Obesity, inflammation, diet, gut microbes, and lymphatic system communications with the brain and the impact of lymphatic system

Neil Piller

The gut and its wall is like the skin — a barrier between our internal and the external environment. Often, all is well and the barrier is structurally sound and functions as it should. However, sometimes things can go wrong and these aberrations can become chronic. It's not an impermeable barrier. Many things have to cross it to ensure our optimal health; for instance, evaporative fluid loss and core temperature regulation though vasodilation and constriction. Gross changes — when we have a serious wound involving the epidermis, the dermis and other layers that can lead to uncontrolled blood loss, allowing entry of uninvited bacteria leading to subsequent infection. Diseases and disorders of the skin, such as psoriasis acne, eczema, shingles, rosacea, hives and cold sores, lead to chronic long-term changes to the skin and affect our body's ability to defend its self.

The gut is similar — its layers (like those of the skin) can be damaged or dysfunctional and for the body this can be just as serious in terms of health outcomes.

We should recognise the importance of the gut, acknowledge the impact or our worsening obesity crisis, our diet and its composition and the impact on the microbiome along with what can go wrong. But importantly, we should be aware of what we may be able to do to bring it back to a normal function range. It's clear now that we can't consider the gut in isolation, we also must consider the lymphatic system and its functional state as a key factor in it all, as Escobedo and Oliver (2017) have indicated in their recent excellent review.

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Some of the ideas and information is not all based on randomised controlled trial (RCT) outcomes, but RCTs are not the only useful information source (Piller, 2018) and some is not based on human studies and we need to be aware of the translational issues to humans, but more researchers are melding what we know of the gut, the microbiome, the lymphatic system, obesity and its role, linkages and impact on the brain.

Armed with this new synthesis of information, the onus should be placed on the translation to a clinical situation and what a lymphoedema practitioner might do to remediate these changes (or prevent them from worsening) by improving lymphatic function and flow — after all, the lymphatics are a sewer and we all know what happens when they are blocked or dysfunctional! (Taylor, 2017).

Context

The gut has many functions. Closely integrated with it and to these functions are the lymph vessels and nodes. Their roles, nature and specific details regarding the intestinal environment maintenance and the impact intestinal health and disease has on them are unclear and understudied. We know they function as conduits for lymph and immune cells and there is some significant adaptation to gut nutrient and barrier functions.

We know that obesity has a significant impact on lymphatic function. We also know that the lymphatics are essential for absorption and transport of nutrients, hormones, many medications, and other extracellular components from the digestive tract directly or indirectly to the blood. We know this transport also includes bacteria and viruses.

We know lymph contains chylomicrons and hormones produced by the range of entero-endocrine cells and we believe that the nerves of the lacteals are a part of a neuro-lymphocrine system, which is likely stimulated by the contents of interstitial fluid.

We know so much ... or do we?

We are aware that during infection, increased lymph flow limits oedema, up to when it reaches maximum transport capacity. We know lymph stasis will lead to chronic inflammation so its optimal function and maximal function load and drainage is critical.

But it's not always this simple and sometimes a lymphatic system functioning maximally might not be the best in terms of cell and tissue health and the immune system. We know that infections can result in damage to the peripheral/central nervous system through the replication of bacteria within the nervous tissues and sometimes through an uncontrolled immune response; the latter of which can be a significant issue.

However, the two body systems (lymphatics and microbiota) critical for whole body homeostasis are often ignored as we have seen (Rockson, 2017)

Obesity — cause or consequence?

We are all cognisant of the issue of obesity, but we often are unaware of its relationship with metabolic syndrome/poor metabolic health, these impacts on gut permeability 'leakiness' and the microbiome.

We know that what's going on in the gut is 'messaged' to the rest of the body (most often by the lymphatics). We also know about the regional lymph nodes and their role in the immune response, but we know little of the lymph vessels linking them and what changes to their status mean. Some

diseases/disorders (chylo-thorax, filariasis, metastatic spread and nodal swelling in infection) do remind us of the lymph vessels, but we need more research here.

Adipose tissues

Adipose tissues seem to be one of the culprits behind many of our issues of lymphatic dysfunction. Adipose tissues are normally located in the viscera and subcutaneously. Its volume changes depending on energy intake and metabolic needs. Excessive amounts of white adipose tissue (as occurs in obesity) shows within it signs of chronic inflammation (Ge et al, 2014). The reason behind this is that visceral adipocytes promote inflammation by secreting mediators such as interleukin (IL)-6, tumour necrosis factor (TNF)-α, and leptin. Associated with inflammation is a macrophage accumulation/proliferation within these tissues (Amano et al, 2014). Then, as part of their expected tissue homeostatic and normalisation role, there is further macrophage differentiation and phagocytosis of necrotic adipocytes, which again leads to higher cytokine and chemokine concentrations and additional inflammatory cell recruitment, and so the cycle continues (Torrisi et al, 2016).

Adipose tissue composition

All adipose tissue contains a rich vascular capillary network. Adipose tissue can exhibit unlimited expansion when energy supplies are high and metabolic demands low and any expansion requires a new network of new blood vessels to support delivery of oxygen and nutrients. This expansion is linked to angiogenesis through the expression of Vascular Endothelial Growth Factor (VEGF).

Adipose tissue expansion thus involves continuing 'cross talk' between adipocytes and the blood vasculature. But we must consider its impact on the lymphatic system, its proliferation and of the outcome of good or poor lymphatic outflow (and perhaps inflow) on the adipocytes and associated tissue (Harvey, 2008; Tran et al, 2015).

Lymph and the lymphatic system

The lymphatic collectors have spontaneously contracting smooth musculature, a defined basement membrane, the inter-endothelial junctions, and the presence of valves. This, together with the contraction of surrounding skeletal muscles, intra-abdominal and intra thoracic pressure variations (related to respiratory phases) and arterial pulsations, ensure good lymph flow — if the system is appropriately loaded! The latter is a critical point that we often ignore.

The lymphatic system in immunopathology

When an acute infection (and associated inflammation) occurs, there is an increase in lymph flow. This is of great benefit since it limits oedema, provides an opportunity for soluble microbial antigens and dendritic cells to present at the regional nodes.

But what if there is lymphatic failure (lymph stasis) due to surgical or radiotherapeutical damage, malformation or disease? It may mean a persistence of immune cells/mediators in tissues. This will lead to chronic inflammation and tissue damage. In terms of the gut, this may contribute to Cohn's and ulcerative colitis. There is another side, however — confinement of pathogens limits their spread so surely that's good?

So where is the best balance point, and how is that often variable 'decision' reached by our systems? Does the presence of excess adipose tissue impact on this decision-making ability?

CrossTalk?

Escobedo and Oliver (2017) indicated some animal models (mice) exhibit a strong link between lymphatic functioning (or not) and obesity. Various research groups indicated in this review have shown that obese mice show impaired lymphatic function, leaky capillary lymphatics a decreased pumping capacity, fewer lymphatics and a decreased lymphatic migration of immune cells.

Further, mice fed a high-fat diet also showed increased inflammation, initially. This became worse with lymphatic injury/dysfunction and resulted in further subcutaneous adipose deposition, inflammation and fibrosis in the longer term. This is the same positive feedback cycle described above relating to adipose tissues and their link to inflammation! [AQ1: are you happy with this rewrite?]

So taking this into the clinical area means obese patients may be at a higher risk for lymphoedema due to reduced lymphatic clearance, and also may be more prone to infection and inflammation after any injury.

But where does it all start? Is some inflammatory event initially responsible for an obesity-mediated lymphatic dysfunction or is it the other way around?

The start point (how much excess white fat) for it all is hard to determine, but we are perhaps now a little more aware of our best leverage point for the majority of situations — that is to improve lymph flow. But we still need a deeper understanding of how obesity impacts on and regulates lymphatic function.

Savetsky et al (2015) suggested that obesity-induced lymphatic dysfunction can intensify the pathological effects of obesity in other organ systems. It seems to do this by regulating leukocyte infiltration and in the expression of inflammatory cytokines By examining this, we can see that obesity-related lymphatic dysfunction could, and will, worsen any pathological changes associated with obesity and may cause pathological changes in other tissues as well.

Microbes and the gut

We hear about 'good' and 'bad' bacteria. Is that really so (Tsunoda, 2018)? Is it a myth perhaps? We might say a bacteria that helps ageing, reduces obesity and can supress other bacteria and their infections, and which may reduce issues related to brain disease is a 'good' bacteria, while the 'bad' bacteria, well they are just that "bad" and let's leave it at that! That's just not so! Take for instance *Clostridia P* and *Helicobacter P* (associated with poisoning, gastritis and gastric cancer); their levels are actually less in multiple sclerosis! So does it means 'bad' can become 'good' (and vice versa)?

Comparing antimicrobial immune responses with immunopathology

There's a battle between cellular immunity pro-inflammatory Th1 helper cells and the humoral immunity anti-inflammatory Th2/regulatory T cells. Going back to the *Clostridia P* and *Helicobacter P* issue, if *H pylori* is not eradicated, the immune response is skewed to an anti-inflammatory one, meaning protection of the immunopathology at the expense of

bacterial persistence (Tsunoda, 2018). Does this make sense? Sometimes it can be hard to digest and to gain that understanding we need to look at the big picture.

Inflammatory environments induce changes in gene expression in the lymphatic endothelial cells (LECs). This change leads to an expansion (lymph-angiogenesis) of the lymphatic network in the inflamed tissue, and in the draining regional nodes. When one experimentally blocks (or enhances lymph-angiogenesis), these outcomes will modulate the course of the inflammatory and immune responses — so lymph-angiogenesis and its regulation is at the core of what happens when there is an immune challenge.

Is perhaps this gene expression on LECs a new therapeutic target? Just think for a moment about when we are undertaking a technique to improve lymph flow. What are we doing to this modulation and are we thinking enough about it as a potential additional outcome to our key intent?

The microbiome and the brain

Gut microbes can be linked to mood, emotion, appetite, fullness, learning and memory, so these microbes appear to help maintain brain function. But they may also influence anxiety and depression.

There are some similarities/parallels in some aspects of the functioning of the immune and nervous systems. For instance, immune cells and neurons can produce and sense many of the same molecules/chemicals, but some microbes produce chemicals/molecules, which impact on behaviour without affecting the immune system.

How do gut microbes communicate with the brain? They may do this in one of three ways:

- Directly via the vagal nerve (which is the key gut-brain connector nerve)
- Through circulating immune cells, which are 'trained' in the gut and then travel to brain via the lymphatics or venous systems (so much for the blood brain barrier)
- By metabolites/chemicals produced by gut microbes that enter the blood and circulate to the brain where they may influence behaviour.

When there are communication systems, as we all know in our wider lives, sometimes things go wrong and it seems this may also happen with the gut-brain pathway. As an example, there may be a link between neurodegeneration and the microbiome. Alzheimer's, Parkinson's and amyotrophic lateral sclerosis may have a gastro intestinal component linked to them. For instance, in some patients with these conditions, there seems to have been some gut disturbances many years before motor system issues appeared. Just remember though that many of these statements are based on association rather than causation, but it's an interesting finding.

This begs the question 'does a healthy weight and a normal range of white adipose tissue and a diverse microbiome, mean a healthy body and a healthy brain and if there is 'poor health' in any of these areas, how might improved lymphatic function and drainage and other strategies be able to help?'

There are some reasonable steps to improve this health if its poor and that could start with white adipose tissue management, through diet and diet compositional management and, thus, perhaps by helping to increase gut microbe diversity. Generally, our gut diversity is decreasing as we live in cleaner environments, and consume more prepared heated or microwaved foods. But on the positive side, apparently spinach has about 800 different species of bacteria in its leaves and they are not always destroyed during cooking!

Further, fruits and vegetables, resistant starches found in seeds and nuts, as well as perhaps anti-inflammatory, Omega-3-based foods may all help bacterial diversity. Will this mean a healthier gut population, less inappropriate signalling to the brain via the mechanisms mentioned above and will this be likely to have an impact on the initiation or severity of some of these neurodegenerative diseases?

For all of you who know how to improve lymphatic system functioning, if we improve/modulate lymph flow from the brain will we be able to have a positive impact on brain health? Perhaps an example of this is that Parkinson's is linked to a mis-folding of a protein in nerve fibres — and it may start in the gut.

The reason is that the bacterial population may be linked to virus that kills 'good' gut bacteria. Yes, I did say earlier that there is really no 'good' or 'bad' bacteria, but remember, it all depends on numbers (concentrations) and their location.

So the event of a viral attack may result in a chain reaction originating in the digestive

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system and resulting in nerve damage in the brain. Those with Parkinson's disease have only about one tenth of the levels of *Lactococcus* compared to those without it and they had twice the levels of a virus (bacteriophage), which invades and destroys these bacteria.

Keep an eye out for more information about the very exciting developments on some of these fantastic and hitherto unknown inter-relationships between the gut and the brain.

Lymphatic drainage from the brain

This is also one of the keys in our health maintenance. We have rediscovered that meningeal lymphatic vessels drain macromolecules from the CNS (cerebrospinal/interstitial fluids) into the cervical lymph nodes. Michael Földi had an inkling of this last century, but we have seen it now in many studies (Földi, 1975; Nedergaard, 2013; Borthwick, 2015; Absinta et al, 2017; Thomas, 2017). When this lymphatic function is impaired it slows the para-vascular entry of macromolecules into the brain and their exit from the interstitial fluid. This induces cognitive impairment — at least in mice (Blum et al, 2014). Treatment of aged mice with VEGF-C can enhance macromolecular lymphatic drainage from the cerebrospinal fluid, thus improving brain perfusion with an outcome of an improvement in learning and memory — again in mice. When the meningeal lymphatic vessels in transgenic mouse models of Alzheimer's disease were disrupted then amyloid-β deposition occurred in the meninges, which is much like human meningeal pathology, and which further aggravates parenchymal amyloid-β accumulation. Since this lymphatic dysfunction is likely to be an aggravating factor in Alzheimer's disease and age-related cognitive decline, any improvement of meningeal lymphatic function may be useful for preventing or delaying a range of age-associated neurological diseases (Da Mesquita et al, 2018).

It's over to you!

Can you complete the picture — if there are changes in brain structure (and function) and if these are linked to the microbiome, and this to obesity (excess white fat deposition) and what this might do to the brain via the lymphatic system (sending molecular messages, inflammatory agents etc.) ... and if you can improve brain lymphatic drainage (remember that the brain has a lymphatic system!), reducing the concentration of these and improving the milieu of the cells, the integrity of their connectors and the astrocytes, perhaps if this can prevent or have an impact on a range of brain degenerative diseases then we are looking at broadening of the benefits of improving health. Not only by impacting on the lymphatics, but also by considering and manipulating the gut and its microbiome, our diet and its composition!

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