

Lymphatic senescence - can we counteract it through lymphatic system stimulation?

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Abstract No-one it seems is immune from cellular senescence, as we age. We often focus on this, and the reason is clear; in its chronic form it's part of the process of aging (and eventually dying) of some form of cancer, and/or system dysfunction, be that cardiovascular, intestinal or some other. However, senescence is also a necessary part of living, having an important role in embryogenesis, wound healing and the tissue remodeling process. None of our body systems is immune from it, including the vascular and lymphatic systems which are the focus of this article. In terms of senescence of the lymphatic system there are structural and thus functional changes affecting its ability to function optimally. Some evidence indicates a reduction in lymphatic density and pumping abilities (at least in skin) But we may be able to make a difference through the application of lymphatic stimulation techniques such as Complex Decongestive Therapy. Manual Lymphatic Drainage and electrostimulation. However, we need more research into their benefits in the older population groups in which we have also some evidence of senescence.

Keywords Aging, lymphatic Senescence, lymphatic dysfunction, treatment, MLD

Background

A recent article in our journal¹ (Onorato, et al, 2024) stimulated my interest in this area.

The Authors indicated that lower limb oedema becomes more frequent as we age and that it may be linked to a deterioration of lymphatic function due to the system's senescence¹.

Our lymphatics maintain body homeostasis by recirculation of fluid, its contents and cells and that senescence will induce lymphatic dysfunction. This includes impaired contractile function which is caused by reduced lymphatic (and other surrounding muscle cell strength as well as a reduction in nitric oxide in the aged lymphatic collectors, together which lead to reduced lymphatic drainage and the associated consequences of it. Further, the aging-induced loss of the endothelial glycocalyx and the increased production of inflammatory cytokines as well as a failure to remove them increases the lymphatic collector's permeability. There is also a poorer immune response¹.

Unno et al (2011)² examined the influence of age and gender on lymph pump pressures in the leg. There was no mention of senescence, but it was clear that age did have a significant influence on lymph pumping pressure as did gender with the decrease in pumping pressure being more marked in females than males. Further indicating the impact of gender on lymphatic function/dysfunction, Trincot and Caron, (2019)³ indicated we still know little of this gender difference and how gender affects lymphatic endothelial cell growth, function and dysfunction in disease and how knowing more of this could lead to new and improved treatments, including pharmacological interventions and perhaps biomarkers.

To understand the differences and perhaps how they develop and progress they indicated future studies should be taken in both male and female model organisms, cell lines, and patients.

Lymphatic drainage

We could go through the lymphatic drainage systems of each of our major organs and structures including the skin and subcutaneous areas, but the principles are similar irrespective of whether it's the gut, brain, heart.

Taking the lymphatics of the heart as an example

Why is this so important? Well, the cardiac lymphatics can be targeted therapeutically to restore lymphatic drainage in the heart to limit myocardial oedema and chronic inflammation see Brakenhielm & Alitalo, 2019⁴. We can also do the same for the lymphatics of other structures.

The question remains is whether these strategies could work when there is lymphatic senescence but we know that MLD and other lymph stimulatory activities work in older people with chronic oedema and lymphoedema when there are likely to be underlying issues of senescence within the lymphatic and other systems.

Senescence

Senescence is the process by which damaged cells enter irreversible growth arrest but stay alive and continue to secrete substances that damage surrounding tissues, which for example, contribute to blood vessel problems as people age Han and Kim (2023).

When senescence of the cells associated with the lymphatic system occurs it induces lymphatic dysfunction. There is impaired contractile function caused by low muscle cell strength and a decrease of nitric oxide in aged lymphatic collectors, leading to poor drainage of lymph. Aging-induced loss of endothelial glycocalyx and production of inflammatory cytokines as well as the critical need to efficiently remove them increases the permeability of lymphatic vessels - and so the cycle continues.

Cells that stop proliferating but remain metabolically active offer a promising therapeutic target for the treatment of age-related vascular diseases. Han and Kim (2023)⁵ also showed in their review that the 'zombie' cells then fuel the development of atherosclerosis, hypertension, and other vascular disorders. They indicate that Diagnostics that test for indicators of senescence especially those affecting the lining of blood vessels could help reveal the severity of vascular damage, as could medications which influence the function of senescent cells.

Senescence and pathophysiology and the lymphatic vessels

What does senescence mean in terms of the initial lymphatics and the lymphatic collectors? This area is well covered in an article by Shang, et al 2019⁶ but what follows

are some specific details about it. Knowing these can help understand how we might target the changes and help improve lymphatic function.

The primary function of the lymphatics is to transport lymph and its contents back into the venous system, some occurring within the lymph nodes and the remainder at the jugular subclavian vein junctions near the scapula. Importantly, the intrinsic contraction of the lymphatic muscle cells (determined by their state of stretch) determine the forward movement of lymph (subject to patent valves), often against a pressure gradient. Each lymphangion contracts relatively independently but as lymph is pushed into the next more proximal one, it too contracts propagating a peristalsis-like wave.

Aged lymphatic vessels have changes in their lymphatic muscle cell composition. Often there are fewer muscle cells and sometimes discontinuous or irregular muscle cell organization (Bridenbaugh et al 2019)⁷. What this can mean is a limitation in terms of the ability of these muscle cells to mediate a proximal directional propagation of contractile waves (Zawieja, et al 1993)⁸. Perhaps more significant is the fact that the loss of, or the inability to function properly of the muscle cells may lead dysfunctional lymphatic valve closure leading to a reflux of lymph. This can mean a reduced effectiveness in clearing inflammatory mediators and compromised pathogen clearance. In fact it's been shown that pathogens may move proximal to distal as the lymphatic valve gating fails (Bridenbaugh et al 2019)⁷. These issues have been indicated to be mostly concerning the more distal lymphatics with those more proximal being less affected, at least that is what an older but well conducted study indicated in rats (Nagai et al 2011)⁹.

What this does suggest from a therapeutic point of view (which I'll discuss later) is that it's possible if we can get lymph and its contents into the lymphatics and get it flowing in the more distal areas, once it reaches proximal areas the remaining relatively functional lymphatic system may be able to handle the load and clear the lymph and its contents.

This is potentially very important since when lymph flow is high (at least in an animal model) there was no significant inhibition of lymph pumping in the aged group at high levels of imposed flow at least in a thoracic duct model of rats (Gasheva et al 2007)¹⁰.

Helping lymphatic drainage

Manual Techniques

Kasseroller and Brenner (2024)¹¹ in their recent study showed CDT with MLD as the core component

was beneficial in reducing significantly Breast Cancer Related Lymphoedema (BCRL). However other studies and reviews (Thompson et al 2020)¹² have not always been as positive with many citing the need for further research. So much more needs to be done. But it's often reported by therapists that on an individual basis some patients respond very well to the MLD while for others the outcomes are not so good. So, it would seem it's a heterogenous response to MLD. The reasons for this are unclear but maybe its linked to senescence.

Nevertheless, CDT and its other components still form a mainstay of lymphoedema treatment irrespective of whether its arm, leg or other part of the body.

Our main strategy revolves around Manual Lymphatic Drainage techniques and associated actions, which include concentrated diaphragmatic breathing, skin care and diet and the like. It's without doubt that good lymphatic drainage helps remove accumulated fluids and their contents from the tissues, but can it do it if the endothelial cells and associated musculature is suffering a degree of senescence?

We do know however that even a moderately dysfunctional lymphatic system irrespective of the cause of it (be it age, gender, genetics, Surgery, radiotherapy, soft tissue trauma, obesity etc) can be helped to work better by often simple strategies such as improved diaphragmatic breathing, MLD compression, diet changes etc. Some examples of this come from the study of Shillinger et al (2006)¹³ who showed MLD to more rapidly decrease serum levels of muscle enzymes which they suggested was linked to improved regenerative processes in terms of damaged muscle cells. Foeldi et al (2000)¹⁴ reported a decrease in a range of pro-inflammatory genes after Complex Decongestive Therapy, Zebrowska et al (2019)¹⁵ showed lymphatic drainage methods including MLD and electrostimulation improved post exercise regeneration of muscles while Kim et al (2009)¹⁶ showed an ability of MLD to reduce the activity of the sympathetic nervous system (related to the heart). So, we see a huge range of impacts of MLD some of which suggest the likelihood of significant benefit across all aspects of tissue damage/repair and in deleterious outcomes. The question remains is whether these strategies could work when there is lymphatic senescence, but we know that MLD and other lymph stimulatory activities work in older people with chronic oedema and lymphoedema when there are likely to be underlying issues of senescence.

The answer is yet to be determined with certainty but given the existence of initial lymphatics and collecting lymphatics and clear pathways to nearby lymph nodes and to the subsequent drainage paths to the left and right jugular subclavian junctions the answer could be "yes"!

Why? Because normal lymphatic function is determined by neurogenic/myogenic stimulation caused by the contents of the lymph awaiting removal as well as by signals from the brain and the impact of MLD which we know has two important actions of loading the lymphatics with fluids and their inflammatory mediators lymphokines and cytokines and helping clear these along the lymph collectors and away from the affected area.

At a basic level MLD can do this by creating a pressure gradient (especially when the more proximal areas are emptied) and through tissue stretching and relaxing which also helps movement and importantly creating a variation in pressure all of which can facilitate proximal movement of lymph and its content.

In further dealing with pressure, when externally applied either through compression bandages, garments or wraps are used we know it can help compress the tissues, helping dysfunctional inter lymphangion valves improve their competency and as mentioned above provide an effective pressure gradient. Certainly in the aged population group where senescence is likely to be an issue elastic compression can certainly help in symptomatic relief (Simon, 2014)¹⁷.

Electrical Stimulation

A previous article reviewed the possibility of helping to improve lymphatic drainage by electrical stimulation, either directly to the musculature of the lymphatics or to the surrounding skeletal musculature or to the nerves supplying the muscles. (Piller, 2023)¹⁸. It's likely that this also may be able to overcome some of the issues of senescence and should be investigated along with MLD and other lymphatics stimulatory therapies. Certainly, in a study by Zebrowska et al (2019)¹⁵ on the recovery of athletes they were able to show a benefit of manual lymphatic drainage or electrostimulation methods in improving the health of muscles after intensive activity.

Conclusion

It's clear that lymphatic function declines with age and is perhaps related also to gender and our understanding of the mechanisms of this is improving. But we are not there yet in terms of having the ability to intervene in the processes which may be leading to these changes, but we do know that lymphatic senescence is a significant problem in aged communities and of particular importance for older persons who are immobile and overweight.

On the other side of the coin, we know of many ways in which we can improve lymphatic function but using well known programs encompassing CDT of which MLD is a key component, and compression and breathing improvement as occurs during Yoga and Tai Chi training.

But we don't seem to be focusing on the underlying issues of senescence – we spend most of the time focusing on the genetics, the type of cancer surgery and other treatments they have had to lead to the lymphatic dysfunction and thus the lymphoedema. Maybe it's time for a change, given our increasing knowledge of senescence and why it occurs and how we might better manage. In the meantime, our core treatments will prove beneficial

I'm sure if senescence is found to be a major reason for the decline in lymphatic function, maybe it's time to apply these treatments and record their impact while we await other solutions. Our next step: Share your ideas and likely measuring methods to monitor lymphatic system senescence so we can look forward to improved outcomes in older people with lymphoedema or at risk of it.

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