of the drainage becomes patently manifest.

Conclusion

Bringing together the opinions currently expressed in the literature concerned with lymphatic, venous and skin disease we conclude that low cost, self-help, management of lymphoedema can be advocated. It is an amalgam of systems already in use, and although the evidence base is not yet perfect, there have been many studies which give support to the management schemes described above. The interaction of factors determining loss of barrier function (to infective organisms, allergens and irritants) and the chronic effects of venous hypertension with lymphatic failure are amenable to therapy. Even the grossest of skin hypertrophy can be reversed over time so that the handicap caused by lymphatic filariasis can be eliminated as well as the causative organism. It requires the co-operation of the patient and a concordance program that includes the patient's community, fits in with their lifestyle, and assuages conflicting elements. This regime of therapy is designed to do just that.

If this regime of therapy works, which includes elevation, movement and skin care, it is likely to be of benefit in the management of many other important diseases. This includes management of the skin of patients with AIDS, or for the management of breaks in the surface continuity of epithelium that are highly prevalent in the tropics and in metabolic diseases such as diabetes mellitus or in vulnerable groups such as the bedridden elderly.

It requires recognition that the grotesque changes that occur in the most severe cases of lymphoedema are not merely a consequence of lymphatic failure alone. There is in all cases a strong component of both venous and epidermal failure, which responds to therapies specifically aimed at the veins and epidermis.

Competing interests

None declared.

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