UNDERSTANDING LYMPHOEDEMA IN THE NEW MILLENIUM

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We face three major issues in lymphoedema management: reducing the risk of secondary lymphoedema; early detection; and providing solid evidence for the management and treatment of patients. We have seen advancements in our understanding of lymphoedema at the genetic, molecular, cellular and tissue level, helping us to understand that more than just a damaged lymphatic system contributes to lymphoedema. The involvement of other systems means we need to have an integrated approach and use expertise from areas such as dermatology and phlebology. Standardisation is needed if we want to compare techniques and strategies.

Key words

Exercise
Detection
Lymphoedema
Lymphangion
Treatment

The lymphatic system was first described by Hippocrates in about 400 BC, and it was investigated later by Aselli in 1622. The focus of curiosity then moved to the vascular system and details of its importance emerged in 1628. Research into the lymphatic system then languished until the beginning of the twentieth century when it blossomed, but the recognition of its role in many systems was not widely acknowledged. If the final recognition of a system's importance is discussion of it in *Nature*, then it was not until 2005 that the lymphatic system finally arrived (Brown, 2005). Its final acknowledgment was not at the gross anatomical level, but at a molecular and genetic one.

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The new knowledge revolved around the discoveries by Kaipainen and his group (Kukk et al, 1996) that there was a new receptor for endothelial growth. Importantly, this was found in the endothelium of the lymphatics and, more significantly, when stimulated by a newly-discovered vascular endothelial growth factor (VEGF-C), growth only occurred in the lymphatic vessels and not in the vascular system. The whole medical and scientific community were excited by this, not because of the discovery *per se*, but because of what it meant at a clinical level: if a growth factor and its receptor was in existence, not only could new vessels be grown, but vessel growth could be halted, maybe slowing the spread and growth of cancers. The lymphatic system had achieved international publicity at the highest level when it was featured in *Nature*, but what difference has that made to the treatment and management of patients with lymphatic disorders, and what are the major questions we have yet to answer?

This article will not describe the reviews and information available about lymphatics and lymphoedema on the Cochrane databases, as many of the recent reviews have excellently covered this, as well as presenting us with indications of our depth of knowledge or ignorance (Badger et al, 2004a,b,c; Moseley et al, 2006), while others have attempted to set models for best practice through consensus and international comment (Bernas and Witte, 2004; Moffatt, 2006). In all instances, the use of these documents must evolve with time, and, as Bernas and Witte (2004) stated, 'be utilised, challenged, modified and revised' as our knowledge evolves.

Uncertainties

Our knowledge of the lymphatic system in health, disease and disorder remains poor. Witte et al (2006) have emphasised the need for continuing review of our knowledge, so we can expose 'what we don't know (especially wrongly answered questions)', and explore and gain answers to what they have termed, 'the expanding universe of unanswered questions', as well as bringing together what we think we know. Rockson (2004) has suggested that despite the recent increase in knowledge about the lymphatic system, it remains in the hands of the expert and interested few, and that little formal teaching appears in most medical and other healthcare professional courses, thus further feeding our general ignorance, frustration, confidence and competence to gain excellent patient outcomes. Education of practitioners

and patients is paramount, but getting to them can often be difficult.

Structural and functional aspects

Improving our understanding of the impact of pre-existing abnormalities of the lymphatic system is one key area. We know, for instance, that there is a continuum between lymphatic hypoplasia, normal range and hyperplasia, but it is strange how little we know about why a lymphoedema develops in some 30% of people who have had axillary clearance and radiotherapy. Is it a pre-existing mild hyperplasia, or the extent of the damage to the lymphatic system, and are all lymph drainage systems 'normal' in the amount of fluids they can drain per hour? Are those who have one or two nodes removed in axillary sampling, who develop lymphoedema mildly or significantly, hypoplastic?

We need to learn more about lymphatic variation, both in lymph vessel numbers, functional capabilities and their locations (Foeldi et al, 2003) if we are not, in the future, to be beset with the rather too frequent 'surprise' lymphoedema, due to apparently inconsequential damage to the lymphatic system. One answer to this lack of knowledge seems to be further investigations into the role of lymphoscintigraphy (Burnand et al, 2002), but issues of standards are far from clear, significantly reducing its benefit as a diagnostic tool in lymphoedema.

Lymphangiogenesis

It was the combination of three discoveries: VEGF-C and its receptor in genetically-engineered mice, that were specific to lymph and not blood vessels by Alitalo's group (Joukov et al, 1996), and later VEGF-D by Achen and his colleagues (1998), and then the finding of a specific marker of lymphatic endothelial tissue called lymphatic vessel endothelial receptor 1 (LYVE-1) by Jackson's group (Banerji et al, 1999) that have allowed us to think about detailed examination of lymph vessels. Even more exciting and critically acclaimed, was the not unexpected, but hitherto unproven fact, that when the VEGF-C and D receptors were blocked, there was no longer lymph vessel growth, and their networks in tumours shrank. Tumours rich in lymph vessels also shrank, thus reducing the spread of tumour (Karpanen et al, 2001). This knowledge, along with other genetic-engineering tools such as transgenic and knockout mice, have already aided us in understanding the development of the lymphatic system, and how we might manipulate it to achieve better patient outcomes (Suri, 2006). Regrowing diseased and disordered lymph vessels is one exciting possibility that is already under way, but issues of patency remain, as does the potential side-effect of a simulation of lymphangiogenesis and its potential to stimulate cancer recurrence.

The immune connection

Parallel to lymphangiogenesis, we are seeing stronger evidence for the role of the lymphatics in the immune response and, in particular, its role in exacerbating inflammatory events. Some of this was not new knowledge, but looking at it from new angles meant that we could apply other meanings to previous findings.

For instance, Kerjaschski et al (2004) indicated that lymphatics proliferate in situations of tissue rejection, such as kidney transplants, and that they clearly bring the immune cells to the area until the graft is destroyed. This comes from a protein called podoplanin, which normally adheres to a signalling molecule called chemokine ligand 21 (CCL21) most commonly found in the walls of the lymph vessels. While the signalling molecule is bound to the podoplanin, all is well and it is relatively inactive, but, should it break away, many more inflammatory cells are attracted to the region.

Adding to this was the work of Baluk et al (2005), who showed significant lymphatic vessel growth in the tracheas of mice with an asthma-like condition which did not shrink (while blood vessels did) when antibiotics were administered. This may indicate that the lymphatics are ready and waiting to set up further rapid, and, perhaps, over-the-top immune responses to infection, thus precipitating and exacerbating the inflammatory cycle.

The adipose connection

While we have learnt much about the absorption of fats as chylomicrons from the small intestine, there has been little else to excite except the relationship between fats and the lymphatic system. A number of groups are now investigating the adipo-lymphatic connection. It has long been known through the work of Clark and Clark in the 1940s, Casley-Smith in the 1980s, and others, that middle- and late-stage lymphoedemas have significantly disproportionate amounts of subcutaneous fats and that, currently, one option for dealing with them is liposuction. However, this strategy remains controversial, even though aspirates from patients with non-pitting lymphoedema often contain up to 90% adipose tissue (Brorson, 2004).

Rockson (2004), like Brorson and others (Harvey et al, 2006), has suggested and shown that in chronic cases of lymphoedema, the adipose elements replace tissue water, further suggesting that lymph possesses adipogenic activity. In suggesting a basis for this, Schneider et al (2005) found that in mice the absence of the Prox 1 gene led to compromised lymphatic endothelial integrity, and that the mice became abdominally obese as they aged. It seemed that having more leaking lymph vessels encouraged more local area fat deposition, with those with the most disorganised and leaky vessels becoming the most obese. Something in the lymph was believed to be adipogenic. Schneider et al (2005) then cultivated pre-adipocytes with chyle from mice and showed strong adipogenesis. One could see how stagnating lymph (at least in the abdominal areas) could lead to increased adiposity in that area. However, the cutaneous lymphatic networks were shown to be under a different regulatory mechanism

(Karkkainen et al, 2001), and the Prox 1-deficient mice showed no cutaneous fatty depositions. A group of mice which were heterozygous for an inactivating mutation of the VEGFR3, were found to have additional subcutaneus fat, as would be expected in association with the hypoplastic cutaneous lymph vessels and their associated poor flow (Karkkainen et al, 2001).

Rosen (2002) has indicated that fat is always found closely associated with lymph nodes (apparently independent of nutritional status), leading to the idea that this is perhaps an energy source for the lymphoid cells, especially during challenges to the immune system. Also exciting is the finding that the adipocytes near the nodes are relatively sensitive to cytokines associated with lymph drainage, such as tumour necrosis factor-alpha (TNFα) and interleukins 4 and 6 (IL4 and 6) (Mattacks and Pond, 1999), suggesting that good lymph flow is essential for optimal immune response.

Out of all of these quiet, complex experimental investigations, came the now relatively well-substantiated claim that slow, or poor 'lymph (flow) makes you fat' (Schneider et al, 2005); establishing the link between what is seen clinically, and what is happening at the molecular level. Yet another exciting and, perhaps, alarming link in this area of research, is the finding that diet may have an influence not only on these processes, but also on the immunomodulation of the lymphatic system (Rockson, 2004). This developing knowledge has significant clinical ramifications and we need to look for strategies for its application. Given that we are aware of the outcomes of an immunocompromised patient in terms of cellulitis, and of the significant epi-fascial fatty tissue build up, it is easy to see the benefits of further investigations to substantiate these discoveries.

Why the swelling — what's it all about?

There seem to be three concurrent events occurring, which either singularly, or in combination, could lead to the swelling of an affected limb. The first is an enhancement of the network of lymph vessels in a lymphoedematous limb, either through re-routing and/or recruitment of dormant lymph collectors, or perhaps by lymphangiogenesis (Mellor et al, 2000). This observation was not noted in patients with unswollen limbs after similar treatment for cancer, suggesting the changes in the lymphatic system are related to the appearance of the lymphoedema, rather than the events associated with the treatment of the cancer.

The second event is dermal angiogenesis: the occurrence of which was found to be greater in the swollen limb in patients who underwent a modified radical masectomy. Micro-vessel numbers in the expanded skin increased to maintain a density found in the normal limb, i.e. the vessels increased in number, but the density remained the same (Mellor et al, 2002). These outcomes might be a compensatory mechanism to deal with the need for increased lymphatic drainage in the face of an increased load brought about by changes in the blood vascular system supply, but they do represent a significant clinical issue.

The third event for patients with lymphoedema, is an increase in arterial flow through the axillary area. Interestingly, in patients who had similar interventions but who did not have lymphoedema, there was also an increased arterial inflow (Yildirim et al, 2000). In a lymphoedematous limb, we have potential lymphangiogenesis, angiogenesis and increased arterial inflow. Dealing effectively with each, or all of these, may help in lymphoedema control and treatment.

The lymphangion — lymphatic muscle

While lymphangiogenesis work has helped us to understand the endothelium of both the lymph and blood systems, we know almost nothing of the lymphatic muscle. While one of our issues is how to load the lymphatic system, the other major one is how do we get the lymphatics to work well? To do this, knowledge of lymphatic contraction is essential. In a review by Bridenbaugh et al (2003), some important points were made about the intrinsic and extrinsic lymph-pumping mechanisms, with evidence indicating a strong inhibitory role of inflammatory mediators on the lymph pump, while the state of stretch and pressure within the vessel influences the lymphatic contraction frequency and the strength of contractions. On the other hand, it is the variation in external forces caused by skeletal muscle contractions, respiratory and gastrointestinal peristaltic motility, on which the extrinsic pump relies for the generation of the hydrostatic pressure gradient, which produces flow. It is crucial that there is a variable reliance in the intrinsic and extrinsic pumps between tissues, and that it is the lymphatic muscle elements which, in the main, contract or relax in a coordinated way to meet the needs of that tissue.

Little is understood about human lymphatic contractility, and, until we know more, discovering the most effective treatment for lymphoedema will be difficult. To do this we will have to learn much more about these forces related to the gentle tonic contractions of a resting lymphatic and the stronger, forceful phasic contractions, and how we might influence them. It all hinges around knowing more about the lymphatic collector muscle and the mechanisms which control it. A tall order, but it is where a significant difference might be made.

Early detection

Measurement of lymphoedema is a difficult issue, but even more problematic and perhaps even more important, is the early detection of lymphoedema before it becomes clinically manifest (which is either a 2 cm circumference difference, or a 200 ml volume difference, or a 10% volume difference, or a combination of these).

There is no doubt that subjective indications of the presence of sub-clinical lymphoedema can be beneficial since, certainly then, the patient has limb problems, such as general heaviness and tension, which need to be addressed, although most of the literature indicates the need for lymphoedema to be confirmed as clinically manifest by one or more of the means presented above. This confirmation is not always easy, given the errors of measurement and other limitations of devices and techniques, and in some countries, there is the tension that payment for treatment is often linked to the firm diagnosis of clinical lymphoedema. In a way, we are presented with the dilemma of knowing, or being told something has happened, or is happening in the affected limb, but not having the power in terms of accurate information, or financial recompense, to undertake the necessary prophylactic treatment, which may halt the progression of the clinically manifest lymphoedema.

However, one means of gaining some necessary objective evidence stems from the new technique of multifrequency bio-impedance. It is not without error, but it does seem to be a reasonable and reliable means of determining changes in, and the presence of, extracellular fluids (the first sign of lymphatic failure). Cornish et al (2001) were the first to demonstrate the potential of multifrequency bio-impedance, and Hirst et al (2001) have shown that it was able to detect the onset of lymphoedema up to 10 months earlier than normal clinical diagnosis. The sensitivity and specificity of the test was almost 100% (Hirst, 2001) compared with that for circumferential measurements, which was about 5%. We can see why this might be so, since multifrequency bioelectical impedance analysis (MFBIA) measures only fluids, while circumference and perometry measure total limb volume changes. Additional studies since that time (Hayes et al, 2005), showed similar outcomes, but also indicated that the self-report method was more sensitive than the time-consuming circumference methods.

These, and other related findings, show that multifrequency bio-impedance has a strong role in the early detection of lymphoedema, and of the effects of treatment on fluid content. The results show that the use of circumference measurement to arrive at a diagnosis of lymphoedema should be questioned, but also that we need further evidence for the role of bio-impedance. Since early detection and early prophylactic intervention should be one of our aims, this area warrants further investigation.

Imaging

Two major areas of imaging are relevant. First, methods to help in the visualisation of the lymph vessels during surgery or other interventions: the aim being to preserve or prevent damaging them. Second, for those with lymphoedema, to discover blockages, functional pathways and areas of backflow.

Lymphoscintigraphy has captured the interest of lymphologists over the past six years and, in some ways, is perceived as the gold standard for functional lymphatic visualisation (Williams et al, 2000; Witte et al, 2000). It is not without its problems, however, due to a lack of standards and incorrect use and, until these are solved, it will be little more than a useful, qualitative tool for lymphatic function. However, used correctly, with appropriate controls and standards, lymphoscintigraphy will be able to offer enormous advances in objective and quantitative knowledge of lymphatic transport rates, the location of functional collectors and dysfunctional capillaries, and of how treatments are working to make a difference.

Exercise and activity

One of the aspects of lymphoedema research which has been progressing, but has not held much of the limelight, is exercise and, to a lesser extent, posture. There are still many contradicting views among patients and therapists and many myths prevail, and yet, it may be one of the simpler and easier management strategies available. However, we need to further investigate the breathing component (which leads to variation in intra-thoracic and intra-abdominal pressures), and that of variation in muscular tone (which varies interstitial tissue pressures), both of which are believed to improve lymph flow. Certainly, the combination of both, in simple exercises similar to Tai Chi has been found to help secondary arm lymphoedema (Moseley et al, 2005).

The literature indicates that attempts to control cancer locally frequently results in a reduced range of motion, and a loss of muscular strength (Johansson et al, 2001). Many patients are not encouraged to undertake exercise, and many do not wish to do so due to a perceived risk that it may precipitate or exacerbate lymphoedema. On the negative side, lack of exercise can further reduce range of movement, see a further loss of muscular strength, and facilitate weight gain. On the positive side, there is the possibility of reducing fatigue and improving oxygen uptake during radio- and chemotherapy (Gulvao et al, 2005) and reducing the risk or recurrence of cancer (Holmes et al, 2005).

So, does exercise make lymphoedema worse, or precipitate it? Apparently not. Harris and Neisen-Vertommen (2000) were the first to show this. McKenzie and Kalda (2003) have shown in a small study that a progressive eight-week upper body programme of resistance training and aerobic exercise did not worsen lymphoedema, and that measures of quality of life, including physical functioning, general health and vitality all improved statistically.

Recently, these findings have been supported by Johansson et al (2005) and Lane et al (2005). While the wearing of compression garments is of additional benefit under any condition, in one study (Johansson and Piller, 2006) they were not worn – to no detriment to the patient. More

recently, in a randomised controlled trial (RCT) of weight training, it was clear that a six-month intervention of resistance exercise did not increase the risk of, or excacerbate the symptoms of, lymphoedema (Ahmed et al, 2006). Thus showing that even high levels of activity and exercise are not, as previously thought, bad for the patient.

Evidence-based actions

Major issues need to be addressed in the next five years, including: the way in which lymphoedema is managed; patient outcomes; the costs of care; and the variation in the frequency of the various medical and surgical processes leading to lymphoedema and associated with its control. In part, these issues are raised in the consensus document for the Best Practice for the Management of Lymphoedema and in the International Society for Lymphology consensus document. These guide our direction and strategies, but there is no doubt that the key issues are those of early detection and, at a more basic level, the prevention of lymphoedema as a sequelae of cancer treatment by attempting to change surgical and radiotherapy practice (but ensuring that a patient's longevity is unaffected). At all stages, quality of life should be optimised by minimising the burden which lymphoedema brings. It is unlikely that we will be able to eradicate it, but there is a potential to reduce its prevalence. For primary forms, reduction lies in better understanding of lymphangiogenesis, while for secondary forms, it lies in educating surgical and radiation oncology staff about the lymphatic system, and how best to protect it. From what we know, there has to be serious damage or dysfunction to the lymphatic system for it to fail under normal loading conditions.

The 'evidenced-based' label is similar to 'low fat', 'low GI', or 'low salt' and it is well known that not all of these 'evidence-based' claims are justified. We are often not sure which standard, criteria or measurement technique is used to describe 'low'. While rigorous methods are to be found for identifying, appraising and drawing together the available evidence from clinical and experimental studies, often these methods are not used consistently, leading to variations in the validity of our decisions and recommendations, which have the evidence-based tag associated with them. Evidence is often not available for all components of a recommendation at the same level of rigour. We have to take great care that the label, if applied, really does apply, since its attachment will have a significant effect on patient outcomes and on the breadth and depth of subsequent research. Some research might not even occur if it is believed that strong and valid evidence already exists.

The next five years

Concentrating on the key issues which face us as far as secondary lymphoedemas are concerned, it is clear that the immediate future research should focus on the visualisation and protection of all lymph vessels (and nodes) which are not concerned with any detected cancer. This is not greatly different from the techniques which are currently used in sentinel node identification, but in the reverse (identifying non-breast and non-groin draining vessels). Further, the use of multifrequency bio-impedance seems to have a strong advantage in the early detection of additional extracellular fluids over other means, although perometry and tape will continue to be useful for assessing total limb volume changes. For those with lymphoedema, the issue will be to discover if the remaining lymph vessels can be stimulated to work more effectively through their optimal loading and pulsation. Also for this group of patients, is the exciting prospect of encouraging lymphangiogenesis while holding angiogenesis at bay. The negative, however, is the anticipated risk of encouraging cancer recurrence.

Using lymphoscintigraphy to learn more about the functional status of using this information to target, direct and assess treatment will be crucial. Undertaking studies which better allow sequencing and targeting of treatment will give better outcomes. However, none of these potentially exciting areas of investigation will be any good unless we can all measure the same person and come up with the same diagnosis and make similar treatment recommendations. Working on, and the publication of standards and the seeking of consensus is crucial, if not mandatory. JL

Key Points

- The risk of lymphoedema can be reduced.
- Early detection of lymphoedema should be a target goal.
- New lymphoedema knowledge will come from better understanding of genetic molecular and cellular events.
- Our actions must continue to be supported by evidence, but we must not close our minds to new treatments.
- Exercise and activity may play a key role in lymphoedema control treatments.

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